Ganglion-Cell Tumor of the Filum Terminale: Immunohistochemical Characterization

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KIKUCHI, K. and SAITO, M. *Ganglion-Cell Tumor of the Filum Terminale: Immunohistochemical Characterization.* Tohoku J. Exp. Med., 1999, 188 (3), 245-256 — A case of an unusual spinal neuronal tumor is described in a 36-year-old woman presenting with a buttock pain. The spinal tumor was fully characterized by neuroradiological means, and in particular MRI was of significant value in delineating the extension of the tumor within the spinal canal and its exophytic growth pattern. Pathologically, a well circumscribed tumor originating from the intradural filum terminale characteristically comprised both large and small cells, resembling mature and immature neuronal cells, respectively. In addition, two neuronal markers, i.e., chromogranin A (CGA) and neuron-specific enolase (NSE), and other markers such as glial fibrillary acidic protein (GFAP), S-100 protein, HNK-1, tyrosine hydroxylase and beta 2-microglobulin were investigated immunohistochemically. We found that both neuronal cells expressed immunoreactivity for CGA and NSE, and small neuronal cells showed more intense CGA immunoreactivity, indicating an earlier stage of neuronal differentiation. Weakly positive immunoreactivity for HNK-1 was also demonstrated in small neuronal cells, consistent with evidence of maturation along a neuronal differentiation. From these findings a pathological diagnosis of ganglioneuroma was made. This unique group of ganglion-cell spinal tumors is reviewed in the literature and differential diagnosis and immunohistochemical features are discussed. ——— ganglioneuroma; filum terminale; spinal tumor; chromogranin A; HNK-1 © 1999 Tohoku University Medical Press

Neuronal tumors of the central nervous system are rare and estimated to comprise approximately 0.4% of all intracranial tumors (Zülch 1965). They are usually classified into gangliocytoma, ganglioglioma, ganglioneuroblastoma, anaplastic ganglioglioma and neuroblastoma (Zülch 1979). According to the WHO's new classification on the tumors of the central nervous system (CNS), neuroblastoma and ganglioneuroblastoma are classified both into the categories of neuronal tumors and embryonal tumors (Kleihues et al. 1993). Ganglion cell tumors arising from the spinal cord is extremely rare; only 22 cases have been documented in the literature to date (Pick and Bielschowsky 1911; Kernohan et al. 1932;

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Lichtenstein and Zeitlin 1937; Lerman et al. 1972; Garrido et al. 1978; Bevilacqua and Sarvelli 1979; Albright and Byrd 1980; Johannsson et al. 1981; Schmit et al. 1982; Steinberg et al. 1984; Wald et al. 1985; Azzarelli et al. 1991; Ng et al. 1991; Coca et al. 1994; Sibilla et al. 1995). We herein describe an unusual case of ganglioneuroma originating from the filum terminale of the spinal cord in a middle-aged woman. We also report our observations on the immunohistochemical features of the neoplastic cells as monitored by chromogranin-A (CGA), HNK-1 and neuron-specific enolase (NSE), and discuss the significance of these immunoreactivities in the current tumor.

CASE REPORT

This 36-year-old woman presented with an 8-month history of pains on the posterior aspects of both thighs and buttocks. The pain was exaggerated by lying, and there was no urinary retension. There was no history of back injury. On neurological examination she had normal muscle power and tone, but a reduction in sensation in both L2-5 dermatomes. The reflexes were normal. Anal sphincter tone was good. Lumbar spine roentgenograms were normal. Lumbar myelography with water-soluble contrast medium revealed a cap-like filling defect at the level of L1-2 vertebrae, consistent with an intradural extramedullary mass lesion. A computerized tomography (CT) scan of the lumbar spine following intrathecal administration of contrast medium confirmed a lobulated intradural soft tissue mass surrounded by the enhanced subarachnoid space (Fig. 1). Magnetic resonance (MR) imaging with T1-weighted images demonstrated that a well-defined intradural mass was isointense to spinal cord, containing a small spot of signal void on the ventral surface of the mass.

Fig. 1. CT of the lumbar region after intrathecal administration of contrast medium, revealing an intradural mass grow in an exophytic fashion.

Fig. 2. A, T1-weighted magnetic resonance images of the spine with sagittal view, demonstrating a well-defined intradural mass isointense to spinal cord (left) and intensely enhanced with gadolinium (right) (TR 420 milliseconds, TE 10 milliseconds). A small spot of signal void on the ventral surface of the mass is seen, consistent with a draining vein. B, The mass is of high intensity on both proton density (left) (TR 2000 milliseconds, TE 30 milliseconds) and T2-weighted (right) images (TR 2000 milliseconds, TE 80 milliseconds).

Intravenous administration of gadolinium produced intense and homogenous enhancement of the mass (Fig. 2A). The lesion was of high intensity on both proton density and T2-weighted images (Fig. 2B). Spinal angiography showed a hypervascular mass fed by a dilated Adamkiewicz artery originated from the right T9 intercostal artery, and draining into the dilated, tortuous vein on the ventral surface of the spinal cord (Fig. 3). In view of its hypervascularity and location, a presumptive diagnosis was made of hemangioblastoma or ependymoma of the cauda equina region.

Fig. 3. Spinal angiography, showing a hypervascular mass fed by a dilated Adamkiewicz artery (left) and draining into the dilated tortuous vein on the ventral surface of the spinal cord (right).

Fig. 4. Operative photograph, showing the ganglioneuroma buried beneath the cauda equina. The tumor was found to grow exophitically from the filum terminale, and totally excised after amputating the filum terminale proximal to its attachment.

The patient underwent a T12-L2 laminectomy. When the dura mater and the overlying arachnoid were opened and the nerve roots of the cauda equina were retracted, a firm and circumscribed tumor was exposed (Fig. 4). A dilated feeding artery and a “red” draining vein were seen on the filum terminale running parallel to and from the tumor. The tumor was not attached to the conus medullaris or caudal nerves, but directly arose from the filum terminale itself.

TABLE 1. *Immunohistochemical analysis*

	NSE	CGA	HNK-1	GFAP	S100	TH	B2M
Large cells	++	++	—	—	—	—	+
Small cells	++	+++	+	—	—	+	—
Stroma	++	—	—	—	++	—	—
Vessels	—	—	—	—	—	++	++

Immunoreactivity for the markers are scored as —, when absent; +, when minimal; ++, when more extensive; +++, when very extensive. GFAP, glial fibrillary acidic protein; NSE, neuron-specific enolase; CGA, chromogranin A; TH, tyrosin hydroxylase; B2M, β 2-microglobulin.

The tumor was totally removed after amputating the filum terminale proximal to the attachment.

Postoperatively the patient became completely free of any pain, but transiently developed neurogenic bladder dysfunction and hypesthesia over the distribution of the left S1. These neurologic deficits were attributable to manipulations on the nerve roots of the cauda equina during surgery. Two months later her bladder and sensory function returned to normal. She has now returned to her previous job.

Histological and immunocytochemical analysis

The tumor tissue obtained at surgery were fixed in 10% buffered formalin and embedded in paraffin for histopathological examinations. Sections were cut at 5 μ m and hematoxylin and eosin (H & E) stain was prepared. For immunohistochemical studies, paraffin sections were stained with primary antisera against glial fibrillary acidic protein (GFAP) (Dako Laboratories, Carpinteria, CA, USA), neuron specific enolase (NSE) (Dako Laboratories), S-100 (Dako Laboratories), chromogranin A (CGA) (Dako Laboratories), tyrosine hydroxylase (TH) (Chemicon, Temecula, CA, USA), β 2-microglobulin (B2M) (Cosmo Bio, Tokyo), and HNK-1 (Becton Dickinson Immunocytometry System, Mountain View, CA, USA) according to the avidin-biotin-peroxidase complex method of Hsu et al. (1981) (AB Complex HRP kit; Dako Laboratories). Peroxidase was visualized with 0.05% diaminobenzidine and 0.01% hydrogen peroxide.

Routine histological examination of the surgical specimen was characterized by two different types of neoplastic cells. One component consisted of small, round cells with poorly defined cytoplasm, distinct oval nuclei, and pale vesiculated nucleoplasm. Mitotic figures were also seen. Another cell component was large cells, which were sporadically distributed in the fibrillated stroma. Their nuclei, often eccentrically situated in the cytoplasm, were vesiculated and possessed distinct nucleoli. These small and large cells resembled relatively immature and mature ganglion cells, respectively. This conformed to the appearance of ganglioneuroma (Fig. 5A). Both cells were not observed to express for

Fig. 5. Photomicrograph of the tumor specimen. A, There are two types of neoplastic cells: fairly compact collection of small, round cells with ill-defined cytoplasm and distinct vesicular nuclei (immature ganglion cells) (single arrow), and the presence of large cells with eccentrically situated nuclei (mature ganglion cells) (arrow heads) in the fibrillated stroma. H & E, $\times 200$. B, Neuron-specific enolase (NSE) immunohistochemistry demonstrates positive reactivity for both immature (single arrow) and mature ganglionic cells (arrow heads). $\times 200$. The degree of NSE immunoreactivity is evaluated roughly the same for both cells. C, An adjacent section processed for chromogranin A immunohistochemistry shows there is a positive staining in immature (single arrow) as well as mature ganglionic cells (arrow heads), but more intense in the former. $\times 200$. D, A HNK-1-stained section demonstrates immature (single arrow) rather than mature ganglionic cells (arrow heads) favored the expression of HNK-1. $\times 200$.

GFAP or S-100, indicating the absence of glial components in these neoplastic cells. However, numerous cells staining for S-100 were identified in the stroma-rich portion and many of them in the perivascular area. By contrast, immunoreactivity of NSE was diffusely seen in both neoplastic components of the tumor, which confirmed both cells were of neuronal origin (Fig. 5B). Similarly, CGA immunohistochemistry showed immature as well as mature ganglionic cells strongly favored the expression of CGA, but more pronounced immunoreactivity was observed in the former (Fig. 5C). As to HNK-1 immunohistochemistry there was a weakly positive staining in immature rather than mature ganglionic cells (Fig. 5D). These neoplastic cells did not show conspicuous immunoreactivity of TH and B2G.

DISCUSSION

Classification of ganglion-cell tumors

Ganglion-cell tumors involving the CNS include gangliocytoma, ganglioglioma, ganglioneuroblastoma, anaplastic ganglioglioma, and neuroblastoma (Zülch 1979). Gangliocytomas and gangliogliomas contain a varying proportions of both mature neuronal (ganglion) and glial cells, and neuroblastomas consist of immature neuroblasts. When tumors comprise mature ganglion cells with discrete nodules of immature neuroblasts, they are designated as ganglioneuroblastomas. However, the most recent classification of the CNS tumors by WHO includes neuroblastoma and ganglioneuroblastoma in the categories of both "neuronal" and "embryonal" tumors (Kleihues et al. 1993). There are still significant controversies as to their classification and nomenclature (Berger et al. 1983; Nishio et al. 1990). On the other hand there is another subgroup of neuroblastomas together with ganglioneuroblastomas and ganglioneuromas, which occur in the peripheral nervous system (PNS) originating from embryonic sympathetic nervous tissue differentiated from the neural crest (Zülch 1979). These tumors are often placed in the broad group of neuroendocrine tumor (Molenaar et al. 1990). Therefore, there are two types (central and peripheral) of ganglion-cell tumors, which differ each other in respect to location and histologic findings.

Literature review of ganglion-cell spinal tumors

Ganglion-cell tumors originating from the spinal cord are extremely rare. The first case of a histologically verified spinal cord ganglioneuroma was reported by Pick and Bielschowsky (1911), and since then only 21 other cases (Kernohan et al. 1932; Lichtenstein and Zeitlin 1937; Lerman et al. 1972; Garrido et al. 1978; Bevilacqua and Sarvelli 1979; Albright and Byrd 1980; Johannsson et al. 1981; Schmit et al. 1982; Steinberg et al. 1984; Wald et al. 1985; Azzarelli et al. 1991; Ng et al. 1991; Coca et al. 1994; Sibilla et al. 1995) have been so far reported. Zimmerman (1971) showed an incidence of 1.1% of all spinal cord tumors, accounting for about 10% of spinal cord gliomas. Among 23 cases of ganglion-cell tumors of the spinal cord, including one of our own, there are 9 gangliogliomas, 9 gangliocytomas or ganglioneuromas, 3 mixed tumors, 1 ganglioneuroblastoma, and 1 neurocytoma. Fifteen tumors occur exclusively in the cervical and thoracic spinal cord. One of them is an extension from the medulla oblongata into the cervical cord (Garrido et al. 1978). The entire spinal cord is involved in 2 cases. By contrast there are 5 tumors situated at the regions of the conus medullaris, cauda equina, and filum terminale. Of particular interest is that 3 of these tumors are mixed with either paraganglioma, chemodectoma, or ependymoma. Ganglioneuromas also occur in the paraspinal region as benign, slow-growing tumors of the paravertebral sympathetic ganglia (Oro and Geise 1983). Thirty percent of these ganglioneuromas of paraspinal origin grow through an

intervertebral foramen into the spinal canal as extradural dumbbell tumors (Ljung et al. 1984). It is extremely rare to find ganglioneuromas involving exclusively intradurally. In addition paraganglioma of the cauda equina and the filum terminale is being increasingly recognized (Lerman et al. 1972; Djindjian et al. 1990; Pigott et al. 1990; Araki et al. 1993; Toyota et al. 1993; Sharma et al. 1998), and there are now more than 50 cases recorded in the literature.

Differential diagnosis

The major differential diagnosis involving the current case includes ependymoma, hemangioblastoma and paraganglioma. The majority of spinal ependymoma are located in the cauda equina and originate from the conus medullaris or filum terminale, and histologically known as myxopapillary ependymoma. GFAP, a component of glial filaments, is frequently found in fibrous astrocytes filled with glial filaments. GFAP immunohistochemistry applied to the current tumor demonstrated the absence of GFAP-positive cells. It is frequently demonstrated that the presence of GFAP is identified in ependymomas (Nishio et al. 1990). The angiographic and MR features are characteristic in the present tumor, resembling such vascular tumors as hemangioblastoma. Spinal hemangioblastomas, often associated with intramedullary cyst formation, tend to arise the cervical and thoracic regions, and rarely occur in the filum terminale region. Paraganglioma in the region of the cauda equina or filum terminale has been reported several times (Djindjian et al. 1990; Nishio et al. 1990; Pigott et al. 1990; Araki et al. 1993) since the first description by Lerman et al. (1972). Araki et al. (1993) documented MR findings of paraganglioma of the cauda equina, which are very similar to the current tumor. Paragangliomas are histologically characterized by the presence of oval cells with a tendency to form nests or lobules, commonly designated as "Zellballen" (Pigott et al. 1990). In the present tumor, however, the typical Zellballen is not conspicuous. Such ganglion-cell tumors as paragangliomas and ganglioneuromas should be included in the preoperative radiological diagnosis of spinal tumors involving the conus medullaris, cauda equina, and filum terminale.

Immunohistochemical features

CGA, first discovered in adrenal medulla, is a major constituent of the neurosecretory granules of chromaffin cells, and therefore localized predominantly in the vesicles of neurons and endocrine cells (Nolan et al. 1985). It has been demonstrated in CNS and PNS neurons as well as in retinal photoreceptor cells (Nolan et al. 1985). The expression of this protein has been also noted in a number of embryonal CNS tumors including medulloblastomas, neuroblastomas, pineoblastomas, retinoblastomas and ependymoblastomas (Kleinert 1991). Kleinert (1991) claimed CGA to be the best neuronal marker for poorly differentiated neurons, in contrast to synaptophysin, another reliable neuronal

marker, which is known to be the best marker for well-differentiated neurons. In the current tumor there is a clear distinction between the small and large cell components in terms of CGA immunoreactivity. Smaller cells demonstrated more prominent immunoreactivity over the large ones, and it may indicate this spinal tumor contains two different neuronal cells with different stages of neuronal differentiation.

The anti-HNK-1 antibody recognizes the CD 57 antigen on natural killer cells, and cross-reacts with a sulfated carbohydrate epitope shared by neural cell adhesion molecule (N-CAM), neuronal-glia cell adhesion molecule (Ng-CAM) and myelin-associated glycoprotein (Sato et al. 1983; McGarry et al. 1983; Cooper et al. 1990a). In humans, HNK-1 epitope is expressed in several cell elements of the CNS and PNS. In the CNS it is expressed by oligodendrocytes, myelin and the luminal surface of the ependyma cells. The majority of the neurons appear not to express this epitope. However, a few neurons may present anti-HNK-1 labeling after delipidation of the tissue sections (Schuller-Petrovic et al. 1983). In the PNS, Schwann cells and myelin sheaths are strongly labeled by the anti-HNK-1 antibody (Perentes and Rubinstein 1986). Neuroepithelial tumors expressing HNK-1 include the majority of gliomas and embryonal CNS tumors such as medulloblastomas, pineoblastomas and neuroblastomas (Perentes and Rubinstein 1986; Schwechheimer et al. 1992). Expression of HNK-1 is also reported in central neurocytoma (Hassoun et al. 1993). Immunoreactivity for HNK-1 has been postulated to indicate ganglionic differentiation in neuroblastoma with improved patient survival (Cooper et al. 1990b). In the present tumor there appears to be a difference in HNK-1 immunoreactivity between small and large neuronal cells, indicating the small cells are more immature in cellular differentiation, consistent to the results of CGA immunohistochemistry.

Cooper et al. (1990b) presented a model of human adrenal medullary histogenesis that incorporates the chromaffin, ganglionic and sustentacular lineage known to constitute the parenchymal cells of the adult adrenal medulla. The adrenal medulla is derived from primitive, multipotential neural crest stem cells. Descendants of these cells that migrate from the neural crest at the 18th to 24th somites, invade the fetal adrenal cortex and give rise to the adrenal medulla are designated as adrenal medullary precursor cells (Le Douarin et al. 1977). Ganglion cells of the PNS undergo a similar process of maturation from the division of a primitive neural crest stem cells. Paragangliomas, which are of neural crest origin, intradurally occur exclusively in the most caudal part of the spinal cord such as cauda equina and filum terminale (Lerman et al. 1972; Schmit et al. 1982; Djindjian et al. 1990; Pigott et al. 1990; Araki et al. 1993). In order to evaluate the hypothesis on histogenesis that the current ganglioneuroma tumor cells may also correspond to arrested differentiation of the neural crest-derived ganglionic progenitor cells, which otherwise would have been destined to become parenchymal cells of the adrenal medulla if not entrapped or incorporated into yet unclosed

caudal neural tube, we examined on the tumor cells the expression of adrenal medullary developmental markers: CGA, TH and B2M are markers of the chromaffin lineage; S-100 is a marker of sustentacular cells; and HNK-1 is a marker of fetal adrenal medullary ganglion cells (Cooper et al. 1990a, b). The results of the present investigation failed to document that the current ganglioneuroma cells are of neural crest origin, because both CGA and HNK-1 demonstrate immunoreactivity on a variety of CNS tumors as mentioned earlier and therefore cannot be defined as a specific marker for the adrenal medulla alone. These two markers, however, may be useful for immunohistochemical analysis of ganglion-cell tumors in the CNS, especially for evaluation of the stage of neuronal differentiation in the tumor cells.

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