A Patient with an Extra-adrenal Pheochromocytoma and Germ-line SDHB Mutation Accompanied by an Atypical Meningioma

Tsuguka Shiwa¹², Kenji Oki¹, Masayasu Yoneda¹, Koji Arihiro³, Haruya Ohno¹, Rui Kishimoto¹ and Nobuoki Kohno¹

Abstract

The gene succinate dehydrogenase subunit B (SDHB) encodes a protein comprising part of the mitochondrial complex II, which links the Krebs cycle and the electron-transport chain. Heterozygous germ-line SDHB mutations causes familial pheochromocytoma-paraganglioma syndrome and has also been linked to gastrointestinal stromal tumors, as well as renal cell carcinomas. We herein report a patient with a germ-line SDHB mutation who presented with an atypical meningioma that was identified as originating from a somatic SDHB mutation. The 41-year-old man, who had a surgical history of extra-adrenal pheochromocytoma at 23 years of age, recently developed gait disorder and hypertension. At the radiological examination, a tumor was detected in the cervical spinal cord at the C6-7 intervertebral level. The pathological findings of the isolated tumor were atypical meningioma assessed as grade II according to the World Health Organization criteria. Inherited neoplasia syndrome was suspected because of the patient’s history of early-onset extra-adrenal pheochromocytoma and the development of meningioma. We therefore performed molecular genetic analyses. A direct sequence analysis revealed a heterozygous germ-line frameshift mutation in SDHB, specifically an 11-nucleotide deletion, c.305-315delCAATGAACATC, in exon 4, resulting in a frameshift p.A102EfsX12. Additionally, the sequence analysis of the tumor DNA revealed only a mutated allele with a frameshift mutation in the germ-line SDHB. Our findings suggest that SDHB plays an important role in the pathogenesis of meningiomas as well as pheochromocytomas. Therefore, a differential diagnosis for metastatic pheochromocytoma and other new onset tumors, including meningioma, particularly in patients with germ-line SDHB mutations and a previous history of pheochromocytoma should be carefully made.

Key words: succinate dehydrogenase subunit B gene, atypical meningioma, extra-adrenal pheochromocytoma

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Introduction

Pheochromocytoma and paraganglioma are defined as catecholamine-secreting tumors which arise from chromaffin cells in the adrenal medulla or in the sympathetic ganglia in the thorax, abdomen, or pelvis (1). Some patients with pheochromocytoma or paraganglioma exhibit certain hereditary pheochromocytoma-paraganglioma syndromes, including neurofibromatosis type 1 (NF1), von Hippel-Lindau syndrome (VHL), multiple endocrine neoplasia type 2 (MEN2), and pheochromocytoma-paraganglioma syndrome type 1 (PGL1), PGL3, and PGL4 (2-5). Although the majority of pheochromocytoma and paraganglioma cases are likely to be sporadic, genetic studies have revealed that 25% of the patients that present as sporadic pheochromocytoma had a germ-line mutation in NF1, VHL, RET, succinate dehydrogenase subunit B (SDHB), SDHC, or SDHD (3).
The SDHB gene is located on chromosome 1p36.1-35 and codes a protein comprising part of the mitochondrial complex II. It is an important enzyme for the Krebs cycle and the electron-transport chain (3, 4). The Krebs cycle has gained attention in the field of tumor biology and has emerged as containing components that act to suppress tumors (6). The suppression or mutation of SDHB results in mitochondrial complex II destabilization and activates hypoxia-inducible factor 1α (HIF-1α), which regulates the expression of vascular mitogens, including vascular endothelial growth factor (VEGF), predisposes the patient to tumor genesis, and has a very strong association with malignant glioma (1, 2). Additionally, the malignant state and abdominal onset of sympathetic ganglion tumors (GISTs) and renal cell carcinomas (RCCs) (2, 3, 5).

We herein report the case of a 41-year-old man with a heterozygous germ-line SDHB mutation who had previously undergone surgery for an extra-adrenal pheochromocytoma at the age of 23 years, and who was diagnosed with an atypical meningioma on admission to our hospital. In addition, molecular genetic analyses from the isolated tumor showed a homozygous SDHB mutation.

**Case Report**

A 41-year-old patient developed gait disorder and hypertension. He had previously undergone surgery for a retroperitoneal tumor at 23 years of age, and the histological examination at that time revealed an extra-adrenal pheochromocytoma. Cervical magnetic resonance imaging (MRI) at the recent hospital visit revealed a tumor measuring 23×23 mm in the cervical spinal cord at the C6-7 intervertebral level, showing a hypointense signal on both the unenhanced T1- and T2-weighted images and a markedly enhanced image on gadolinium-enhanced MRI (Fig. 1). 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) indicated an increased FDG uptake (maximum standardized uptake value, 9.0) in the cervical tumor. A 24-h urine catecholamine assay was normal [adrenaline 14.5 μg/day (normal range, 3.0-41.0 μg/day), noradrenaline 150.1 μg/day (normal range, 31-160 μg/day), dopamine 799 μg/day (normal range, 280-1,100 μg/day), metanephrine 0.07 mg/day (normal range, 0.04-0.18 mg/day), and normetanephrine 0.14 mg/day (normal range, 0.10-0.28 mg/day)]. Additionally, the plasma catecholamine levels were within the normal ranges [adrenaline 0.03 ng/mL (normal range, ≤0.10 ng/mL), noradrenaline 0.18 ng/mL (normal range, 0.10-0.50 ng/mL), and dopamine <0.01 ng/mL (normal range, ≤0.03 ng/mL)]. These findings were distinct from the characteristics of metastatic pheochromocytomas or new onset of pheochromocytoma. We suspected from the imaging and endocrinological findings that the cervical tumor was a meningioma and thus performed surgical resection as the treatment methodology.

The isolated tumor measured 23×21×20 mm, thus showing a grayish-white color on the cut surface with no apparent metastasis of the spinal cord (Fig. 2A). According to a histological examination, the tumor was found to be composed of solid nests surrounded by fibrous septae associated with geographic coagulative necrosis (Fig. 2B). The tumor cells were polyhedral or spindle shaped and showed cheat-like growth (Fig. 2C). Furthermore, the nuclei were large in shape and showed eight mitoses per high-power fields. On the immunohistochemical examination, the tumor cells measured positive for epithelial membrane antigen (EMA) and S-100 protein, but negative for chromogranin A (Fig. 2E), synaptophysin (Fig. 2F), and CD56. The Ki-67 labeling index was approximately 60% (Fig. 2D). Based on...
these findings, the isolated cervical tumor was diagnosed as "atypical meningioma," grade II, according to the World Health Organization (WHO) criteria. Because the Ki-67 labeling index is identified to be an independent predictor of meningioma recurrence (9), this patient developed local recurrence and received reoperation and stereotactic radiosurgery two years after the first resection of the meningioma.

Although there was no family history of endocrine tumors, a germ-line mutation associated with inherited neoplasia syndromes was suspected, because the patient had previously experienced early-onset extra-adrenal pheochromocytoma and on this occasion developed a meningioma. A germ-line SDHB mutation is the most frequent cause of sporadic extra-pheochromocytoma in inherited neoplasia syndromes (2). NF1, VHL, MEN2, PGL1 and PGL3 mutations were considered to be less possible based on his family history and past illness. We thus performed a genetic analysis of the SDHB gene. We received the patient’s consent in writing to conduct the gene analysis of SDHB as approved by the ethics committee at Hiroshima University. The methods of genomic DNA sequencing are described in detail elsewhere (10). Briefly, DNA was extracted from the meningioma tissue, and exons 1 to 8, including the flanking regions of the SDHB gene, were amplified by polymerase chain reaction (PCR). For exons 1 to 8, specific primers were self-designed, and the direct sequencing of amplified SDHB products was performed. Molecular genetic analyses revealed a heterozygous germ-line SDHB mutation with an 11-nucleotide deletion in exon 4, c.305-315delCAATGAACATC (Fig. 3A). The mutated allele with a frameshift mutation of germ-line SDHB was identified in the isolated meningioma (Fig. 3A), and it appeared...
Figure 3. A: Direct sequence analysis of SDHB. A heterozygous germ-line SDHB mutation with an 11-nucleotide deletion in exon 4, c.305-315delCAATGAACATC, resulted in the identification of a frameshift mutation. From the sequence analysis of tumor DNA, it was apparent that the mutated allele, a frameshift mutation of germ-line SDHB, was in excess of the wild-type allele, indicating either the amplification of the mutated allele or loss of the wild-type allele. B: The amino acid sequence was hypothesized to be a frameshift p.A102EfsX12, with the DNA sequence around the mutation extensively conserved among species.

Discussion

The patient, who had a history of an extra-adrenal pheochromocytoma 18 years previously, presented with an atypical meningioma. A heterozygous germ-line SDHB mutation and homozygous SDHB mutation in the meningioma were identified in this patient.

Several cases of pheochromocytoma accompanied by meningioma have been previously reported (Table) (11-16). In these reports, however, there were no common clinical findings in respect to patient gender, age, or the site of onset of pheochromocytomas and meningiomas. The pathological findings in the present case indicated atypical meningioma; unfortunately, the details of the pathological findings in the other cases were not indicated. Although the causation of the other tumors may have been associated with inherited neoplasia syndromes, a molecular genetic analysis was performed only in our study, thereby leading to the identifica-
tion of the aforementioned SDHB mutation.

The SDHB mutation may have been associated with the development of the meningioma in our case because the genetic analysis showed a loss of heterozygosity and suggested truncated SDHB protein. The SDHB mutant enzyme in vitro confers hypersensitivity to oxidative stress, induces reactive oxygen species production, and increases mtDNA mutability (7). The knock-down of SDHB resulted in major impairments in cellular proliferation and induced upregulation of HIF-1α and HIF-2α (8). A characteristic cytogenetic alteration was identified in meningiomas on the short arm of chromosome 1 (1p) losses, where the SDHB gene is located (17). In addition, higher expressions of HIF-1α and VEGF suggest there to be a high risk of meningioma recurrence (18). Taken together, the meningioma as well as the pathogenesis of pheochromocytoma in our patient can both be explained by the dysregulation of SDHB expression. Furthermore, our case had high levels of Ki-67 expression and developed local recurrence. Based on the clinical course, pathological findings and the previous basic studies, the severity of meningioma may be induced by the SDHB mutation.

Whether a pheochromocytoma is benign or malignant cannot be determined on the basis of histological features alone (19). The diagnosis of a malignant pheochromocytoma is often made only after the occurrence of metastasis (20). Such metastases are detected most frequently in the bone, the liver, and the lungs and it can take as long as 20 years after the initial presentation for metastases to appear (21). Pheochromocytomas with inherited genetic mutations have the potential to relapse and develop into other malignant tumors (2-5, 21). Thus, it is important to make differential diagnoses for metastatic pheochromocytoma and other new onset tumors, such as meningioma, in order to determine strategies for treatment in pheochromocytoma patients with inherited genetic mutations.

In conclusion, our case with a heterozygous germ-line SDHB mutation, identified as a homozygous SDHB mutation, developed an atypical meningioma. Our findings indicate that mutant SDHB not only plays a role in the pathogenesis of pheochromocytoma but may also be involved in the development of meningioma. Therefore, a differential diagnosis for metastatic pheochromocytoma and other new onset tumors, including meningioma, especially in patients with germ-line SDHB mutation and a previous history of pheochromocytoma, should therefore be carefully carried out.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
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References

Table. The Clinical Characteristics of Previous and Our Cases with Pheochromocytoma Accompanied by Meningioma.

<table>
<thead>
<tr>
<th>Country and Gender</th>
<th>Pheochromocytoma Age at diagnosis and Site of onset</th>
<th>Meningioma Age at diagnosis and Site of onset</th>
<th>Gene mutation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Poland female</td>
<td>31 yrs retroperitoneum</td>
<td>54 yrs Meckel’s cavity</td>
<td>germline SDHC mutation</td>
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<tr>
<td>Sweden male</td>
<td>59 yrs left adrenal gland</td>
<td>59 yrs cerebral region</td>
<td>germline NF1 mutation</td>
<td>12)</td>
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<td>Israel male</td>
<td>47 yrs right abdominal</td>
<td>33 yrs left frontal cortex</td>
<td>no data</td>
<td>13)</td>
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<tr>
<td>Germany female</td>
<td>38 yrs left adrenal gland</td>
<td>29 yrs cerebral region</td>
<td>no data</td>
<td>14)</td>
</tr>
<tr>
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<td>57 yrs cerebral region</td>
<td>loss of heterozygosity of D1S7 in pheochromocytoma</td>
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<td>56 yrs Foramen magnum</td>
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<td>23 yrs retroperitoneum</td>
<td>41 yrs cervical region</td>
<td>germline SDHB mutation</td>
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