Extended remission of a recurrent median nerve malignant peripheral nerve sheath tumor after multimodal treatment

Case report

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Malignant peripheral nerve sheath tumors (MPNSTs) are difficult to control despite aggressive treatment. In this report the authors describe the treatment and follow-up review of a patient with neurofibromatosis Type 1 who harbored a recurrent median nerve MPNST. The man underwent preoperative intraarterial and intravenous chemotherapy followed by additional surgery for gross-total removal and postoperative radiotherapy. Two courses of preoperative intraarterial cisplatin and intravenous Adriamycin produced significant tumor shrinkage. Gross-total removal of the remaining tumor without amputation of the arm was followed by fractionated radiotherapy (total minimum tumor dose 6485 cGy, maximal dose 6575 cGy). The patient is alive 9.5 years after treatment without evidence of tumor recurrence and with only focal median nerve functional deficits. A review of the patient’s treatment is warranted to provide a description of a regimen that may be useful in the treatment of similar patients in the future.

KEY WORDS • chemotherapy • malignant peripheral nerve sheath tumor • median nerve • radiotherapy • surgery

Malignant peripheral nerve sheath tumors are difficult to control despite aggressive treatment, which may include amputation of an extremity. The available literature provides only limited guidance regarding management of this disease. In this report we describe the treatment and follow-up review of a patient with neurofibromatosis Type 1 who harbored a recurrent median nerve MPNST. The man underwent preoperative intraarterial and intravenous chemotherapy followed by additional surgery for gross-total tumor removal and postoperative radiotherapy; extended tumor-free survival was achieved. A review of this patient’s treatment is warranted to provide a description of a regimen that may be useful in the treatment of similar patients in the future.

Case Report

History. The patient is a right-handed man with NF1 who was 29 years of age at presentation. Four years earlier, he had undergone removal of a cervical neurofibroma. Three years after that operation he noted the development of pain in the left upper extremity; left hand weakness, and an enlarging mass in the left medial arm. After 5 months of progressive symptoms, he underwent removal of a peripheral nerve tumor (maximum diameter 5 cm). The pathologist who evaluated the lesion described a schwannoma with extensive necrosis and cystic degeneration. Four months postoperatively the patient noted a recurrent mass that continued to enlarge, and 8 months postoperatively additional surgical exploration revealed a recurrent tumor. Only a small portion of the lesion was removed at that time. The patient was referred to the first author 7 weeks after the second upper-extremity operation. At that time, he had pain in the left arm, dysesthesia in the left thumb and left index finger, paresthesia in the left middle and ring fingers, anesthesia in the first four digits of the left hand, and an additional decrease in left hand strength. The patient’s history was otherwise remarkable for childhood seizures with a nondiagnostic computerized tomography scan of the brain obtained when he was 25 years of age. There was no family history of NF1.

Examination. The patient had multiple subcutaneous tumors, scattered café-au-lait spots, and a large fusiform mass in the medial aspect of the left arm with a well-healed overlying incision. The left thenar eminence was atrophic, and there was no function in the flexor carpi radialis, flexor pollicis longus, and flexor digitorum profundus muscles to the index and middle fingers, and no thumb opposition. The strength of the flexor digitorum superficialis muscle was 3/5. A dense hypesthesia was present in the median nerve distribution. Deep tendon reflexes were absent in the biceps muscle bilaterally, and the scores for the brachioradialis and
triceps reflexes were 1+. The remainder of the patient’s neurological examination was unremarkable. Electromyography and nerve conduction studies demonstrated a left median nerve dysfunction with axonal degeneration and no ulnar or radial nerve dysfunction.

Magnetic resonance images of the patient’s left arm revealed a large tumor (9 cm craniocaudad × 5 cm transverse × 4 cm anteroposterior) that evidenced a slightly hyperintense signal on T₁-weighted images, a markedly hyperintense signal on T₂-weighted images, and Gd enhancement (Figs. 1 and 2). Multiple other small nodules were seen in relation to the skin and muscles; all of these were less than 2 cm in the greatest dimension. The MR images of the cervical spine revealed postoperative changes and the MR images of the brain were unremarkable. Computerized tomography scans of the chest, abdomen, and pelvis revealed multiple small nodules scattered in relation to the skin, subcutaneous tissue, and muscles. A radionuclide bone scan demonstrated no osseous metastasis.

Pathological Findings. Reevaluation of the original left upper-extremity tumor (Fig. 3) showed moderately high cellularity with round nuclei and thin cytoplasmic processes. Scattered nuclei appeared large and hyperchromatic, and rare mitoses were observed. The tumor cells were arranged in a loose fascicular pattern, and large regions of tumor necrosis with acute inflammation and recent necrosis of single tumor cells were observed. The impression was that the tumor was actually an MPNST. A reevaluation of the earlier intraspinal tumor confirmed that it was a benign neurofibroma.

Management. A multidisciplinary management plan was formulated including preoperative intraarterial and intravenous chemotherapy, resection, and postoperative fractionated radiotherapy. Eleven months after the original tumor was removed, a right femoral angiography catheter was positioned in the left brachial artery proximal to the tumor. Two hundred milligrams of cisplatin (100 mg/m²) in 1 L of normal saline was infused over a 4-hour period. Intravenous dexamethasone, ondansetron, and hydration were administered. The next day the patient was given 120 mg of Adriamycin (60 mg/m²) intravenously over a 10-minute period along with intramuscular prochlorperazine. Immediately af-

**Management of malignant nerve sheath tumor**

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**Fig. 1.** Sagittal unenhanced MR images (TE 20 msec, TR 2000 msec) of the left arm revealing recurrent tumor.

**Fig. 2.** Axial Gd-enhanced MR image (TE 16 msec, TR 733 msec) of the left arm demonstrating recurrent tumor.

**Fig. 3.** Photomicrographs of specimens of the original tumor removed at the referring hospital. **Upper:** Note the moderately high cellularity in the specimen. **Center:** Note the necrotic region in the upper left quadrant adjacent to a cellular region in the lower right quadrant. **Lower:** Note the moderately high cellularity. H & E, original magnifications × 40 (upper and center) and × 100 (lower).
After the intraarterial chemotherapy, the patient experienced weakness (strength 0/5) of extension of the left wrist and fingers. This radial nerve deficit was treated with a wrist splint and later improved. Two weeks after the first session of chemotherapy, the tumor size was significantly decreased; however, the patient had dysphagia, cough, chills, a fever of 100˚F, and a white blood cell count of 1500/mm$^3$. He was treated with vancomycin, piperacillin, and filgrastim, and he quickly recovered. A second chemotherapy course was initiated 6 weeks after the first session and involved a 25% reduction in drug dose (intraarterial cisplatin 150 mg and intravenous Adriamycin 90 mg). His left wrist drop, which had recovered to a strength of 2/5, again deteriorated but recovered. The tumor size continued to diminish; repeated MR images demonstrated a tumor size of $5 \times 2.5 \times 2.5$ cm, more heterogeneity on T$_2$-weighted images, and less enhancement (Fig. 4). The patient's chemotherapy-related alopecia later recovered.

Two and one half months after the second round of chemotherapy, the original incision was reopened and dissection around the tumor was performed using a fine-point bipolar coagulation technique. There was considerable scar tissue. The position of the brachial artery was verified by monitoring the radial pulse during compression of surrounding soft tissue, and soft tissue encasing the brachial artery was dissected off the lateral aspect of the tumor. The ulnar nerve was dissected off the medial side of the tumor; electrical stimulation was used to aid in the identification of the ulnar nerve. The median nerve was transected 3 cm distal and 3 cm proximal to the tumor to complete the gross-total removal. Frozen-section margins at the proximal and distal stumps of the median nerve displayed evidence of neurofibroma without definite malignant changes. After surgery, there was additional hypesthesia on the left proximal volar forearm but no other neurological changes.

The pathological findings consisted of an MPNST with epithelioid features. The bulk of the tumor displayed hypocellularity with predominantly epithelioid pleomorphic cells, mitoses, and areas of necrosis. The more peripheral areas had features of plexiform neurofibroma, and both margins contained small foci with features of plexiform neurofibroma. The peripheral regions of the tumor were mostly confined within the nerve; one area had prominent granulation tissue and reactive changes in connective tissue mixed with some atypical cells that may have represented tumor. Immunoperoxidase stains for desmin, epithelial membrane antigen, and keratin yielded negative findings.

Six weeks after surgery, the patient began treatment with fractionated radiotherapy to the left arm, which was performed using shrinking field techniques to a total minimum tumor dose of 6485 cGy with a maximal dose of 6575 cGy. He tolerated treatment well with moderate desquamation.

The patient recovered normal strength in his left wrist and finger extensors; 9 years after treatment his deficits included paralysis of the left flexor pollicis longus muscle, thumb opposition, and first flexor digitorum profundus muscle, with sensory deficits restricted to the first two digits. Serial MR images obtained as late as 8.5 years after treatment revealed no evidence of residual or recurrent tumor in the left arm (Fig. 5), and chest radiographs have shown no metastases. After 9.5 years of follow-up review, there has been no evidence of recurrence of the MPNST.

During the 9th posttreatment year, burning and numbness developed in the patient’s right hand. An MR image demonstrated a small enhancing tumor deep to the right pronator quadratus muscle; MR images of the remainder of the right upper extremity and the right brachial plexus revealed only scattered subcutaneous lesions. Removal of the right wrist tumor relieved the patient’s symptoms; the pathological finding was benign neurofibroma.

**Discussion**

Rates of successful treatment of MPNST are generally low, and these tumors are particularly aggressive in patients with NF1. In a situation such as the one described in this report, the available literature provides only limited guidance regarding disease management. Published series contain only small numbers of patients treated for recurrent MPNST in an extremity. Authors describe the use of adjuvant treatment with radiotherapy and chemotherapy.
Management of malignant nerve sheath tumor

...py but provide few details of results obtained using specific chemotherapy regimens. In a review of 134 patients with MPNSTs treated with modern techniques between 1975 and 1993, the 5-year local tumor relapse rate was 49%. Only two of the 134 patients were treated with a combination of surgery, radiotherapy, and chemotherapy for recurrent tumors. The specific outcomes of those two patients were not mentioned. Several factors identified with a worse prognosis in that study apply to our patient: concomitant NF1, the presence of necrosis, and the epithelioid histological subtype. In another study of 28 patients, only two patients were treated with combined surgery, chemotherapy, and radiotherapy; one patient died of the disease 52 months after diagnosis, and the other was free from disease 10 years after diagnosis.

The patient described in this report has experienced extended remission of his MPNST. In a situation in which there is apparent control of a dismal disease, the question reasonably arises as to the accuracy of the histopathological diagnosis. Reviews of the tissue by three neuropathologists who reached a consensus of diagnosis, coupled with the rapid large recurrence of the tumor after the original operation, lend credence to the diagnosis of MPNST.

The most common recommendation for treatment dwells on the desirability of radical excision, but the difficulty of obtaining margins clear of tumor, even when a wide excision is made, has been reported. Amputation of an upper extremity is a difficult proposition to offer a patient, especially when radical surgery does not guarantee a cure. With a recurrent tumor, which has already been surgically manipulated, the likelihood that amputation alone would prove curative is low, and this step may actually provide no benefit. In this case, gross-total removal of the tumor did not produce significantly more neurological deficit than the tumor had already produced.

Radiotherapy has been found to improve local tumor control; however, one commentator has expressed the opinion that no data are available to prove that adjuvant radiotherapy or chemotherapy is of any value in the treatment of MPNST. Chemotherapy was administered to our patient in an attempt to reduce the bulk of the local disease and to control any microscopic metastatic disease. The intraarterial segment of the treatment was particularly intended to make excision an easier and more effective undertaking. Preoperative chemotherapy may also have reduced the capacity of the tumor cells to become metastatic disease as a result of further surgical manipulation.

Conclusions

This patient has had an excellent response thus far to multimodal treatment of a particularly malignant neoplasm. This specific combination of intraarterial cisplatin, intravenous Adriamycin, surgery, and radiotherapy is recommended for consideration in future patients in similar clinical circumstances.

References