Intracerebral malignant peripheral nerve sheath tumor in a child with neurofibromatosis Type 1 and middle cerebral artery aneurysm treated with endovascular coil embolization

Case report

MICHAEL J. ELLIS, M.D.,1 SAMUEL CHESHIER, M.D., PH.D.,1 SUNJAY SHARMA, M.D.,1 DEREK ARMSTRONG, M.D., F.R.C.P.C.,2 CYNTHIA HAWKINS, M.D., PH.D., F.R.C.P.C.,1 ERIC BOUFFET, M.D.,4 JAMES T. RUTKA, M.D., PH.D., F.R.C.S.C.,1 AND MICHAEL D. TAYLOR, M.D., PH.D., F.R.C.S.C.1

Divisions of 1Neurosurgery and 2Neuroradiology, and Sections of 3Neuropathology and 4Neuro-oncology, Hospital for Sick Children, University of Toronto, Ontario, Canada

Among the neoplastic conditions that affect patients with neurofibromatosis Type 1 (NF1) are malignant peripheral nerve sheath tumors (MPNSTs), which typically arise from peripheral nerves of the limbs, trunk, and lumbar and brachial plexuses. Ionizing radiation is an established risk factor for MPNST development, especially in susceptible patients such as those with NF1. Patients with NF1 are also at risk for intracranial aneurysms, which are increasingly being successfully managed with endovascular therapies. The authors describe the case of a 9-year-old, previously healthy girl who presented in extremis with a right frontal intracerebral hemorrhage resulting from a ruptured right middle cerebral artery (MCA) trifurcation aneurysm. Following urgent decompressive craniectomy, the patient underwent endovascular coil embolization of the MCA aneurysm without complication. Given her mother’s history of NF1, the child underwent genetic testing, which disclosed signs positive for NF1. The patient recovered well, but follow-up MR imaging and MR angiography performed at 14 months demonstrated a large frontotemporal mass encasing the right MCA trifurcation. The patient underwent frontotemporal craniotomy and subtotal resection of the mass, which was histologically found to be an intracranial MPNST. The patient received chemotherapy and focal radiation therapy and remains alive at 6 months postresection. To the authors’ knowledge, this represents the only known case of intracranial neoplasm arising in the region of an intracranial aneurysm repaired by endovascular coil embolization. While patients with NF1 represent a population with genetic susceptibility to radiation-induced tumors, the pathogenesis of intracerebral MPNSTs remains poorly understood. (DOI: 10.3171/2011.7.PEDS11151)

Key Words • malignant peripheral nerve sheath tumor • aneurysm • endovascular • neurofibromatosis Type 1 • coil embolization

Abbreviations used in this paper: MCA = middle cerebral artery; MPNST = malignant peripheral nerve sheath tumor; NF1 = neurofibromatosis Type 1.

Neoplastic conditions that affect patients with neurofibromatosis Type 1 (NF1) include MPNSTs, which often arise from peripheral nerves of the limbs, trunk, and lumbar and brachial plexuses. The occurrence of intracerebral MPNSTs affecting the cranial nerves and arising from the brain parenchyma is exceedingly rare and limited to case reports and a few small series.1,5–7,9,14,20,24,30,31,34,36 One of the established risks factors for the development of MPNSTs is ionizing radiation, which is thought to induce metaplastic changes in Schwann cells and may be even more fundamental in susceptible patients such as those with NF1.11,30

In addition to neoplastic processes, patients with NF1 are also at risk for several cerebrovascular conditions such as moyamoya syndrome, arterial dissections and stenoses, and intracranial aneurysms.8,28,33 Although pediatric aneurysms often differ greatly from their adult counterparts in terms of size, location, and etiology, an increasing number of children are benefitting from endovascular approaches.1,16,29

We report on a case of a young girl who presented with subarachnoid hemorrhage secondary to a ruptured MCA aneurysm. One year after endovascular repair of her aneurysm with coils, the patient developed a large intracerebral MPNST encasing the previously coiled aneurysm and parent vessel. The literature on intracerebral MPNSTs in children is examined to help provide possible explanations for tumor pathogenesis in this case.

Case Report

History. This 9-year-old previously healthy girl ex-
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experienced a sudden loss of consciousness while tobogganing. There was no history of trauma. The patient was evaluated at an outside hospital where she was unresponsive and found to have a right fixed and dilated pupil. She was intubated, treated with mannitol and hypertonic saline and transferred urgently to our institution.

Examination. The patient’s right pupil was minimally reactive, she was hemiplegic on the left side, and flexed her right upper extremity to painful stimuli. Brain CT scanning demonstrated a focal right frontal intracerebral hemorrhage associated with diffuse subarachnoid hemorrhage within the right sylvian fissure, extending over the right convexity and into the basal cisterns (Fig. 1A). The patient underwent urgent decompressive craniectomy and insertion of an intracranial pressure monitor. A follow-up CT angiogram revealed a right 5-mm MCA trifurcation aneurysm, which was confirmed with conventional catheter angiography.

Operation. The patient underwent endovascular coiling of the MCA trifurcation aneurysm with 3 platinum coils (Fig. 1B and C). There were no complications. During the patient’s admission, her mother reported that she had a history of NF1, which prompted a full dermatological examination that revealed multiple café-au-lait spots and axillary freckling. The patient underwent genetic testing, the results of which supported a diagnosis of NF1.

Postoperative Course and Additional Procedures. Follow-up MR imaging at 1.5 months postcoiling showed evolution of residual right frontal hemorrhage with surrounding frontal and temporal encephalomalacia. The patient recovered well from this event, and underwent bone flap replacement 3 months later. Eleven months following treatment of her aneurysm, she underwent follow-up MR imaging and MR angiography, which demonstrated a stable configuration of the coiled aneurysm associated with a subtle, irregularly enhancing mass surrounding the MCA trifurcation. Initially this was interpreted as post-procedural fibrosis or granulomatous change.

Two months later the patient presented with headaches. Follow-up MR imaging and MR angiography revealed spectacular transformation of the enhancing lesion into an 8 × 6.5 × 7–cm (anteroposterior, transverse, cranio-caudal) frontotemporal mass encasing the proximal right MCA with significant mass effect and midline shift (Fig. 2A–D). Magnetic resonance imaging of the entire craniospinal axis revealed no evidence of leptomeningeal dissemination or metastases. Catheter cerebral angiography demonstrated irregular narrowing the MCA sylvian branches, elevation of the proximal MCA M1 segment, and a diffuse neoplastic capillary blush arising from the MCA (Fig. 2E). Fluoroscopy of the skull also demonstrated extrusion of the coil mass into the tumor (Fig. 2F).

The patient underwent frontotemporal craniotomy and subtotal resection of the mass. During resection, the extruded coil was identified within the tumor and removed. Pathological examination of the operative specimen revealed a hypercellular, biphasic neoplasm with epithelial and spindle cell components arranged in a fascicular pattern. A mitotic index of greater than 10 mitoses/hpf was identified as well as immunopositivity for BAF47, Bcl2, PGP 9.5, and S100 (Fig. 3). Molecular testing for synovial sarcoma was negative. The final pathological diagnosis was consistent with an intracerebral MPNST. The patient underwent a full metastatic workup, which showed no unusual findings, and was subsequently treated with the sarcoma ifosfamide, carboplatin, etoposide-ICE chemotherapy protocol and focal radiation therapy with a near-total response (Fig. 4). The patient also required placement of a ventriculoperitoneal shunt for hydrocephalus. She remains alive at 6 months after tumor resection.

Discussion

Neurofibromatosis Type 1 is a cancer predisposition syndrome that affects approximately 1 in 3000 people. Approximately half of patients acquire the disease through autosomal dominant transmission of germline mutations.
of the NF1 gene located on chromosome 17. The other half acquires the disease as a consequence of sporadic new mutations. The NF1 gene acts as a tumor suppressor gene by encoding the protein neurofibromin, which is responsible for inactivation of the ras oncogene. Clinical manifestations of NF1 include café-au-lait spots, axillary and inguinal freckling, Lisch nodules, skeletal abnormalities such as sphenoid wing dysplasia, optic gliomas, and an increased incidence of central and peripheral nervous system neoplasms. Among the peripheral nervous system tumors that infrequently occur in patients with NF1 are MPNSTs. Malignant peripheral nerve sheath tumors are highly aggressive tumors that commonly arise from peripheral nerves of the extremities, chest wall, and major plexuses and are characterized histologically by a combination of epithelial and spindle-shaped cells arranged in a fascicular pattern. These tumors can occur de novo or arise as a consequence of malignant transformation of preexisting schwannomas or plexiform neurofibromas. The risk rate of developing an MPNST in the setting of NF1 is approximately 10% and is up to 18 times higher in those with plexiform neurofibromas. Prior radiation therapy appears to be an important predisposing factor for MPNSTs, a history of which is present in approximately 10% of cases with an average latency of 15 years postradiotherapy. The role of prior radiation is of particular importance in patients with NF1, as there have been reports of radiation-induced MPNSTs described in NF1 patients with a history of radiotherapy for optic gliomas and head and neck malignancies. Despite multimodality therapy, the prognosis of patients with MPNSTs is poor. A 5-year survival rate of 52% has been reported for all sites taken together and a rate of 20% for cases with only head and neck involvement.

In addition to cases in which MPNSTs arise from peripheral nerves, isolated case reports and small series have identified rare patients with MPNSTs of the cranial nerves and brain parenchyma. Similar to their peripheral nerve counterparts, MPNSTs of the cranial nerves may occur spontaneously or evolve from preexisting nerve sheath tu-
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mors. Despite a documented association between NF1 and prior radiotherapy in peripheral and cranial nerve MPNSTs, the role of these factors in intracerebral MPNSTs is unknown. To date, only 7 cases of intracerebral MPNSTs have been reported in the literature. Additional 3 cases of MPNSTs with rhabdomyosarcomatous elements or triton tumors have also been reported. Taken together, 6 of 10 reported cases of intracerebral MPNSTs have occurred in children. The mean age of this pediatric group is 8.2 years (range 14 months to 18 years) including 3 male and 3 female patients. Tumor locations include the parieto-occipital region (3 cases), frontal lobe (1 case), temporal lobe (1 case), and frontotemporal region (1 case). Of the 6 children reported, 1 had a documented history of NF1 and none had a history of radiation therapy. Treatment modalities included resection alone (5 patients; 3 gross-total and 2 subtotal resections) and surgery plus adjuvant radiation and chemotherapy (1 patient). Two children died of postoperative complications relating to intracerebral hemorrhage (10 days postoperatively) and sepsis (6 weeks postoperatively). Tumor recurrence was documented in 2 patients, with 1 patient, whose tumor whose recurred at 5 and 8 months and involved the dura, subcutaneous tissue, and skin, surviving 9 months. The second patient recurred at 24, 48, and 66 months with survival after final subtotal resection unknown. Two children treated with gross-total resection alone were alive at 17- and 19-month follow-up (Table 1).

In addition to neoplastic manifestations, NF1 is also associated with a number of cerebrovascular conditions including moyamoya syndrome, intracranial aneurysm, dural arteriovenous fistula, arterial stenosis, ectasia, and occlusion. Although hemorrhage remains one of the most common clinical presentations of pediatric aneurysms, significant differences have been noted in terms of aneurysm location, size, and morphology compared with adult aneurysms. In addition to these differences, the etiology and pathogenesis of childhood aneurysms plays a pivotal role in their clinical presentation and natural history, and has important implications for therapeutic decision making. Modern theories of pediatric aneurysm development suggest that genetic alterations may lead to primary dysfunction of the vessel wall and its repair mechanisms, predisposing it to additional secondary triggers that result in aneurysm formation. Despite the finding of neurofibromin in the endothelial cells of bovine and rat cerebral arteries, and the suggestion that neurofibromin may help mediate vascular smooth muscle proliferation, the pathophysiology of NF1-related vasculopathy and cerebral aneurysms remains unclear. Over the past few decades, the management of intracranial aneurysms has undergone considerable evolution such that endovascular techniques are now being increasingly applied in the pediatric population. Despite encouraging results reported by experienced centers, questions remain regarding the long-term durability of endovascular-repaired aneurysms in the pediatric population and the potential need for retreatment. An additional concern regarding the endovascular approach to pediatric aneurysms is the effect of prolonged radiation exposure on the developing brain and the risk of radiation-induced malignancies.

We have described the case of a 9-year-old girl with NF1 who presented initially with subarachnoid and in-

Fig. 3. Upper: Stain of pathological specimen demonstrating a hypercellular, biphasic neoplasm with epithelial and spindle cell components arranged in a fascicular pattern. H & E, original magnification × 30. Lower: Diffuse immunohistochemical staining for S100. Original magnification × 200.

Fig. 4. Left: Axial T1-weighted post-Gd MR obtained 1 day after craniotomy showing subtotal resection of the mass with postoperative changes and surrounding encephalomalacia. Right: Axial T1-weighted post-Gd MR image acquired 3 months after craniotomy demonstrating residual tumor located in the distal aspect of the sylvian fissure as well as dilatation of the right temporal horn. A ventriculoperitoneal shunt was placed for hydrocephalus.
TABLE 1: Summary of the clinical characteristics of reported cases of intracerebral MPNSTs in children*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Associated Conditions</th>
<th>Tumor Subtype</th>
<th>Location</th>
<th>Management</th>
<th>Clinical Course</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oztanir et al., 2009</td>
<td>1.2, F</td>
<td>NF1</td>
<td>MPNST</td>
<td>frontotemporo-parietal</td>
<td>STR</td>
<td>died of sepsis</td>
<td>6 wks</td>
</tr>
<tr>
<td>Bornstein-Quevedo et al., 2003</td>
<td>3, M</td>
<td>none</td>
<td>MPNST (triton tumor)</td>
<td>parietooccipital</td>
<td>STR</td>
<td>died of ICH</td>
<td>10 days</td>
</tr>
<tr>
<td>Tanaka et al., 2000</td>
<td>4, F</td>
<td>none</td>
<td>MPNST</td>
<td>parietooccipital</td>
<td>GTR</td>
<td>alive</td>
<td>19 mos</td>
</tr>
<tr>
<td>Sharma et al., 1998</td>
<td>8, F</td>
<td>none</td>
<td>MPNST</td>
<td>temporal</td>
<td>GTR</td>
<td>alive</td>
<td>17 mos</td>
</tr>
<tr>
<td>Stefanko et al., 1986</td>
<td>15, M</td>
<td>none</td>
<td>MPNST</td>
<td>parietooccipital</td>
<td>GTR &amp; RT (40 Gy total skull, 10 Gy tumor boost) after 1st op; chemo (IA cisplatin) after 2nd op</td>
<td>recurred at 5 &amp; 8 mos, died</td>
<td>9 mos</td>
</tr>
<tr>
<td>Bruner et al., 1984</td>
<td>18, M</td>
<td>NA</td>
<td>MPNST</td>
<td>frontal</td>
<td>GTR, STR</td>
<td>recurred at 24, 48, &amp; 66 mos</td>
<td>NA</td>
</tr>
</tbody>
</table>

* chemo = chemotherapy; GTR = gross-total resection; IA = intraarterial; ICH = intracerebral hemorrhage; NA = not available; RT = radiation therapy; STR = subtotal resection.

Intracerebral hemorrhage secondary to a ruptured MCA trifurcation aneurysm. One year after undergoing successful coil-based endovascular repair of her aneurysm, the patient developed a large, intraaxial mass encasing the previously treated aneurysm and the parent vessel. She underwent subtotal resection of the mass, which was found to be an intracerebral MPNST, and was subsequently treated with resection, chemotherapy, and radiotherapy. To our knowledge, this case represents the seventh case of pediatric intracerebral MPNST reported in the literature, the third occurring in a patient with NF1, and the first case of any pediatric brain tumor arising in the region of an intracranial aneurysm previously treated with endovascular coil embolization.

While previous reports of intracerebral MPNSTs and schwannomas have offered various theories regarding the etiology of these tumors, the cell of origin and molecular events underlying tumorigenesis remains unknown. Some authors have suggested that that de novo tumors may arise from malignant transformation of perivascular neural tissue or from pluripotent stem cells located in brain parenchyma, but neither of these theories is supported by convincing evidence. Because details of the etiology of intracerebral MPNSTs remain elusive, it is difficult to offer any explanation regarding tumor pathogenesis in this case and its relationship to the patient's previously repaired aneurysm.

One plausible explanation is that the occurrence of an MPNST in the region of the previously coiled aneurysm can be explained by chance alone. From the limited cases reported in the literature, no clear location predilection for MPNSTs has been observed, although all pediatric tumors occurred in the supratentorial compartment.

A second explanation is that the tumor was already present at the time of the intracerebral hemorrhage but escaped initial detection and progressed rapidly over a year later. Although possible, no evidence of an enhancing mass was seen on serial postcontrast CT scans during the patient's initial admission or on the initial follow-up MR images obtained 1 month after the coils were placed. If true, this explanation also lends itself to the possibility that the initial ruptured MCA aneurysm represents a neoplastic aneurysm, caused by the preexisting MPNST. Rare cases of aneurysms encased within or associated with intracranial tumors, such as glioblastoma, and metastatic choriocarcinoma and lung cancer have been reported in adults. Cases of ruptured arterial aneurysms have also been reported in children with pilocytic astrocytoma, anaplastic astrocytoma, and anaplastic sarcoma. Although the mechanisms of neoplastic aneurysm formation are unclear, several authors have suggested that invasion of the vessel wall with tumor cells may lead to segmental disruption of the internal elastic lamina and subsequent aneurysm formation. Whether a primary dysfunction of the vessel wall and its repair mechanisms attributable to the patient's NF1 status may have conferred an increased segmental susceptibility on aneurysm formation in our case is unclear.

The final potential explanation in the present case is that the ionizing radiation from the endovascular repair may have contributed to tumor development, an effect that may have been potentiated by the child's NF1 status. Neurointerventional procedures for aneurysms and arteriovenous malformation rank among the highest of all pediatric interventional radiology procedures in terms of total fluoroscopy time and cumulative radiation dose. Among children undergoing such procedures, one study estimated an increased risk of brain tumor development of 3%–40% depending on the age and sex of the patient as well as radiation dose received. Although the exact radiation thresholds for radiation-induced neoplasm are ultimately unknown, experience with radiotherapy for benign conditions suggests the thresholds may be lower than initially thought. For instance, Ron et al. found a 7-fold risk of CNS neoplasms in a cohort of children in whom the mean radiation dose for tinea capitis was 1.5 Gy. Despite these estimates and an increasing number of children undergoing endovascular therapies, we are unaware of any reported cases of secondary malignancies associated with neurointerventional procedures in the pediatric population. Further evidence against radiation-induced neoplasm in our case is supported by the low...
rate of radiation-induced MPNSTs in patients receiving high-dose therapeutic cranial radiation therapy, as well as the short latency period observed in our case. A recent meta-analysis of secondary malignancies among children undergoing cranial radiotherapy for brain tumors and leukemia identified only 8 cases of radiation-induced sarcoma in the literature, none of which was described as a MPNST. Although cases of radiation-induced malignant brain tumors manifesting in less than a year from treatment were described, the mean latency for the entire cohort was 8 years. Furthermore, the radiation field in our case included the skull and all of the intracranial contents. If the tumor were radiation-induced, it would be quite exceptional for it to occur randomly at the exact site of the aneurysm.

Taken together, the pathogenesis of the intracerebral MPNST in this case remains unclear. We believe there is insufficient evidence to classify our case as a radiation-induced tumor but cannot rule out that the endovascular repair, in a child with an increased susceptibility to radiation-induced neoplasms, did not contribute to the development of an intracerebral MPNST in this case. While acknowledging that initial imaging showed no evidence of a neoplasm, we support the theory that the tumor was present but at a small size or in a preclinical state and likely contributed to the formation of a symptomatic neoplastic aneurysm.

Conclusions

Neurofibromatosis Type 1 is associated with both neoplastic and cerebrovascular manifestations that affect long-term patient survival and quality of life. While patients with NF1 may represent a population with genetic susceptibility to radiation-induced tumors, the contributions of these factors to the pathogenesis of intracerebral MPNSTs remains poorly understood. As endovascular techniques continue to be applied to pediatric intracranial aneurysms, long-term data on the effects of prolonged radiation exposure will emerge.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Taylor, Ellis, Cheshier, Sharma. Acquisition of data: Armstrong, Bouffet. Analysis and interpretation of data: Hawkins. Drafting the article: Ellis, Cheshier, Sharma. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Taylor. Study supervision: Taylor, Cheshier, Armstrong, Hawkins, Bouffet, Rutka.

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Manuscript submitted April 13, 2011. Accepted July 8, 2011.
Address correspondence to: Michael D. Taylor, M.D., Ph.D., F.R.C.S.C., The Hospital for Sick Children, Room 1503, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. email: mdtaylor@sickkids.ca.