Malignant transformation of ganglioneuroma into spinal neuroblastoma in an adult

Case report

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Ganglioneuroma is generally considered to be a benign tumor and potentially surgically curable. The authors present a case of a 21-year-old woman who underwent resection of a retroperitoneal ganglioneuroma and developed spinal neuroblastoma 11 years later. She has survived 10 more years with only recent development of metastases. To the authors’ knowledge, this is the first report of malignant transformation of a ganglioneuroma into a neuroblastoma. Also, such long-term survival in an adult with spinal neuroblastoma has not been reported previously. This case raises the possibility of a dedifferentiating potential for ganglion cells in a ganglioneuroma or the presence of a long-term, quiescent form of neuroblastoma.

KEY WORDS • ganglioneuroma • neuroblastoma • spinal tumor • spinal cord compression • prognosis

S P I N A L neuroblastoma is an extremely rare tumor in adults, with only four cases reported in the literature. The prognosis for patients with this tumor has been uniformly poor, with no long-term survival previously reported. We describe a case of spinal neuroblastoma in a 32-year-old woman who had presented with a history of retroperitoneal ganglioneuroma 11 years earlier. The patient has survived 10 more years with relatively stable disease and the recent development of metastases. To our knowledge, this is the first report of malignant transformation of ganglioneuroma into neuroblastoma.

Case Report

History. In 1976, at 21 years of age, this 42-year-old woman presented with a retroperitoneal mass. The mass was removed at another institution and was diagnosed as ganglioneuroma. Further clinical and surgical details are not available. The surgical specimen was reviewed at our institution. We observed a focal cluster of slightly pleomorphic, multinucleated, mature ganglion cells without satellite cells (Fig. 1). The remainder of the specimen contained poorly myelinated bundles of nerve fibers accompanied by spindle-shaped Schwann cells. The diagnosis of ganglioneuroma was confirmed by the presence of these features. There were no stigmata of neurofibromatosis and no history of childhood neuroblastoma.

Examination and First Operation. In 1987, at 32 years of age, the patient presented to our institution with a few months’ duration of progressive low-back pain radiating into the right leg. A few days prior to presentation she developed urinary retention, and then saddle anesthesia and progressive paraparesis. A computerized tomography (CT) myelogram revealed a complete block at L-1 caused by an extradural mass that had significant bilateral paravertebral extension and affected the L-1 vertebral body. An emergency laminectomy was performed and a sample of the extradural mass, which had a dark and soft appearance, was sent for histological analysis. The patient showed improvement in her neurological function postoperatively.

Histological Examination. Light microscopy studies showed a tumor with moderately pleomorphic, hyperchromatic, oval nuclei and prominent nucleoli with surrounding necrosis (Fig. 2 upper) and no mitoses. There were no mature ganglion cells and no Schwann cell component. Immunostaining with neuron-specific enolase and synaptophysin was positive. Electron microscopy revealed numerous cell processes containing microtubules and neurosecretory granules (Fig. 2 lower left and right). A diagnosis of neuroblastoma was made.

A metastatic workup, which included chest x-ray films, CT scans of the abdomen and pelvis, bone marrow biopsy, and bone scan, was negative. The patient’s 24-hour urinary excretion of vanillylmandelic acid was normal. She received a course of focal radiation (2500 rad in five fractions). No chemotherapy was administered.

Initial Postoperative Course. The patient remained neurologically and systemically well, aside from labile hyper-
tension that had been diagnosed prior to her presentation. Her follow-up review included serial imaging, which demonstrated that the L-1 spinal lesion grew only slightly during several years. In 1995, a second spinal lesion involving the T-9 vertebral body and containing a small paravertebral mass was demonstrated on magnetic resonance imaging (Fig. 3). A further course of local radiation therapy was administered to this region. A workup revealed the presence of metastatic lesions in the lungs and bones as well. A course of chemotherapy (VP-16 and cisplatinum) was administered at this time.

Second Operation. In February 1997, the patient developed subacute onset of paraparesis with urinary retention caused by additional compression at the T-9 level. An emergency T8–9 laminectomy was performed and a specimen of the tumor was obtained. Examination again revealed neuroblastoma with a patchy spindle cell component, but no mature ganglion cells. The histological and immunostaining features of the tumor were similar to those observed in the specimen obtained in 1987.

Discussion

The presentation of neuroblastoma as an adult spinal tumor is extremely rare: to our knowledge, only four such cases have been reported. In children this is a much more common entity, accounting for 20 to 30% of primary extradural spinal tumors. There is no consensus on the most appropriate therapy for these tumors in adults, but judging from the far greater pediatric experience, a combination of surgery, radiation, and chemotherapy would likely provide the optimum therapy. Despite the availability of various therapeutic modalities, there have been no reports of survival beyond 2 years in an adult with this disease. We present the first case of long-term survival in an adult with spinal neuroblastoma.

Of particular interest in this case is the patient’s history of ganglioneuroma 11 years prior to presentation with neuroblastoma. Although this may represent a simple coincidence, it seems highly unlikely that two such rare, related tumors would develop in the same area in an independent fashion. In 1927, Cushing and Wolback were the first to recognize the potential for differentiation of neuroblastoma into ganglioneuroma or ganglioneuroblastoma, especially in early childhood. However, in this particular case, if a connection does exist between the ganglioneuroma found in 1976 and the neuroblastoma treated in 1987, then we can speculate about two possible scenarios. First, it is possible that the patient did, in fact, harbor a neuroblastoma with a prominent, differentiated ganglioneuroma component in 1976 and only that component was resected and diagnosed. However, this would mean that she had survived free of symptoms for 11 years with an untreated neuroblastoma until she presented in 1987. In total she would have had relatively stable neuroblastoma for nearly 21 years, most of which time elapsed before the initiation of treatment. From what we know about the poor survival rates with even aggressively treated adult neuroblastoma, such a postulate seems highly improbable unless this tumor represents a previously undescribed unique, quiescent form of neuroblastoma.

A second postulate is that residual ganglioneuroma from 1976 dedifferentiated into a true neuroblastoma. Ganglioneuromas have generally been considered very benign tumors for which surgical resection often leads to cure. However, there have been at least seven documented cases of transformation of ganglioneuromas into malignant nerve sheath tumors. Although malignant transformation involving the spindle cell component of a ganglioneuroma is a rare but proven event, to our knowledge, malignant transformation of the ganglion cell component into neuroblastoma has never been reported. The argument against this theory is that the neuronal component of a ganglioneuroma is presumably composed of mature, well-differentiated, postmitotic ganglion cells that...
should have lost the capacity to proliferate. Similarly, malignant transformation of gangliogliomas of the brain is caused by anaplastic changes in the glial component, not the mature ganglion cell component. In the present case dedifferentiation would presumably require at least some population of mitotically active neuronal cells associated with a series of genetic changes. The most common molecular anomalies associated with neuroblastoma are deletions in the short arm of chromosome 1 and amplification of the N-myc oncogene. Unfortunately, the surgical specimens from this case were not tested for such anomalies.

If such an analysis could have been performed it would have been valuable to investigate whether a series of cumulative genetic changes was associated with the malignant transformation.

Of note in this regard is an interesting case reported by Kaye, et al., in which a calcified suprarenal mass was noted in a 38-year-old woman 9 years prior to diagnosis of neuroblastoma. In a footnote added to the original article, it was reported that after her death, approximately 3 years later, an autopsy revealed a ganglioneuroma in this mass, concomitant with active, metastatic neuroblastoma.

![Fig. 2. Microscopic studies of the neuroblastoma found in the same patient in 1987. Upper: Photomicrograph showing a nest of small, oval cells with no evident mitoses. H & E, original magnification × 80. Lower: Electron micrographs demonstrating multiple neuronal processes containing microtubules cut longitudinally and in cross section (lower left), bar = 1 μm, and demonstrating numerous neurosecretory granules within cell processes (lower right), bar = 0.5 μm.](image-url)
Transformation of ganglioneuroma to neuroblastoma

though the authors did not comment further on this finding, it is possible that the ganglioneuroma predated the development of neuroblastoma by several years, similar to our report.

Regardless of how one postulates a connection between the ganglioneuroma and neuroblastoma, another very striking feature of our patient’s illness is her prolonged survival with stable disease. The reasons for this are not obvious. The histological features of the neuroblastoma, aside from the presence of necrosis, did appear relatively benign, with no evidence of mitoses. It is also possible that neuroblastoma occurring as a result of dedifferentiation may carry a more favorable prognosis than de novo neuroblastomas. However, if the patient in the report by Kaye, et al., also had a differentiating ganglioneuroma, the survival of that patient for only 3 years does not bear out this theory. It has been suggested that spinal neuroblastoma in children may have a more favorable prognosis than this type of lesion in other locations, with a lower incidence of disseminated disease at presentation, especially in infants younger than 1 year of age. The experience in adults is too limited to extrapolate this conclusion reliably, but, to our knowledge, no patient surviving more than 2 years has previously been reported.1,9

Conclusions

Ganglioneuroma, an otherwise benign tumor, appears to have the rare capacity to develop into neuroblastoma in a delayed fashion. This is either because of dedifferentiation or the long-term presence of a unique, quiescent form of neuroblastoma. Based on our case, the natural history of neuroblastoma in a patient with previous ganglioneuroma may be more favorable than in patients presenting de novo with this tumor type. If further cases are recognized, genetic analysis of the lesions might provide great insight into the development of this disease.

References


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