Radiation-induced malignant triton tumor associated with severe spinal cord compression

Case report and review of the literature

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A malignant triton tumor (MTT) is a variant of malignant peripheral nerve sheath tumors. The authors report a case of radiation-induced MTT in a patient with severe cervicothoracic cord compression and review the related literature. This 36-year-old man presented with pain and weakness in his left arm. His medical history was significant for a biopsy procedure involving the sampling of an aneurysmal bone cyst located at T1–3 near the left lung apex; this was performed 6 years prior to presentation and was followed by radiotherapy. Neurological examination demonstrated radicular findings involving the left C-8 and T-1 nerve roots. Neuroimaging studies revealed a large mass lesion extending from C-6 to T-2 along the vertebral column, invading the upper thoracic cavity and the adjacent lung apex, and infiltrating the paravertebral muscles. A subtotal resection was performed, but the tumor regrew extensively within a short time. It invaded the spinal canal and caused significant cord compression. The patient underwent surgery two more times for tumor debulking and to relieve progressive airway and spinal canal compromise. He eventually became quadriplegic, however, and died 13 months after diagnosis of MTT. This is the seventh case of radiation-induced MTT and the fifth of MTT with spinal canal involvement to be reported in the literature.

KEY WORDS • neurofibromatosis Type 1 • radiation-induced tumor • radiotherapy • spinal cord compression • triton tumor

Case Report

History. This 36-year-old man presented with a several-month history of increasing burning pain and weakness of his left arm. Medical history was significant for previous operations and radiotherapy. In 1994, he had undergone a procedure in which a biopsy specimen was excised from an aneurysmal bone cyst located at T1–3 near the left lung apex; this was performed 6 years prior to presentation and was followed by radiotherapy. Neurological examination demonstrated radicular findings involving the left C-8 and T-1 nerve roots. Neuroimaging studies revealed a large mass lesion extending from C-6 to T-2 along the vertebral column, invading the upper thoracic cavity and the adjacent lung apex, and infiltrating the paravertebral muscles. A subtotal resection was performed, but the tumor regrew extensively within a short time. It invaded the spinal canal and caused significant cord compression. The patient underwent surgery two more times for tumor debulking and to relieve progressive airway and spinal canal compromise. He eventually became quadriplegic, however, and died 13 months after diagnosis of MTT. This is the seventh case of radiation-induced MTT and the fifth of MTT with spinal canal involvement to be reported in the literature.

Abbreviations used in this paper: ABC = aneurysmal bone cyst; MPNST = malignant peripheral nerve sheath tumor; MR = magnetic resonance; MTT = malignant triton tumor; NF1 = neurofibromatosis Type 1.
Presentation and Examination. The patient was admitted to our clinic for further evaluation and treatment in September 2001. Physical examination on admission revealed a large 15 × 10–cm palpable subcutaneous mass covering his neck along the left lower cervical and upper thoracic regions. No café-au-lait spots or neurofibromas were present and he denied a family history of NF1. Neurological examination was remarkable for radicular findings involving the left-sided C-8 and T-1 nerve roots; left arm weakness and sensory loss at the left C8–T1 distribution were present. Electrophysiological studies confirmed a severe axonal disruption proximal to the dorsal root ganglia of the C-8 and T-1 nerve roots. Magnetic resonance imaging of the chest and cervicothoracic region revealed a large C6–T2 mass lesion along the vertebral column, invading the upper thoracic cavity and the adjacent lung apex and infiltrating the paravertebral muscles.

Operation. The patient underwent surgery via a posterior approach to expose the C6–T2 levels. The tumor was solid, rubbery, moderately vascular, and severely infiltrative. The tumor infiltrated the paravertebral muscles and osseous structures by destroying them in the involved areas and it penetrated into the spinal canal through the foramina of the C-7, C-8, and T-1 nerve roots. Only a subtotal resection of the mass lesion, including its intrafornaminal parts, could be achieved because of the tumor’s invasive nature.

Histopathological Examination. Histopathological examination showed a malignant tumor composed of fascicles of tightly packed, hyperchromatic spindle cells intermingled with round or strap-shaped eosinophilic cells. The scattered spindle tumor cells were positive for S100 protein. The rhabdomyoblasts were immunoreactive for desmin. Morphologically the tumor was an MPNST showing rhabdomyosarcomatous differentiation—that is, an MTT (Fig. 1).

Second Presentation. The patient’s recovery was uneventful. Two months after the operation, however, he was readmitted with quadriparesis and urinary incontinence. Neurological examination demonstrated severe myelopathy, and MR imaging revealed aggressive regrowth of the tumor, filling the entire resection cavity, invading the spinal canal, and causing complete canal compromise. There was a large epidural mass resulting in severe C6–T3 cord compression (Fig. 2). The tumor also infiltrated the paravertebral muscles and invaded the adjacent lung apex and thoracic cavity by extending from C-4 to T-5.

Second Operation. The patient underwent reoperation in November 2001. We performed C7–T3 laminectomies to “unroof” the spinal canal, and the spinal cord was decompressed by removing the entire epidural component of the tumor. A subtotal excision was undertaken because it was not thought to be completely removable.

Second Postoperative Course. This procedure afforded the patient temporary relief by partly restoring motor function for a short time. He experienced progressively worsening quadriparesis again, however, within the following weeks. Postoperative MR imaging revealed a total collapse of the T-2 vertebral body and severe tumor infiltration; a mass extending along the vertebral column caused osseous destruction at C-7, T-1, and T-3. He did not respond well to chemotherapy (iprophosphamide 2500 mg/m², mesna 2500 mg/m², etoposide 120 mg/m²) and developed neutropenia after the first course. He suffered severe neurogenic pain that was unresponsive to any type of medication. By four months postoperatively he had become quadriplegic and the tumor had become huge, extending from C-3 to the T5–6 interspace. He experienced severe respiratory difficulties, became ventilator dependent, and died 13 months after MTT was first diagnosed.

Discussion

Malignant triton tumor is a histological variant of MPNST with rhabdomyoblastic differentiation; fewer than 100 cases have been reported in the literature.8,15,17,18,22,23 The mean age at presentation of patients with primary MTT has been reported to be 31.7 years, although the disease may affect any person between the ages of 0 and 75 years.20 Malignant triton tumor has an equal sex distribution. In 44 to 69% of cases NF1 coexists with MTT. Male predominance and presentation at a younger age are common characteristics of MTT associated with NF1. This
particular group of patients harbor mutations in the NF1 tumor suppressor gene, whereas p53 suppressor gene mutations are involved in both hereditary and sporadic MTT. Malignant triton tumor is a very aggressive tumor with a very high rate of metastasis (48%) and local recurrence (43%). The overall survival rate in patients with MTT is low (2- and 5-year survival rates 15 and 11%, respectively). Although statistical analysis is limited by the short duration of follow-up periods and the small number of cases in the series, the main determining factors for survival seem to be tumor location and the extent of the excision. Patients with head and neck or extremity neoplasms survive longer than those with neoplasms of the buttocks, trunk, or retroperitoneum. Complete resection appears to be associated with an improved chance of survival, a decreased rate of local recurrence and metastasis, and a better response to adjuvant therapies; however, these lesions frequently lead to death within months despite all the available treatment modalities.

The triton tumor was first described by Masson in 1932 as a neurogenic tumor with mature rhabdomyoblasts scattered throughout sheets of Schwann cells. Woodruff, et al., described the following set of criteria for the diagnosis of MTT. 1) The tumor arises along the course of a peripheral nerve, in a patient with NF1, in a location typical for peripheral nerve tumors, or represents a metastasis resulting from such a tumor. 2) It largely shows the growth characteristics of Schwann cells. 3) It contains bona fide neoplastic rhabdomyoblasts that arise from within the peripheral nerve tumor but not from extension of or metastasis resulting from an extrinsic rhabdomyosarcoma. Later, Daimaru, et al., appreciating the difficulty encountered in diagnosing an MTT in patients not exhibiting the stigmata of NF1, suggested that this definition of MTT be broadened to the following: 1) tumors in patients without NF1 that are microscopically compatible with malignant schwannoma and contain focal rhabdomyoblasts, and 2) tumors consisting predominantly of rhabdomyoblastic differentiation with focal Schwann cell elements occurring within a nerve or in patients with NF1. Today, a diagnosis of MTT is based on these criteria as well as immunohistochemical evaluation. The presence of positive immunoreactivity to S100 protein and Leu-7 indicates nerve sheath differentiation, whereas rhabdomyoblastic cells have a positive immunohistochemical reaction to desmin, muscle-specific actin, myosin, vimentin, and myoglobin. Tumors may contain other heterologous elements in addition to rhabdomyosarcoma, and the tumors with this feature have been designated “pluridirectional MTT.”

The pathogenesis of MTT remains controversial. Masson suggested two possible mechanisms for its origin. He proposed that because Schwann cells were capable of inducing muscular differentiation of other endoneural cells, it was possible to observe rhabdomyosarcomatous components within the substance of a peripheral nerve tumor. He also proposed a second theory that malignant Schwann cells could transform into striated muscle cells (Masson’s metaplastic theory). This explanation is supported by some studies conducted by embryologists who demonstrated that embryonic cells of the neural crest possess the ability to differentiate into both ecto- and mesodermal elements. Thus, it is assumed that Schwann cells retain this capacity for latent divergent differentiation and they may differentiate into bone, cartilage, and muscle during the process of malignant transformation. The capacity of malignant Schwann cells for latent divergent differentiation has also been shown in vivo and in vitro experiments. The presence of some neural tumors with rhabdomyoblastic differentiation in the central nervous system could support this view.
Radiation-induced malignant triton tumor

TABLE 1
Summary of cases involving postirradiation MTT*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex†</th>
<th>NF1</th>
<th>Location</th>
<th>Treatment</th>
<th>Yrs Btw XRT &amp; MTT</th>
<th>Primary Tumor Type</th>
<th>XRT Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodruff, et al., 1973 (Foley, et al., 1980)</td>
<td>F, 53</td>
<td>no</td>
<td>T1–2 intradural extramedullary temple</td>
<td>multiple excisions XRT 3000 rad multiple excisions</td>
<td>10</td>
<td>infiltrative ductal breast Ca</td>
<td>NA</td>
<td>died in 7 mos</td>
</tr>
<tr>
<td>Ducatman &amp; Scheithauer, 1983</td>
<td>M, 9</td>
<td>yes</td>
<td>Lt buttock</td>
<td>NA</td>
<td>5</td>
<td>optic chiasm astrocytoma</td>
<td>4925 rad</td>
<td>recurred in 15 mos, died in 7 mos</td>
</tr>
<tr>
<td>Daimaru, et al., 1984</td>
<td>M, 29</td>
<td>yes</td>
<td>Lt buttock</td>
<td>NA</td>
<td>19</td>
<td>not known; buttoc subcutaneous mass uterine cervical ca</td>
<td>NA</td>
<td>lung metastasis, died in 18 mos</td>
</tr>
<tr>
<td>Woodruff &amp; Perino, 1994</td>
<td>F, 55</td>
<td>no</td>
<td>Sciatic nerve, buttoc sacrum</td>
<td>NA</td>
<td>21</td>
<td>adenocarcinoma of endometrium</td>
<td>50 Gy</td>
<td></td>
</tr>
<tr>
<td>Yakulis, et al., 1996</td>
<td>F, 67</td>
<td>no</td>
<td>Supraclavicular region, T1–3 roots C6–T3 canal</td>
<td>wide excision</td>
<td>13</td>
<td>total excision; XRT 10</td>
<td>unknown</td>
<td>NA</td>
</tr>
<tr>
<td>Özer, et al., 2002</td>
<td>M, 24</td>
<td>no</td>
<td>Supraclavicular region, T1–3 roots C6–T3 canal</td>
<td>total excision; XRT 10</td>
<td>21</td>
<td>unknown</td>
<td>NA</td>
<td>died in 18 mos</td>
</tr>
<tr>
<td>present case</td>
<td>M, 36</td>
<td>no</td>
<td>Lt thoracic cavity, C6–T3 canal</td>
<td>multiple excisions; chemo</td>
<td>6</td>
<td>T1–3 ABC</td>
<td>65 Gy</td>
<td>died in 13 mos</td>
</tr>
</tbody>
</table>

* Ca = cancer; chemo = chemotherapy; NA = not applicable; XRT = radiotherapy.
† Age represents that at the time of presentation.

System, such as rhabdomyosarcoma, ocular medulloloblastoma, and ganglioneurolblastoma, further supports Masson’s theory of metaplasia.1,12,17,21

The patient presented here represents an unusual case of MTT, not just because of the tumor’s spinal involvement but also because of its etiopathogenesis—namely, the history of radiotherapy. It is well known that radiotherapy is associated with the development of secondary soft-tissue malignancies.9,13 The most common postirradiation sarcomas have been reported as malignant fibrous histiocytoma and less often as fibrosarcoma or osteosarcoma, and they are associated with a worse prognosis than spontaneously occurring sarcomas.10,13,20,23 Although poor differentiation itself is an important factor related to the dismal prognosis of postirradiation sarcomas, other explanations have also been proposed for their increased aggressiveness and higher mortality rate. It has been suggested that an immunosuppressive effect of the primary malignancy or the therapy, lymphatic obstruction, vascular compromise, radiation-induced fibrosis, and delays in recognition and diagnosis of the secondary sarcoma may all be instrumental in the increased aggressiveness and higher mortality rates associated with postirradiation sarcomas.7,23 Although radiation-induced MPNST has been reported in up to 11% of patients in large series,5,6 MTTs related to radiotherapy are extremely rare. We found six cases reported in the literature, only one of which was a pluridirectional MTT.4,5,7,15,21–23 The clinicopathological features of these cases are summarized in Table 1. The tumor in our case was diagnosed as a radiation-induced tumor based on previously defined criteria of postirradiation neoplasms: 1) a history of irradiation; 2) development of the secondary neoplasm within the irradiated field; 3) a latency period of at least 2 years before the appearance of the second tumor; and 4) proof that the secondary neoplasm is histologically different from the irradiated primary tumor.2,3,23 Our case satisfied all four criteria: the MTT occurred within the radiation field in a patient treated 6 years previously for an ABC, and the postirradiation histopathological diagnosis (that is, MTT) was completely different from the primary diagnosis (that is, ABC). Another unusual characteristic of this case is the spinal canal involvement. It is well known that MTT frequently develops in the head and neck region, but spinal canal involvement is extremely rare. We found only four other cases in which MTT was involved with the spinal canal in our extensive literature search.5,8,19,21 The tumor in our case showed a very aggressive course and caused our patient to suffer a very painful and dismal end of life. Although it is known that spinal malignant schwannomas are associated with a worse prognosis than those in other locations, the number of spinal canal–involved MTT cases is too small to allow conclusion that spinal MTTs have a poorer prognosis.3,8

Conclusions

Based on our case, we emphasize that caution should be exercised when undertaking radiotherapy in patients with clinically apparent NF1 findings or a family history of NF1. In view of the long period of latency between irradiation and the clinical presentation, we also stress the need for a careful follow-up examination during a prolonged period after irradiation. Additionally, it should be emphasized that the best treatment for ABC is complete resection, when possible, and selective arterial embolization. In cases involving subtotal resection of ABC, the option of radiotherapy should be evaluated meticulously.

References


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