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Cervical ganglioneuroma arising from the dorsal root ganglion: illustrative case

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BACKGROUND Ganglioneuroma is a benign and well-differentiated tumor derived from neural crest cells, which occurs infrequently, with most patients being female and adolescents. While predilection sites are the posterior mediastinum and retroperitoneal cavity, ganglioneuroma originating from the dorsal root ganglion is very rare. Here the authors report a case with C2 dorsal root ganglion-derived ganglioneuroma with some literature review.

OBSERVATIONS A 45-year-old male patient complained of persistent right-side throbbing occipital headache for more than a year. Magnetic resonance imaging (MRI) of the cervical spine revealed a dumbbell-shaped intradural extramedullary tumor from the C2 posterior surface of the odontoid to right C1–2 intervertebral foramen with high T2- and low T1-weighted signal intensities. The tumor displayed homogeneous contrast enhancement by MRI. The authors suspected schwannoma and performed a tumorectomy for both diagnosis and treatment purposes. Intraoperative findings showed that the tumor originated from the dorsal root ganglion, and pathological examination revealed ganglioneuroma. Immediately after the tumorectomy, the throbbing occipital headache disappeared and the patient was discharged from the hospital without major complications.

LESSONS Although ganglioneuroma derived from the dorsal root ganglion is very rare, a differential diagnosis of the ganglioneuroma should be made, when schwannoma is suspected.

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KEYWORDS ganglioneuroma; dorsal root ganglion; dumbbell-shaped tumor; cervical spine

Ganglioneuroma (GN) is a rare benign tumor derived from sympathetic ganglion or neural crest cells within the adrenal medulla. It occurs in 0.1–0.5% of central nervous system tumors, and it is predominantly found in females and adolescents.[1] The most frequent predilection site is the dorsal mediastinum followed by the retroperitoneal cavity, whereas previous reports showed GN derived from dorsal root ganglion was very rare.[2–5]

The tumor growth rate of GN is slow and major predilection sites, i.e., dorsal mediastinum and retroperitoneal cavity, infrequently develop clinical symptoms. Therefore, GN is coincidentally found at imaging tests in many cases although it does not have GN-specific image characteristics.[6] When it is found in a retroperitoneal cavity, a tumor biopsy can be carried out for diagnosis. However, when the tumor is found and a biopsy cannot be performed, it is difficult to diagnose preoperatively. The GN is pathologically the most differentiated tumor among peripheral neuroplastic tumors,[2] and matured ganglion cells are found in the interstitium.[7] Although it is a benign tumor, local tumor recurrence and/or malignancy transformation cases have been reported.[8] Resection of the tumor is the first-choice therapeutic option, and the long-term prognosis is favorable including cases of incomplete tumor resection.[9]

Here we report a case of GN found at the dorsal root ganglion. We discuss clinical and pathological characteristics and treatment along with a literature review.

Illustrative Case

A 45-year-old male presented with no remarkable past medical history. He presented to a nearby neurosurgery clinic because of a persistent right-sided throbbing occipital headache for more than a year. Because his headache had worsened, brain and cervical magnetic resonance imaging (MRI) were performed, and a dumbbell-shaped intradural extramedullary tumor from the C2 posterior

ABBREVIATIONS CT = computed tomography; GN = ganglioneuroma; INPC = International Neuroblastoma Pathology Classification; MEP = motor evoked potential; MRI = magnetic resonance imaging; NF-1 = neurofibromatosis type 1; SSEP = somatosensory evoked potential.

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surface of the odontoid to the right C1–2 intervertebral foramen was found. Although his symptom was limited to throbbing headache and no spinal cord symptoms developed, the tumor markedly compressed the spinal cord from the right side. Thus, the patient was referred to our hospital. When he presented to our hospital, he still complained of a right-sided throbbing occipital headache and abnormal perception. His limb movement was normal and sensory disturbance was not found. Other neurological abnormalities were not reported.

The cervical spine radiograph did not show any of bone destruction, abnormal expansion of the intervertebral foramen, and malalignment of the cervical spine. Plain computed tomography (CT) imaging showed the tumor as a homogenous mass without calcification, and contrast-enhanced CT displayed very weak contract enhancement without abnormal vasculature. Cervical spine MRI revealed a 20 $\times$ 15 $\times$ 25 mm, dumbbell-shaped homogeneous tumor with a clear boundary from the C2 posterior surface of the odontoid to right C1–2 intervertebral foramen. The tumor exhibited high T2- and low T1-weighted intensity signals indicating intramural extramedullary tumor (Fig. 1A and B). Contrast-enhanced spinal cord MRI showed homogenous contrast enhancement (Fig. 1C–E). No additional intracranial and spinal cord lesions were found on MRI. We suspected schwannoma with a differential diagnosis of meningioma. Although the patient only complained of right-side throbbing occipital headache, the abnormal sensation was being deteriorated with remarkable spinal cord compression by the tumor. Therefore, we planned a tumorectomy.

The tumorectomy was performed via a postmedian skin incision with the patient prone and under general anesthesia. Somatosensory evoked potentials (SSEPs) and motor evoked potential (MEPs) were used as intraoperative monitoring to minimize nerve injury. Following exposure of C1 posterior vertebral and right half of C2 vertebral arches, C1–2 hemilaminectomy using a diamond drill was performed. We found a bulging of the epineurium at the C2 nerve root (Fig. 2A). When an incision was made at the bulged epineurium, a grayish-white soft tumor appeared (Fig. 2B). The boundaries between tumor and epineurium were relatively clear. The tumor was excised piece by piece and the outer border of the tumor was confirmed. We found that several nerves were circumvoluted by the tumor and we dissected the nerve root from the external side. We also found the tumor at the right ventral side of the spinal cord within the dura matter. When the tumor was carefully pulled up from the outside, no adhesion between the tumor and the spinal cord was confirmed and the tumor was easily pulled out from the dura matter. We dissected nerves, which were thought to be the origin of the tumor and a total tumorectomy was performed (Fig. 2C). Both SSEPs and MEPs were not significantly changed before and after the tumorectomy.

Histopathological examination revealed the presence of degenerating multiple peripheral myelinated nerve bundles with fibrosis and mucilaginous changes between bundles. Tumor cells had curved jewel-shaped nuclei and exhibited a nondysplastic appearance. There were matured ganglion cells disseminating across interstitial space. Schwann cells and satellite cells surrounding ganglion cells were positive for immunostaining for S-100 protein (Fig. 3A and B). Thus, we diagnosed GN by histopathological examination.

After the tumorectomy, the patient's right throbbing occipital headache disappeared, and only mild sensory disturbance remained. The patient did not develop any other neurological symptoms. His postoperative course was favorable, and he was discharged from the hospital on postoperative day 8. Since the patient received a complete

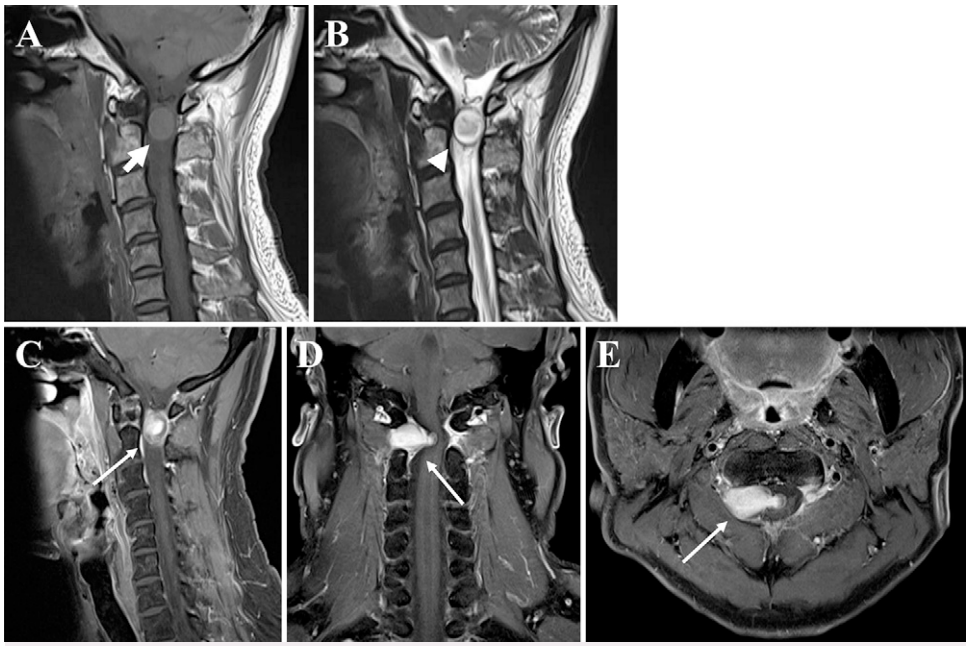

FIG. 1. Preoperative MRI. Sagittal T1-weighted magnetic resonance image (**A**) showing a mass with moderate signal intensity and a clear boundary (*white arrow*). Sagittal T2-weighted magnetic resonance image (**B**) showing a mass with high signal intensity and clear boundary (*white arrowhead*). Sagittal (**C**), coronal (**D**), and coronal (**E**) fat-suppression contrast T1-weighted magnetic resonance images display a tumor with heterogeneous contrast enhancement (*white arrows*).

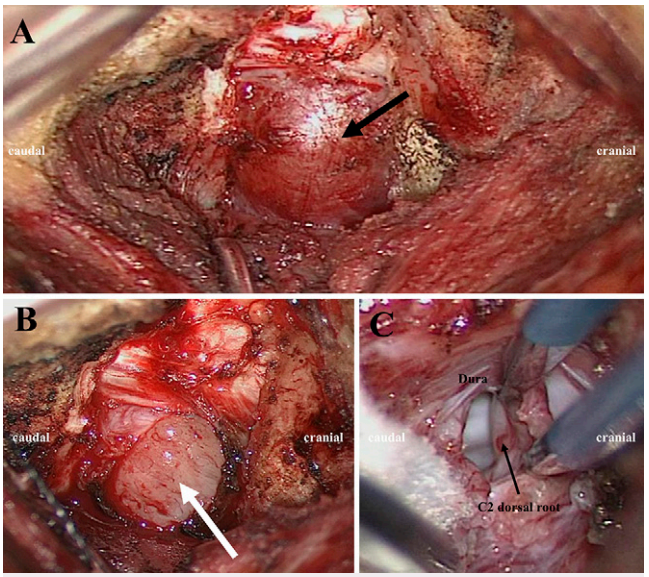

FIG. 2. Intraoperative findings. **A and B:** When the right C1–2 vertebral arch was resected, bulged C2 epineurium was observed (*black arrow*). There was a grayish-white soft tumor under the dissected epineurium (*white arrow*). **C:** No residual tumor was confirmed inside the dura mater after total tumorectomy.

tumorectomy and was diagnosed with GN without malignant change, we determined that no adjuvant chemotherapy and radiation therapy were necessary. We confirmed complete tumorectomy at the 3-month MRI follow-up.

Discussion

Observations

The first GN case was reported in 1970.[10] GN is a well-differentiated benign tumor derived from neural crest cells and occurs more frequently in females and those less than 20 years old.[11,12] Previous reports showed that predilection sites are posterior mediastinum (41.5%), retroperitoneal cavity (37.5%), adrenal gland (21.0%), and cervical sympathetic ganglia in some cases.[13–15] Fewer than 10% of patients develop GN within the spinal canal[16] in which GN at the cervical spine occurs most frequently followed by the thoracic and lumbar spine.[17] Among them, dorsal root ganglion-derived GN is extremely rare[18] and only 10 cases of intradural GN derived from cervical dorsal root ganglia have been reported.[3,19–25] We summarize the previously reported cases and the current case and found that a dumbbell-shaped tumor is most frequently seen and half exhibit multiple tumors (Table 1). Although multiple-tumor cases suggest an association with neurofibromatosis type 1 (NF-1), it remains unknown genetic relation between NF-1 and GN.3 Sporadic cases tend to exhibit C2 dorsal ganglion-derived GN similar to the current case, implying an association with GN development. In cases in which GNs were located within the spinal canal, various neurological symptoms are presented by compression of the spinal cord and cauda equina. In such cases, the most frequently observed symptoms are paraplegia and gait disturbance.[26,27] In the current case, we speculated the tumor was derived from the dorsal root ganglion, which compressed the cervical nerve root and ganglion resulting in occipital headache and dysesthesia. Because predilection sites of GN are the posterior mediastinum and retroperitoneal cavity, many cases are asymptomatic, and the tumor is incidentally detected by imaging tests such as MRI. There are reports of hormonal secreting GN, which displays symptoms depending on secreting hormone.[7,16] In addition, attention should be paid to NF-1 and multiple endocrine tumor type 2B in some cases.[12] We did not perform endocrine tests in the current case because the patient did not have a family medical history and no physical findings indicated endocrine abnormalities.

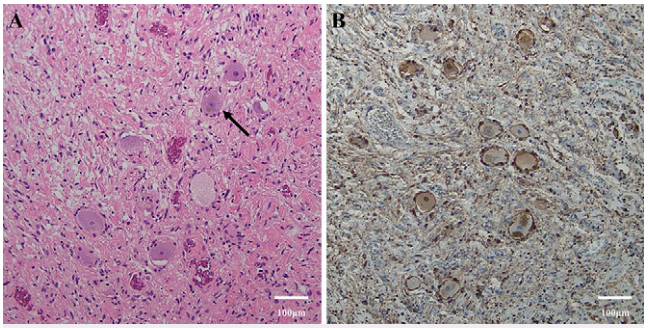

FIG. 3. Pathohistological images of resected tumor. **A:** Matured ganglion cells were disseminated within tumor tissue (*black arrow*). Hematoxylin and eosin staining. **B:** Satellite cells surrounding ganglion cells and Schwann cells were positive to S-100 protein immunostaining.

Although imaging tests are essential for preoperative diagnosis and surgical plan, GN does not have characteristic image findings and it is difficult to diagnose before the surgery if the tumor is developed other than at predilection sites. CT scanning image displays a tumor with a clear boundary in general,[11] and calcification is reported in 42% to 60% of cases,[28] which was not seen in the current case. Although the MRI image of GN exhibits a homogenous and low to the middle signal intensity of the T1-weighted image, the T2-weighted image of GN is heterogeneous with middle to high signal intensity signals. Diffusion-weighted imaging shows middle signal intensity,[28] however, it is not characteristic of GN and individual variations of intratumor tissues, such as collagen fibers, adipose tissue, Schwann cells, myxoma-like interstitium, and ganglion cells, affect MRI findings.[29] A previous report of contrast enhancement MRI also showed the degree of contrast enhancement varied from poor to strong suggesting a heterogenous structural component of the tumor.[29] Dynamic MRI also showed various enhancement patterns depending on microvascular permeability and vasculature distribution within the tumor. Therefore, some cases exhibit earlier enhancement effects due to enriched vasculature and increased vascular permeability whereas others exhibit late enhancement due to poor vascular with enriched mucinous interstitium.[30] In the current case, although we did not perform dynamic MRI, contrast MRI displayed low to moderate levels of contrast enhancement suggesting fewer feeding vessels in the tumor.

A definite diagnosis of GN can be made by histopathological analysis. The peripheral neuroblastic tumor is classified into four groups by the International Neuroblastoma Pathology Classification (INPC), which includes neuroblastoma, ganglioneuroblastoma intermixed, ganglioneuroma, and ganglioneuroblastoma nodular.[31] The INPC was originally proposed based on Shimada's classification in 1999 and was partially updated in 2003.[32,33] It is an important classification for the prediction of prognosis and useful for risk

TABLE 1. Summary of previously published case reports with cervical intradural or intradural/extradural ganglioneuroma arising from the spinal dorsal root ganglion

Authors & Year	Age (yr)	Sex	Origin	Laterality	Dumbbell Shape	Multiplicity	Basal Disease	Treatment	FU (mo)	Recurrence/ Regrowth
Shephard & Sutton, 1958[19]	35	M	C2–7	Unilateral	+	+	NF-1	Total resection	30	None
Sinclair & Yang, 1961[20]	44	F	C2–5	Unilateral	+	+	NF-1	Total resection	NA	NA
Strang & Nordenstam, 1962[21]	63	F	C2–4	Unilateral	+	–	–	Total resection	4	None
Kyoshima et al., 2004[3]	35	M	C1–3	Bilateral	+	+	NF-1	Subtotal resection	NA	NA
Tei R et al., 2007[22]	51	F	C1	Unilateral	–	–	MHS	Total resection	NA	NA
Hioki et al., 2014[23]	72	M	C1–2	Bilateral	+	–	–	Subtotal resection	24	None
Tan et al., 2019[24]	27	M	C1–2	Bilateral	+	–	NF-1	Total resection	1	None
Sun et al., 2021[25]	40	F	C1–2	Unilateral	–	+	–	Subtotal resection	106	None
	26	M	C1–2	Unilateral	–	–	–	Total resection	63	None
	42	F	C1–2	Bilateral	–	+	NF-1	Subtotal resection	44	None
Present case	45	M	C1–2	Unilateral	+	–	–	Total resection	3	None

FU = follow-up; MHS = multiple hamartoma syndrome; NA = not available; + = yes; – = no.

assessment in clinical studies. GN is the most matured morphology among the four groups and the exclusion of neuroblasts, extreme dysplastic cells, mitotic division, and necrosis is essential for definite diagnosis.[34] The presence of matured ganglion cells within the interstitium is a major and characteristic component of GN and the interstitium composes of bundles of nerve fibers including Schwann cells and connective tissue including inner and outer membranes. The immunohistochemical test shows positive for S-100 protein, synaptophysin, and neurofilament.[3,14] In the current case, matured ganglion cells within the interstitium were found and immunostaining against S-100 protein was positive corresponding to GN.

Percutaneous needle biopsy is a rapid and cost-effective test, which is useful for differential diagnosis. However, it is difficult to perform due to the tumor site, and a previous study showed that 60% of GN cases failed in diagnosis.[12] The most effective therapeutic option for GN is resection and it is also useful for definitive diagnosis.[35] Although total tumorectomy is desirable, it cannot be performed when the tumor is present close to critical organs. In such cases, total tumorectomy should be avoided. Decarolis et al.[36] reported that an incomplete tumorectomy with remnant tumor size at 2 cm or less have a low risk for tumor progression. In the current case, we determined the risk of postsurgical paralysis of C2 nerve root resection was very low and unilateral nerve root resection did not develop severe neurological dysfunction and then performed a successful total tumorectomy. Postoperative local radiation therapy or adjuvant chemotherapy after total tumorectomy is not effective and the long-term prognosis of GN after total tumorectomy is favorable.[37] Sun et al.[25] reported the long-term postoperative outcome of 31 spinal GN cases. In their report, 18 cases with total tumorectomy and 13 cases with partial tumorectomy were included, and the mean follow-up period was 64.13 ± 22.67 months. No local recurrence or malignant transformation cases were reported. On the other hand, Fernandes et al.[38] reported an observational study of 30 spinal nerve sheath tumor (schwannoma and neurofibroma) cases in which 96% underwent total tumorectomy and 3.3% developed tumor recurrence. Their results suggest the long-term outcome of GN is favorable compared to schwannoma or neurofibroma. However, a previous report also showed GN cases of local recurrence and malignant transformation.[8] Therefore, it is necessary to accumulate further cases.

Lessons

Dorsal root ganglion-derived GN is very rare. We reported a case of dumbbell-shaped GN from the C2 posterior surface of the odontoid to the right C1–2 intervertebral foramen. When we see a case suspecting schwannoma, a differential diagnosis of GN should be made regardless of less frequent occurrence.

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Disclosures

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

Author Contributions

Conception and design: Torimaki, Sasaki, Hoshimaru. Acquisition of data: Torimaki, Sasaki, Hoshimaru. Analysis and interpretation of data: Torimaki, Sasaki, Hoshimaru. Drafting the article: Torimaki, Sasaki, Ueda, Hoshimaru. Critically revising the article: Torimaki, Sasaki, Hoshimaru. Reviewed submitted version of manuscript: Torimaki, Sasaki, Hoshimaru. Approved the final version of the manuscript on behalf of all authors: Torimaki. Statistical analysis: Sasaki. Administrative/technical/material support: Sasaki, Ohara, Hoshimaru. Study supervision: Sasaki, Ueda, Hoshimaru.

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