Case Report

Retroperitoneal Paraganglioma With Asymptomatic Follicular Lymphoma: A Case Report

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Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; GAPP, Grading system for Adrenal Pheochromocytoma and Paraganglioma; HIF, hypoxia-inducible factor; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PCC, pheochromocytoma; PET, positron emission tomography; PGL, paraganglioma; WES, whole exome sequencing; WHO, World Health Organization.

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Abstract

Paraganglioma (PGL) is a rare tumor originating from extra-adrenal paraganglionic chromaffin tissues, and most sympathetic PGLs have excessive catecholamine secretion. However, nonfunctional PGLs are sometimes found. Although malignant PGL is defined by metastasis to nonchromaffin tissues, it is difficult to predict malignancies due to the lack of reliable markers of potential malignancies. We report the case of a 69-year-old Japanese woman with an incidental retroperitoneal tumor and multiple enlarged mesenteric lymph nodes simultaneously. The patient had no subjective symptoms and there were no laboratory findings suggesting catecholamine hypersecretion. Both the retroperitoneal tumor and the enlarged mesenteric lymph nodes showed high accumulation of fluorodeoxyglucose (FDG), whereas metaiodobenzylguanidine (MIBG) was accumulated only at the retroperitoneal tumor. Although a retroperitoneal tumor was diagnosed as nonfunctional PGL by examination including MIBG scintigraphy, the cause of enlarged mesenteric lymph nodes could not be diagnosed by imaging and biochemical tests. As a result of retroperitoneal tumor resection and mesenteric lymph nodes sampling, histopathological examination revealed that a retroperitoneal tumor was PGL and enlarged mesenteric lymph nodes were follicular lymphoma. To reveal an underlying genetic factor, we performed whole exome sequencing of genomic DNA, and we identified 2 possible candidate variants in SDHD and DLST, but the pathogenicity of these
variants remains uncertain in the present case. This rare case reinforces the importance of histopathological diagnosis of nonchromaffin tissue lesions in patients with PGL for the appropriate treatment strategy.

Key Words: paraganglioma, follicular lymphoma, succinate dehydrogenase D subunit (SDHD) gene, dihydrolipoamide S-succinytranferase (DLST) gene

Paraganglioma (PGL) is a rare catecholamine-secreting tumor originating from extra-adrenal paraganglionic chromaffin tissues [1]. Most PGLs that occur outside the skull base and neck are of sympathetic origin and have excessive catecholamine secretion, predominantly noradrenaline [2]. According to the World Health Organization (WHO) classification in 2017, all pheochromocytomas (PCCs) and PGLs have a malignant potential [3]. Malignant PGL is defined by metastasis to nonchromaffin tissue, such as lymph nodes, bones, liver, and lung, and approximately 15% of all PCCs/ PGLs develop metastatic disease [4]. It is difficult to predict malignancy in patients with primary PGL without metastases because there are no reliable markers of potential malignancy.

Here, we report the case of a patient with simultaneous detection of abdominal PGL and mesenteric malignant lymphoma. Although metastasis of PGL to the mesenteric lymph nodes could not be ruled out by imaging and biochemical tests, pathological examination revealed that these were separate diseases, and we were able to select the appropriate treatment strategy.

Case Presentation

A 69-year-old Japanese woman presented to the hospital with developing varicose veins in her lower extremities. There was no apparent family history of endocrinial diseases. She had taken only pravastatin for dyslipidemia. A computed tomography scan of the abdomen incidentally revealed a 25-mm hypervascular retroperitoneal tumor and multiple enlarged mesenteric lymph nodes (Fig. 1A and 1B).

She was 167 cm in height and 49.9 kg in weight, with a body mass index of 17.9 kg/m^2. Her blood pressure and pulse rate were within normal range (120/68 mmHg and 67 beats per minute). There were no obvious clinical symptoms suggesting catecholamine hypersecretion, such as headache, palpitation, hyperhidrosis, and weight loss. Laboratory findings, including plasma catecholamine and urinary catecholamine metabolites were all in the normal range (plasma: adrenaline 30 pg/mL, noradrenaline 178 pg/mL, dopamine 9 pg/mL; urinary: metanephrine 0.08 mg/day, normetanephrine 0.17 mg/day). T2-weighted magnetic resonance imaging (MRI) did not depict the fat in this tumor (Fig. 1C and 1D). Metaiodobenzylguanidine (MIBG) scintigraphy revealed strong accumulation at the retroperitoneal tumor, whereas no accumulation at enlarged mesenteric lymph nodes. Both a retroperitoneal tumor and the enlarged mesenteric lymph nodes showed high accumulation of fluorodeoxyglucose (FDG) on positron emission tomography (PET– computed tomography (CT) (Fig. 1E and 1F). Malignant disease of the intestinal tract was negative by upper and lower endoscopy, and malignant lymphoma was not strongly suspected because the soluble interleukin-2 receptor was in the normal range. From these results, excluding mesenteric lymph node metastasis of nonfunctional PGL originating from the retroperitoneum was not possible without confirming the histology. Therefore, retroperitoneal tumor resection and mesenteric lymph nodes sampling were performed under laparotomy.

Immunohistochemical staining results of enlarged mesenteric lymph nodes showed CD3 (−), CD20 (+), BCL2 (+), CD21 (+), CD23 (+), Ki67 (<10%), CD10 (+), BCL6 (+), and cyclin D1 (−) (Fig. 2). These findings support the definitive diagnosis of follicular lymphoma, WHO grade 1, whereas the pathological findings of the retroperitoneal tumor showed tumor cells with abundant vesicles exhibited nesting pattern (zellballen pattern). Immunohistochemical staining was positive for chromogranin A and synaptophysin (Fig. 3A and 3B). These findings were consistent with PGL. Additionally, the Ki-67 labeling index was less than 1%. According to the Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP), the tumor’s score was 3 (high cellularity and capsular invasion), indicating a moderately differentiated tumor. Additional immunostaining of SDHB was performed, and it was confirmed that the immunoreactivity in tumor cells was not reduced (Fig. 3C). Since PGL was resected without residual and follicular lymphoma was of low grade, we decided to carefully follow up for recurrence or exacerbation of both.

Molecular Studies

To reveal an underlying genetic factor, we performed whole exome sequencing (WES) of genomic DNA. After receiving written informed consent, peripheral blood sample was
obtained from the patient and genomic DNA was extracted. WES was performed by Macrogen Japan Corp. (Kyoto, Japan) using the SureSelectXT Human All Exon v6 (Agilent Technologies, Santa Clara, CA). The libraries were sequenced using Illumina NovaSeq6000 (Illumina, San Diego, CA) with 151-base paired-end reads. Sequence reads were aligned to Genome Reference Consortium Human Build 38 (GRCh38) using the Burrows-Wheeler Aligner (Version 0.7.17) with default parameters. Removal of duplicated reads (MarkDuplicatesSpark) and base quality recalibration (BaseRecalibrator and ApplyBQSR) were performed by GATK Version 4.1.9.0. Variants were identified with the GATK HaplotypeCaller, and raw variants were filtered out when their parameters meet either of the following values: QD < 2.0, MQ < 30.0, FS > 60.0, MQRankSum < −12.5, and ReadPosRankSum < −8.0 for single nucleotide variants, and QD < 2.0, ReadPosRankSum < −20.0 and FS > 200.0 for insertion/deletions. Final variants were annotated with AnnoVar [5] for predictive value of functional impact of the coding variants and assessing allele frequency: in-house database of 218 control exomes, human genetic variation

Figure 1. Radiological findings of the lesion. Contrast-enhanced CT showed a hypervascular retroperitoneal tumor (A, yellow arrow) and multiple enlarged mesenteric lymph nodes (B, blue arrow). T2-weighted MRI revealed a high intensity retroperitoneal tumor on the left dorsal side of the inferior vena cava (C), and chemical shift MRI did not depict the fat in this tumor (D). MIBG scintigraphy revealed strong accumulation in the retroperitoneal tumor, but not in enlarged mesenteric lymph nodes (E). Both a retroperitoneal tumor and the enlarged mesenteric lymph nodes showed high FDG accumulation on PET-CT (F).
database (http://www.hgvd.genome.med.kyoto-u.ac.jp/) [6], the Integrative Japanese Genome Variation Database (8.3KJPN, https://ijgvd.megabank.tohoku.ac.jp/) [7], and the Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/) [8]. Variant pathogenicity was predicted by SIFT, Polyphen-2, CADD [9], and M-CAP [10]. Nucleotide conservation prediction was performed using GERP (http://mendel.stanford.edu/SidowLab/downloads/GERP/index.html) and PhastCons (http://compgen.cshl.edu/phast/). Candidate variants were confirmed by Sanger sequencing using ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA).

Using the WES data, we searched for possible pathogenic variants in 19 causative genes for pheochromocytoma (NF1, RET, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX, KIF1B, PHD2, HRAS, FH, MDH2, EGLN1, EGLN2, SLC25A11, and DLST) and identified 2 possible candidate variants in SDHD (NM_003002.3: c.255G>T, p.[Leu85Phe]) and DLST (NM_001933.4:c.304G>C, p.[Val102Leu]). The c.255G>T variant in SDHD was registered in gnomAD with low allele frequency (0.0001183) and ClinVar (VCV000135198.3) as variant with conflicting interpretations of pathogenicity. Meanwhile, the c.304G>C variant in DLST was not registered in gnomAD and had not been previously reported. Both variants were also not registered in some somatic variant databases including COSMIC, OncoKB, and TCGA. Although both variants were evolutionarily conserved and their pathogenicity was predicted to be deleterious by in silico prediction tools, they were classified as uncertain significance according to the American College of Medical Genetics Standards and Guidelines (Table 1).

**Discussion**

We have encountered a case that developed abdominal PGL and mesenteric malignant lymphoma simultaneously. She did not present any obvious clinical symptoms of catecholamine hypersecretion because her plasma catecholamine levels were within normal limits. PGLs localized in the periaortic and pericaval have been reported to secrete catecholamines at a high frequency (17 of 17 tumors) [2], so we did not positively suspect that the pericaval tumor in this case was PGL. Additionally, due to the different accumulation pattern of MIBG and FDG, it was difficult to reach definitive diagnoses of retroperitoneal tumor and enlarged mesenteric lymph nodes without pathological findings.

When PGL metastasizes to lymph nodes, which are nonchromaffin tissues, it is diagnosed as malignant. After diagnosis of malignant PGL, multidisciplinary treatment...
including systemic chemotherapy needs to be considered [11]. Therefore, when a mass lesion of nonchromaffin tissue is found in a PGL patient, it is important to distinguish whether it is a metastasis of PGL. It has been reported that 18F-FDG PET is more sensitive than 123I-MIBG scintigraphy for metastatic lesions of PCCs and PGLs [12]. In the present case, excluding the lymph node lesions from being PGL metastasis was not possible from the imaging findings since FDG accumulation was positive, so pathological diagnosis was judged to be essential for the detailed examination of multiple enlarged lymph nodes.

The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) has long been used in the histopathological diagnosis of PCCs and PGLs, but PASS is no longer recommended for assessment of malignancy potential due to the large variation among observers [13, 14]. Kimura et al. recently proposed another scoring system, GAPP, for assessment of malignancy potential of PCCs and PGLs [15]. This GAPP system used both histological parameters and catecholamine type for scoring. According to this system, PCCs and PGLs were classified into 3 degrees of differentiation, which has been shown to correlate with survival rate. The PGL in the present case was classified to moderately differentiated based on the GAPP system, so it is not sure to be of a benign clinical course, according to a recent meta-analysis [16]. Thus, we consider that it is important to carefully follow up for recurrence of PGL.

Although the majority of PGLs have been thought to be sporadic, in recent years it has been shown that about one-third to one-half of PGLs are associated with hereditary syndromes [17, 18]. In this case, we identified 2 possible candidate variants in SDHD and DLST. The SDHD gene encodes a subunit of succinate dehydrogenase present in mitochondria. The SDHD gene mutations are associated with familial PCCs and PGLs, especially head and neck PGL [19, 20]. Mutations of SDHD gene lead to overaccumulation of hypoxia inducible factor (HIF) via succinic acid accumulation, followed by promotes angiogenesis and cell proliferation. In recent study, HIF1 is reported to play a dominant role in follicular B-cell maturation and mediate cell growth and aggressive clinical behavior in lymphatic neoplasia [21]. This raises a possibility that pseudohypoxic genomic mutation may lead to hematological malignancy. DLST is a subunit enzyme of the α-ketoglutarate dehydrogenase complex of the Krebs cycle in the mitochondrial matrix. In a previous report, DLST mutations have been identified in cases with PCCs and PGLs, and the mechanism of tumorigenesis is speculated to be associated with the DLST functional abrogation and pseudohypoxia [22]. Though both genes are highly associated with PCCs and PGLs, the pathogenicity of these variants remains uncertain in this case. However, it has been reported that SDHB, C, or D mutated cases display SDHB immunonegativity [23, 24], and the SDHB immunostaining in PGL of this case was positive, so it has been suggested that the pathogenicity of the SDHD variant in this case is low. Meanwhile, 28 gene mutations, including 8 germline mutations, have been reported in follicular lymphoma [25], but no candidate mutations were detected among those genes. Even in the detailed literature discussion on the genetic etiology of follicular lymphoma, variants that may be also associated with the etiology of PCC/PGL have not been reported [26]. From the perspective of the complication of PGL and follicular lymphoma, a case of simultaneous diagnosis of SDHB gene mutation-positive PGL and follicular lymphoma have been reported in the past [27]. No clinically significant SDHB gene mutation was found in the present case, but a recent study also has presented the association between SDHx mutation with lymphoid malignancies [28]. We think that the causal relationship between PGL and follicular lymphoma, and the pathogenic involvement of gene mutations, will need to be investigated after the accumulation of cases.
Conclusion

We experienced a rare case in which asymptomatic abdominal PGL and primary mesenteric malignant lymphoma were found at the same time. When patients with PGL have nonchromaffin tissue lesions, it is important to determine an appropriate treatment strategy through histopathological diagnosis.

Additional Information

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**Data Availability:** The data sets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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