A Case of von Hippel-Lindau Disease with Bilateral Pheochromocytoma, Renal Cell Carcinoma, Pelvic Tumor, Spinal Hemangioblastoma and Primary Hyperparathyroidism

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Abstract. A rare case of von Hippel-Lindau (VHL) disease with bilateral pheochromocytomas, right renal cell carcinoma, right pelvic carcinoma, spinal hemangioblastoma and primary hyperparathyroidism is described. A 78-year-old woman had a history of hypertension from her forties. She suffered from headache and body weight loss. Abdominal CT revealed bilateral adrenal tumors and right external renal tumors enhanced in early stage. MIBG scintigraphy exhibited a high accumulation of tracer in both adrenal glands. On the basis of the radiographic findings and endocrinological results, the patient was diagnosed as having bilateral pheochromocytomas and right renal cell carcinoma. A bilateral adrenalectomy was performed, followed by surgery for resection of the renal cell carcinoma. The other resected right kidney showed a clear cell subtype that was determined to be renal cell carcinoma, and proved that the pelvic tumor was transient cell carcinoma. Spinal MRI showed spinal hemangioblastoma. von Hippel-Lindau (VHL) gene mutation for the patient was found. We diagnosed the patient as VHL because of the existence of spinal hemangioma and a VHL disease gene. Parathyroid echo revealed a hypoechoic space on the back of the left lobe, and serum calcium and intact PTH to be elevated. The patient was diagnosed as primary hyperparathyroidism. We report the first case of a patient with VHL disease complicated with bilateral pheochromocytomas, right renal cell carcinoma, right renal pelvic carcinoma and primary hyperparathyroidism. The life expectancy of affected individuals has been less than 50 years. Since the prognosis may be improved by an early diagnosis, affected individuals with VHL complexes should undergo cranial, spinal MRI and abdomen CT. The families may benefit from presymptomatic detection of affected gene carriers and the exclusion of at-risk family members by negative test results.

Key words: von Hippel-Lindau disease, Renal cell carcinoma, Pelvic carcinoma, Pheochromocytoma, Primary hyperparathyroidism

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VON HIPPEL-LINDAU (VHL) DISEASE is an autosomal dominant familial cancer syndrome predis-

posing to a variety of benign and malignant neoplasms, including hemangioblastoma of the retina (retinal angiomas), of the cerebellum (Lindau tumor), of the medulla oblongata, and of the spinal cord; angiomas of the liver and kidney; adenomas of the kidney and epididymis; tumors and cysts of the pancreas, kidney, and epididymis [1–3]. The identification of the VHL disease gene has provided the opportunity to develop a molecular genetic diagnosis

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for VHL disease by direct mutation analysis [4, 5]. Furthermore, VHL disease complicated by pheochromocytomas and renal cell carcinoma [6] and its relation with RET gene are also of interest [7, 8]. We report here the case of a patient with VHL disease complicated with bilateral pheochromocytomas, right renal cell carcinoma, right pelvic carcinoma and primary hyperparathyroidism.

Case report

A 78-year-old woman was followed up at another hospital with a 3-year history of unstable blood pressure, headache and chest oppression. Her medical history revealed that she had been suffering from hypertension for 35 years. She underwent abdominal dynamic CT examination due to loss of body weight, general fatigue and loss of appetite. Abdominal CT revealed bilateral adrenal tumors and right external renal tumors enhanced in early stage (Fig. 1). In September 1996, she was admitted to our hospital for the purpose of searching the relationship between adrenal tumors and hypertension.

On admission, she was 156.4 cm in height and weight 55 kg. Her blood pressure was 136/80 mmHg, pulse rate was 84 beats per minute with a regular rhythm, and body temperature was 36.6°C. There were no abnormal findings upon the face, chest, abdomen and in neurological examinations. Laboratory findings on admission revealed that urine and peripheral blood cells were normal. Routine biochemi-

cal tests were normal. Endocrinological examinations revealed the following: plasma adrenaline, 30 pg/ml (normal: <100 pg/ml); plasma noradrenaline, 1906 pg/ml (100–450 pg/ml); plasma dopamine, 11 pg/ml (<20 pg/ml), and urinary vanillylmandelic acid, 5.47 mg/day (1.5–4.5 mg/day). Other adrenal functions and thyroid functions were normal. The serum calcitonin and CEA were also normal. Intact PTH was 56.1 pg/ml (6.5–59.7 pg/ml). Urinal cytology was class V (transient cell carcinoma). Subsequent MRI examination revealed bilateral adrenal tumors and right external renal tumors demonstrated with Gd-DTPA on T1-weighted image. MIBG scintigraphy exhibited a high accumulation of tracer in both adrenal glands (Fig. 2). On the basis of the radiographic findings and endocrinological results, we diagnosed the patient as having bilateral pheochromocytomas and right renal cell carcinoma. A bilateral adrenalectomy was performed, followed by surgery for resection of the renal cell carcinoma (RCC) (Fig. 3). Histologically, the resected right kidney showed a clear cell subtype that was determined to be RCC (G2, INF α , pT2), and proved the pelvic tumor to be transient cell carcinoma (G3, INF α , pT3, pR0, pL2, pV0, pN0); there was no transition between renal cell carcinoma and transitional cell carcinoma (Fig. 4A, 4B). On the other hand, the nodular lesions of both adrenal glands were composed of a proliferation of polygonal tumor cells having cytoplasm arranged in nests, showing a Zellballen appearance, bound by a delicate fibrovascular stroma, without convincing evidence of malign-

Fig. 1. Abdominal CT scan of the patient. A: Plain CT showed bilateral adrenal tumors (right mass is 3 cm and left is 2 cm in diameter). B: Enhanced CT showed external renal tumors enhanced in early stage.

A

B

Fig. 2. Subsequent MRI showed bilateral adrenal tumors and right external renal tumors demonstrated with Gd-DTPA on T1-weighted image in early stage. MIBG scintigraphy exhibited a high accumulation of tracer in both adrenal glands.

Fig. 3. A, B: Bilateral adrenal tumors. A is right pheochromocytoma. B is left. C is the renal cell carcinoma (RCC). D showed transient cell carcinoma (TCC) in contact with RCC.

nancy, with most of the tumor cells being positive for chromogranin A (Fig. 4C, 4D). Replacement therapy with hydrocortisone (100 mg/day) was initiated after surgery. After the adrenalectomy the blood pressure was transiently lowered, because the blood pressure had remained at the preoperative value about 1 month later.

In November 1996, fundoscopy did not show vascular abnormalities of the retina. However, as we suspected that the patient had VHL disease, we ordered spinal and head MRI. Although head MRI was normal, spinal MRI revealed an enhancement in ural sac between L1 and L2 (Fig. 5). It showed spinal hemangioblastoma, and therefore we analyzed the patient's VHL gene. PCR-SSCP analysis of the VHL gene for the patient revealed in one case a variant in exon 1 that was caused by a transition A⁵⁰⁶→G in codon 98, resulting in Tyr²⁹³→Cys (Fig. 6). Finally we diagnosed the patient as VHL because of the existence of spinal hemangioma and a VHL disease gene.

In June 1998, though she did not have any complaints and symptoms, her serum calcium had slightly elevated (10.7 mg/ml) and serum IP had decreased (2.4 mg/ml). Although %TRP was 85.7%, Fe_{Ca} was 0.026 and intact PTH was elevated (107.1 pg/ml). Plasma intact PTH level was high despite high serum calcium, indicating the existence of primary hyperparathyroidism. However, parathyroid echo and scintigraphy revealed no evidence of primary hyperparathyroidism, so she was followed up without surgery. In January 2000, follow-up parathyroid echo

Fig. 4. The resected right kidney showed a clear cell subtype to be renal cell carcinoma (A), and proved the pelvic tumor to be transient cell carcinoma (B). The resected adrenal tumors proved to be pheochromocytomas composed of trabecular proliferation of polymorphic cells with chromaffin granules but with no malignant findings.

Fig. 5. Spinal MRI revealed an enhancement in the ural sac between L1 and L2. It showed spinal hemangioblastoma.

Fig. 6. PCR-SSCP analysis of the VHL gene of the patient. One case showed a variant in exon 1 that was caused by a transition A⁵⁰⁶→G in codon 98, resulting in Tyr²⁹³→Cys.

revealed a hypoechoic space on the back of the left lobe (Fig. 7). Her serum calcium was still elevated (10.9 mg/ml), serum IP was decreased (2.3 mg/ml), and intact PTH was 135.4 pg/ml (6.5–59.7 pg/ml). PTHrP and renal function were normal. She was di-

Fig. 7. Parathyroid echo showed a hypoechoic space on the back of the left lobe.

agnosed as having primary hyperparathyroidism. She underwent an operation to resect the left para-

thyroid. Histologically, the resected parathyroid proved to be adenomatous, because it showed a proliferation of predominant chief cells in alveolar nests on follicular structures, supported by fibrovascular stroma. After the parathyroidectomy the serum calcium and intact PTH were transiently lowered, about 1 month after the surgery the serum calcium still remained at the preoperative value. Clinical course is shown in Fig. 8. As we suspected the coexistence of pheochromocytomas and parathyroid adenoma, we analyzed the RET gene. The RET gene was normal.

Discussion

von Hippel-Lindau disease is a dominantly inherited familial cancer syndrome predisposing to a variety of malignant and benign neoplasms, most frequently retinal, cerebellar and spinal hemangioblastomas, renal cell carcinoma (RCC), pheochromocytoma and pancreatic tumors. It has been reported that there are three phenotypes in VHL [9, 10]. The three groups are type 1 (hemangioblastoma), type 2A (hemangioblastoma + pheochromocytoma) and type 2B

Fig. 8. Clinical course of the blood pressure, serum Ca and intact-PTH concentration.

(hemangioblastoma + pheochromocytoma + renal cell carcinoma). This case was regarded as type 2B. Although aging is considered as an important factor of phenotype, the relationship between genotype and phenotype has been determined definitely [9, 10].

William *et al.* reported [11] that cerebellar hemangioblastoma was the source of the initial symptom in 20 (40%) of 50 affected individuals, followed by retinal angiomas in eight (16%) of 50 and renal cell carcinoma in five (10%) of 50. Twelve of the 50 affected individuals were asymptomatic, ten of whom had retinal angiomas and two of whom were found to have renal cell carcinoma. In this case, we detected almost concurrently bilateral pheochromocytomas, renal cell carcinoma and spinal hemangioblastoma. As this patient had been suffering from hypertension for 35 years, bilateral pheochromocytomas may have existed for a long time. It is reported that bilateral adrenal tumors producing catecholamines are usually associated with hyperplasia of adrenal medulla. However, the histological findings in this case were consistent with pheochromocytoma, and similar findings were reported in most of the previous cases of VHL. Furthermore, this case was complicated with RCC. RCC is found in 40% to 70% of the VHL patients [12]. Choyke *et al.* have shown that renal lesions in VHL patients can be divided into three different forms [13]: cystic lesions (found in up to 76% of patients with VHL [14]), cystic-solid lesions, in which the solid (malignant) component gradually increases, and solid malignant lesions. Periodic screening is very important, because, when discovered as a result of symptoms, 30% to 50% of renal lesions have already metastasized to lymph nodes, liver, bone, lung, or brain. Fortunately, there was no metastatic lesion in this patient.

Because transitional cell carcinoma was separated from RCC in this case, it was considered that both appeared spontaneously. RCC complicated with transitional cell carcinoma is very rare. Only 27 cases of RCC with renal pelvic carcinoma have been reported over the last 79 years since 1922 [15–17]. However, a case of VHL complicated with RCC and renal pelvic carcinoma (transitional cell carcinoma) has never been reported. This is the first case of a patient with VHL disease complicated with bilateral pheochromocytomas, right renal cell carcinoma and right renal pelvic.

VHL is a hereditary disease of autosomal domi-

nant form with chromosome abnormalities of 3p25~26 [18]. The VHL gene coding sequence contains the three exons, and two isoforms of mRNA exist, reflecting the presence or absence of exon 2. Tumors arise after the loss of inactivation of the wild type allele in a cell. About 20% of patients have large germline mutations detectable by Southern blot analysis, 27% have missense mutations, and 27% have nonsense or frame shift mutations. In about 20% of VHL families no deletion or mutation can be detected. Families may be characterized by the presence (type 2: 7% to 20% of families) or absence (type 1) of pheochromocytomas. Most type 2 families have missense mutations, whereas most type 1 families are affected by deletions or premature termination mutations [12]. In this patient, a significant mutation can be identified, allowing confirmation of the diagnosis. On the other hand, this case is very interesting, because VHL disease with primary hyperparathyroidism has never been reported. It is not clear whether there is a relationship between VHL and primary hyperparathyroidism. However, as the patient had involved with pheochromocytomas and primary hyperparathyroidism, we suspected that she had multiple endocrine neoplasia type 2a (MEN 2a) [7, 8]. Allele-specific variation in predisposition to pheochromocytoma has also been reported in MEN 2 missense mutations at codon 634 in the ret proto-oncogene which are strongly associated with pheochromocytoma [19]. However, the mechanism of tumorigenesis in MEN 2 and VHL disease differ. Tumors in VHL disease patients, including pheochromocytoma, show chromosome 3p allele loss and the mechanism of tumorigenesis appears similar to that in retinoblastoma [20]. In contrast, MEN 2 mutations in the ret proto-oncogene appear to be activating mutations. In this patient thyroid medullary carcinoma was not found and the RET gene was wild type, so we concluded that MEN 2a could be ruled out. In transitional cell carcinoma, abnormalities of VHL gene have been never reported. Abnormalities in Menin (11q13) [15, 21], HRPT2 (1q25–31) [22] and PRAD1 [23] were reported in familial or sporadic parathyroid adenoma. It is said that losses of material from chromosome 9, 11p, 8p, 4p and 17p or, gains of 8p and 1q were linked with transitional cell carcinoma [24]. Although we could not investigate these abnormalities, other gene abnormalities such as those mentioned above may exist in this case.

In conclusion, we report the rare case of a patient with VHL disease complicated with bilateral pheochromocytomas, right renal cell carcinoma and right renal pelvic carcinoma and primary hyperparathyroidism. This is an interesting case in that it is related to gene abnormalities and tumor genesis. In earlier studies the most common causes of death were complications of cerebellar hemangioblastoma (53%) and metastatic RCC (32%) [25]. The life expectancy

of affected individuals has been less than 50 years. Since the prognosis may be improved by an earlier diagnosis, affected individuals with VHL complexes should have a cranial and spinal MRI, and an abdominal CT. Furthermore, the families may benefit from presymptomatic detection of affected gene carriers and the exclusion of at-risk family members by negative test results.

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