Longest survival by the combination of radiation-therapy and resection in patient with metastatic spinal paragangliomas from primary-neck lesion with succinate dehydrogenase subunit B (SDHB) mutation

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Abstract. Metastatic paraganglioma (MPG) of the spine is a rare condition, with no established management. Herein, we report the longest survival case of a primary neck tumor that caused spinal MPG with a succinate dehydrogenase subunit B (SDHB) mutation (c.470delT, p.L157X) which could have promoted its malignancy. This male patient initially presented with a left neck PG which was diagnosed by a biopsy when he was 54 years-old. Simultaneously performed additional examinations revealed the spinal metastatic tumors on the T5-7 vertebrae and L3 vertebra-sacrum. These primary neck and metastatic spinal tumors’ growths were once suppressed under the radiation therapy. Nineteen years later, he developed acute progressive paraparesis due to a mass located at the T2-3 level, tightly compressing the spinal cord, and protruding into the left thoracic cavity. We resected the maximum possible area of tumor in the spinal canal, confirmed MPG by histological examination, and then, we administered radiation therapy of 40 Gy in 20 fractions. Eventually, the patient was able to walk unaided with no evidential tumor recurrence for 3 years after treatment. Generally, clinical feature of MPG with SDHB mutation from abdominal lesion is thought to be poor prognosis. However, our case suggests the possibility of long-term control of spinal MPG with the adequate combination of radiation therapy and resection if metastatic lesions from primary-neck lesion with an SDHB mutation are remained to spine.

Key words: Metastatic paraganglioma, Spine, Myelopathy, Genetic testing, Succinate dehydrogenase subunit B (SDHB)
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**Case Presentation**

A 73-year-old male with acute progressive paraparesis was admitted to our hospital. His family history was unremarkable. Nineteen years earlier, he noticed a tumor on the left side of his neck, and a biopsy at another hospital revealed a final diagnosis of PG. Furthermore, simultaneously performed additional examinations revealed the spinal metastatic tumors on the T5-7 vertebrae and L3 vertebra-sacrum. He received radiation therapy (40 Gy in 20 fractions) for the primary lesion and both spinal lesions.

On this-time admission, he presented a gradually worsening grade 3/5 motor weakness in both lower extremities and bladder-rectal disfunction. He experienced no headaches, abnormally high blood pressure, or hyperhidrosis. His blood cell count and blood chemistry reports were normal, and serum catecholamine levels were also within the normal range. Based on these data, we suspected that the epidural mass was a recurrent spinal MPG. Magnetic resonance imaging (MRI) identified a mass located at T2-T3, tightly compressing the spinal cord, and protruding into the spinal canal (Fig. 1). No continuity with the cervical mass was identified. Owing to a progressive neurological decline, the patient was subjected to surgery to release the severe compression of the upper thoracic cord by the protruding portion of tumor into the spinal canal. We performed a laminectomy between T1 and T3 and resected the majority of the epidural mass, which was firmly attached to the dural sac (Fig. 2). The tumor was extremely rich in blood vessels, thus intraoperative blood loss was substantial (around 1,500 mL). Following surgery, radiation therapy (40 Gy in 20 fractions) was administered to the C7-T4 level. Finally, the patient become physically independent to perform activity at home and his bladder-rectal disfunction was improved. Histological examination of the resected specimen confirmed the presence of MPG, with tumor cells arranged in distinct nests separated by fibrovascular stroma and sustentacular cells in a Zellballen pattern (Fig. 3A). According to immunohistochemical examination, the chief cells were positive for CD56 marker (Fig. 3B), chromogranin A (Fig. 3C), and synaptophysin.

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**Fig. 1** (A) Sagittal and (B) axial enhanced T1-weighted MRI showing an enhanced mass in the upper thoracic spine protruding into the left spinal canal (arrow) and thoracic cavity (arrow head), and tightly compressing the spinal cord. Initial spinal metastatic lesions on the T5-7 vertebrae were well controlled.

**Fig. 2** Intraoperative photograph showing the tumor and compressed dorsal surface of the spinal dura mater. The tumor is elastic soft and strongly adherent to the spinal dura mater (*).
(Fig. 3D), and S-100 protein (Fig. 3E). No comedo necrosis or vascular invasion was identified. Cellularity was moderate and the Ki-67 index was not more than 5.5%.

Under the patient’s consent and the ethical approval in our institute (No. 137), we conducted genetic testing of the isolated peripheral blood cells. This examination identified a thymine deletion at position 470 in exon 5 of the SDHB complementary DNA sequence (c.470delT, p.L157X) (Fig. 4).

MRI obtained 30 months after the surgery demonstrated multiple bone metastases at T8-T9, T11, and L2 vertebrae, but no evidence of spinal cord compression due to partial tumor regrowth was confirmed (Fig. 5) and his QOL was still maintained, sufficiently. We administered additional radiation therapy (40 Gy in 20 fractions) to the lesions. At 39 months, MRI revealed liver metastasis.
However, the patient refused additional therapy and passed away due to pneumonia at 46 months after the surgery (Fig. 6).

**Discussion**

**The definition of MPG**

The prognosis of MPG remains poor, with 5-year mortality rates greater than 50% [4]. Although all PGs have some metastatic potential, their diagnoses are difficult to perform based solely on pathology [5]. Kimura et al. predicted the PG prognosis based on the pathological findings (GAPP score). While the pathological grading may be useful in predicting malignancy [6], genetic tests are recently emphasized as a predictive examination of prognosis. In our case, genetic testing revealed abnormalities, despite the pathological evaluation developed by Kimura et al. indicated a moderately differentiated PG type, the GAPP score of the tumor was 3, with no malignant features. SDHB and succinate dehydrogenase subunit D (SDHD) gene abnormalities are especially well known as PG cases. SDHB gene particularly codes for the Ip subunit of succinate dehydrogenase that binds to the mitochondria, and SDHD gene encodes the CybS subunit of the succinate dehydrogenase protein.

**Clinical feature of PG with SDHB gene mutation**

Generally, clinical features of PG originated by SDHB mutation include: (1) onset of abdominal tumor formation, (2) occurrence at a young age, and (3) poor prognosis due to metastasis [1, 5-7]. On the other hands, Hamid et al. reported that presence of SDHB mutation had no correlation with short survival [8]. Therefore, it is controversial issue whether SDHB gene mutation correlate with poor prognosis. While, primary abdominal PGs are well known to cause MPGs as described above [9-11]. Many head and neck PGs develop from mutations on the SDHD gene and typically they are hormonally silent and rarely malignant with a low metastatic rate (4%). In head and neck PG, 15 MPG cases were reported [1, 12-14]. Of these 15 MPG cases, only 10 cases which were reported by Mediouni et al. underwent genetic testing: 5 cases (50%) positive SDHB gene mutation and 2 cases (20%) positive SDHD gene mutation. As these values indicates, genetic testing has not been performed sufficiently yet in usual clinical field. Furthermore, reports of spinal MPGs with myelopathy requiring operation from neck lesion are very rare, only 3 cases without genetic testing [1, 12, 13].

Moreover, in the present case, genetic testing showed deletion c.470delT in exon 5 of SDHB. Only four previous reports, notably from Japan, have described this mutation [9-11, 15]. According to the reports, three of these patients harboring the SDHB (L157X) mutation had evident symptoms of an abdominal tumor, and only one case, which was reported by Takeshima et al., had...
head and neck tumor similar to our patient [15]. However, in contrast to our patient, Takeshima et al. described that the patient showed indolent clinical features, with no occurrence of metastatic lesions, and was characterized by symptoms mimicking PG with an SDHD mutation rather than SDHB mutations [15]. In this point of view, our case is valuable because a definitive diagnosis of spinal MPG originating from neck lesion, under the genetic abnormality at SDHB gene mutation was performed.

The management of spinal MPG

The prognosis of patients with spinal MPG are reported to be poor [4, 16]. However, a report suggested that the total removal of spinal MPG led to the favorable outcomes [16]. Actually, resection appears to be abandoned in many cases [16]. For instance, as PG has the vascular-rich histological features, most cases resulted in debulking surgery. Furthermore, presence of multiple lesions makes the total resection difficult to perform [1]. The reported complication rate from surgery achieves to the amazing rate (46.7%) [16]. Average intraoperative blood loss in 25 cases with spinal MPG was reported to be 1,978 mL [15]; however, another case reported over 5,000 mL [13]. Therefore, the radical control of bleeding during surgery with/without preoperative embolization of the feed is important [16, 17].

As other therapeutic methods, PG can also be effectively treated with radiation therapy in terms of the local control of tumor growth [7]. This effect is also expected to the metastatic lesions. Chemotherapy also has a certain degree of effect to disseminated MPG even though it’s no proven efficacy [18]. In the present case, aggressive partial resection of a tumor protruding into the spinal canal and subsequent radiation therapy resulted in the patient’s neurological improvement even on the recurrent spinal metastatic stage. The ultimate goal was to maintain the patient’s QOL, avoiding permanent paraplegia and bladder-rectal disfunction. After the treatment for recurrent spinal MPG, the patient regained independent walking and spent about 46 months at home without QOL loss. Importantly, no tumor recurrence for up to 30 months after the treatment was evident. Even though the prognosis of spinal metastasis is thought to be poor [15], QOL might be maintained beyond traditional expectation under the conditions that the metastatic lesions are remained to spine and are adequately controlled with radiation therapy or aggressive resection. This concept seems to be essential for the treatment of MPG. Finally, if the tumor shows the sign of recurrence, early additional initiation of radiotherapy should be considered as soon as possible. Especially, in case of MPG which is associated with genetic abnormality, close monitoring is mandatory even in the absence of current recurrence.

The main limitation of this case study was that we could not measure blood or urine metanephrine levels and could not evaluate 123I-MIBG scintigraphy.

Conclusion

We reported the longest survival case of a primary neck tumor that caused spinal MPG with an SDHB mutation. Generally, clinical feature of MPG with SDHB mutation from abdominal lesion is thought to be poor prognosis. However, our case suggested the possibility of long-term control of spinal MPG with the adequate combination of radiation therapy and resection if metastatic lesion with an SDHB mutation are remained to spine.

Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing.

Disclosure

The authors declare that they have no conflict of interest.

Funding

None.

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