Composite ganglioneuroma-paraganglioma of the filum terminale

Case report

GANESH M. SHANKAR, M.D., PH.D.,1 LI CHEN, M.D., PH.D.,2 ALBERT H. KIM, M.D., PH.D.,1 GINA L. ROSS, M.D.,3 REBECCA D. FOLKERTH, M.D.,2 AND ROBERT M. FRIEDLANDER, M.D., M.A.1,4

Departments of 1Neurosurgery, 2Pathology (Neuropathology), and 3Neuroradiology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts; and 4Department of Neurosurgery, University of Pittsburgh, Pennsylvania

Extraadrenal paragangliomas are most commonly found in the carotid body and are also found with lower frequency in the CNS. These lesions are derived from the sympathoadrenal lineage of neural crest cells. Here, the authors report a rare case of a composite paraganglioma with ganglioneuromatous components found at the filum terminale in a patient who presented with a brief history of low-back pain and paresthesias in the inguinal region. Immunohistochemical analysis of the resected lesion revealed admixed elements of neuroendocrine and neuroblastic lineages, indicating the presence of divergent differentiation of sympathoadrenal progenitor cells. This case represents a unique opportunity to understand the cell fate of sympathoadrenal progenitor cells. Here, the authors propose that paragangliomas at the filum terminale can revert to a neural crest cell precursor fate, giving rise to divergent neoplastic populations. (DOI: 10.3171/2009.12.SPINE09482)

KEY WORDS • spinal cord • neoplasm • peripheral nervous system • sympathetic nervous system

In adults, the spectrum of primary intradural extramedullary peripheral nervous system tumors detected within the spinal canal predominantly includes schwannomas and, to a lesser extent, neurofibromas and paragangliomas. In children, the range of spinal peripheral nerve tumors more commonly includes spinal foraminal involvement by retroperitoneal neuroblastomas, which may be considered ganglioneuromas with extensive neuronal differentiation. Exceptionally, peripheral nervous tumors can exhibit more than one pattern, raising questions about histogenesis and prognosis.

Paragangliomas arise from sympathoadrenal cells initially derived from neural crest cells. These extraadrenal lesions are generally found outside the CNS, but they have been reported in the spinal column since the first observation by Lerman et al.7 in 1972. The case described here represents a unique presentation of a composite paraganglioma with ganglioneuromatous elements at the filum terminale, as characterized by immunohistochemical markers. Given that few case reports have described these admixed lesions, this particular lesion provides unique clinical evidence for divergent differentiation of the sympathoadrenal lineage into neuroendocrine and neuroblastic components or possibly even transdifferentiation of neuroendocrine cells.3,13,15 The histopathological findings described in this report clearly demonstrate the presence of divergent neoplastic elements at the filum terminale. We propose here that paraganglioma cells revert to a neural crest cell population that subsequently differentiates into neuroblastic components.

Case Report

History and Presentation. This 47-year-old righthanded man initially presented with an 8-week history of
worsening lower-back pain and an intermittent tingling sensation in the inguinal area. Although the patient was continent, he reported painful bowel movements. His medical history was notable for hypertension and proteinuria, for which he was prescribed lisinopril, diltiazem, and indomethacin. A physical examination revealed normal sensation, motor strength, and reflexes bilaterally. The lesion was visualized on MR imaging of the lumbar spine (Fig. 1). The T2-weighted MR image revealed a lobulated intradural extramedullary lesion at the L2–3 level with heterogeneous signal intensity (Fig. 1a). Regions of low signal intensity within the lesion on T2-weighted imaging suggested hemorrhage. The T1-weighted Gd-enhanced MR image demonstrated heterogeneous enhancement. Hypointense foci were again noted with possible flow voids (Fig. 1b). While hypervascularity observed as serpiginous flow voids or intense enhancement is strongly suggestive of paragangliomas, the differential diagnosis of an intradural extramedullary spinal canal lesion includes ependymoma, schwannoma, meningioma, and metastasis. Ependymomas, in particular, can be indistinguishable from paragangliomas with evidence of blood products and marked enhancement. Axial section confirmed hypointense foci (Fig. 1c). Of note, T2-weighted axial imaging of the sacrum revealed a blood-CSF level (Fig. 1d), which has also been reported in 17 patients with spinal ependymomas. While this has been reported in a paraganglioma before, to our knowledge this is the first report of subarachnoid hemorrhage associated with a composite tumor.

Operation. With the assistance of fluoroscopy, the appropriate lumbar levels were identified, and a midline linear incision was made. Laminectomies at L-2 and L-3 were performed, and the dura was opened at the midline. A discrete tumor nodule was immediately visualized deep to the arachnoid. On opening the arachnoid along the inferior aspect of the lesion, xanthochromic fluid was expressed. In contrast, completely clear and colorless CSF was expressed on opening the arachnoid superior to the lesion. Under the operating microscope, the reddish tumor mass displaced the nerve roots laterally and anteriorly, and it was attached to a fibrous structure consistent with the filum terminale at its inferior pole. Two prominent vessels, likely arterial, coursed along the anterior surface of the filum terminale. Whereas motor responses were noted on stimulation of the nerve roots anterior to the mass, none were observed with stimulation of the lesion itself or of the lateral roots, which were likely sensory. Given the size of the lesion (2.6 × 1.7 × 1.2 cm, by gross measurement during pathological examination), internal decompression of the tumor was performed first to facilitate removal. The filum terminale, including the 2 large vessels, was circumferentially dissected approximately 15 mm above the lesion, coagulated, and then cut. The distal filum was subsequently transected immediately inferior to the lesion, allowing the tumor to be removed. An additional 1.5-cm margin of distal filum was removed and sent as a separate section. The dura was then closed in a watertight fashion with a nonabsorbable suture, and the wound was closed in layers.

Postoperative Course. The patient was discharged neurologically intact 4 days after the procedure. He was

![Fig. 1. Magnetic resonance imaging findings of a mass at the cauda equina. a: Sagittal T2-weighted image of the lumbar spine revealing the tumor at L2–3 with heterogeneous signal intensity and areas of low intensity suggesting hemorrhage or vascularity. b and c: Sagittal and axial T1-weighted contrast-enhanced images demonstrating the lesion with heterogeneous enhancement with hypointense linear and punctate foci. The enhancing linear structure (arrow in b) represents an artery appreciated on resection of tumor. d: Axial T2-weighted image at the level of the sacrum demonstrating a blood-CSF level (arrowhead). Sagittal T2-weighted (e) and T1-weighted contrast-enhanced (f) images obtained 10 months postoperatively.](image-url)
asymptomatic with a normal neurological examination, and no radiographic evidence of tumor recurrence at his scheduled 10-month postoperative follow-up (Fig. 1e and f).

**Histological Examination.** The red-brown to pink, encapsulated 2.6 × 1.7 × 1.2–cm tumor contained 2 main components (Fig. 2). First, the lesion had cellular nodules of epithelioid cells with an organoid nested arrangement. These cells were immunoreactive with chromogranin and synaptophysin. Scattered S100 protein–positive sustentacular cells were identified within this neuroendocrine component. A second component of mature ganglion cells that were admixed as clusters and individual cells were seen in multiple areas. These ganglion cells were positive for synaptophysin, chromogranin, and neurofilament. The tumor also had areas of a fasciculated proliferation of Schwann cells that were positive for S100 protein. Because of the presence of the intimately admixed areas of ganglioneuroma and paraganglioma, a diagnosis of composite paraganglioma with areas of ganglioneuroma was most appropriate. There also was evidence of remote hemorrhage in the lesion, based on the presence of clustered hemosiderin deposits in several areas. The distal filum segment submitted as a surgical margin was indeterminate for tumor involvement given the display of hemosiderosis and clustered cells along the surface, most likely of ependymal origin.

To address the etiology of the 2 distinct cell lineages, the tumor was assessed for dedifferentiation of the principal component to a neural crest cell fate. Indeed, immunoreactivity for c-kit, a tyrosine kinase receptor expressed by early neural crest cells at the time of differentiation to a neurogenic or melanogenic lineage, was noted in this tumor (Fig. 3). This suggests that the founder population may have differentiated into another distinct cell line via reversion to a common multipotential precursor, such as neural crest cells.

**Discussion**

Extraadrenal paragangliomas are most commonly found in the carotid body, but they can also arise in the CNS at the petrous ridge, sella turcica, and cauda equina. While these tumors usually originate from neural crest cells that rise to the sympathoadrenal lineage, it has been debated that in the cauda equina they may arise from other cell types that differentiate into a neuroendocrine lineage under the influence of nearby ependymal cells. The prognosis of these tumors can be gauged histologically by the level of necrosis and mitotic activity. Histology also allows for distinguishing between paragangliomas and GFAP-positive ependymomas, which carry a poorer prognosis and occur at a greater frequency in this region of the spinal canal. Specifically, the cytoarchitecture of paragangliomas at the filum terminale are notable for their “zellballen” pattern of large polyhedral tumor cells in organoid configurations, granular argyrophilia and argentaffin, immunoreactivity for S100 in sustentacular cells, and chief cell cytoplasmic immunoreactivity for chromogranin A, synaptophysin, and neuron-specific enolase. However, unlike extraadrenal sites, paragangliomas at the cauda equina display increased ganglion cell differentiation and preferential immunoreactivity toward certain cytokeratins. The T2-weighted images of paragangliomas reveal a lesion with a hypointense rim and serpiginous flow voids. Affected patients commonly present with lower-extremity motor or sensory loss, lumbar pain, or bowel and bladder dysfunction.
Ganglioneuromas arise from neural crest–derived ganglionic progenitor cells and contain a combination of small round cells with poorly defined cytoplasm and large cells with eccentric nuclei. The smaller, immature cells demonstrate a stronger immunoreactivity toward chromogranin A. Isolated ganglioneuromas and para-gangliomas of the cauda equina are similar in their clinical and radiological presentations; therefore, histology is necessary for appropriate classification.\(^6\)

The patient described here likely represents the fifth reported case of a compound ganglioneuromatous paraganglioma of the cauda equina.\(^7,11,13\) Accordingly, the natural history of this heterologous lesion is not entirely clear. However, previous reports of paragangliomas occurring in the filum terminale suggested that these tumors characteristically have a low recurrence rate with complete resection.\(^2,8\) Approximately 75% of spinal paragangliomas are encapsulated in hemosiderin or a fibrous capsule,\(^8\) facilitating complete resection. Radiation therapy may be used in cases with incomplete resection.\(^15\)

As suggested by Pytel et al.,\(^11\) these rare cases of composite ganglioneuromatous paragangliomas help elucidate neural crest cell differentiation. Importantly, the combination of cytokeratin-positive neuroendocrine, ganglion, and Schwann cells suggests that all of these cell types are neoplastic. Consequently, such a lesion reflects the potential for sympathoadrenal cells derived from neural crest cells to undergo divergent differentiation to also form neuroendocrine and ganglion cell components. Alternatively, prior studies have demonstrated that hypoxia promotes dedifferentiation of neuroblastic elements into immature neural crest cells.\(^3\) The c-kit immunoreactivity suggests that this composite tumor does indeed contain admixed elements of common progenitor elements. Although it is not possible to distinguish which neoplastic line was the founder population, the age of this patient suggests that a primary neuroblastoma is less likely. Of note, the data presented here are not sufficient to definitively conclude whether these precursors represent dedifferentiation of an existing neoplastic lineage or retained neural crest cells.

The regulatory network that guides terminal differentiation of neural crest cells has been attributed to genes, such as Sox\(E\), and extracellular ligand signaling pathways, such as those involving neuregulin and glial cell line–derived neurotrophic factor.\(^12\) The admixed nature of the composite tumor described here suggests that the milieu of the lesion provides the factors required for reversion to a precursor phenotype and subsequent divergent differentiation. Continuing to identify the biochemical and molecular characteristics of these extraadrenal composite tumors will provide insights into the life cycle of neural crest cells and stem cell fate.

**Disclosure**

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


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**References**


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Manuscript submitted June 2, 2009. Accepted December 2, 2009. Address correspondence to: Robert M. Friedlander, M.D., M.A., Department of Neurosurgery, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115. rfriedlander@rics.bwh.harvard.edu.