A Case of Von Hippel-Lindau Disease Presented with Multiple Pancreatic Cysts and Medullary Hemangioblastoma

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Von Hippel-Lindau (VHL) disease is a rare inherited cancer predisposition syndrome characterized by benign and malignant tumors in multiple organs, especially cerebellar hemangioblastomas, retinal angiomas, renal-cell carcinoma, and pheochromocytomas. Clinically, VHL disease also presents an increased risk for developing multiple visceral cysts in the pancreas, liver, and kidneys. Regular surveillance for VHL disease-associated tumors after early diagnosis is necessary for better outcomes in VHL disease. An 11-year-old girl was admitted with prolonged fever lasting for more than 10 days and cervical lymphadenopathy. She did not have a family history of cysts or malignancy. Initial blood tests showed mild leukopenia and moderate elevation in aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase, but with normal amylase and lipase. Hepatobiliary ultrasonography and magnetic resonance cholangiopancreatography were done and revealed multiple cysts involving the whole pancreas with cyst sizes up to 1.6 cm, indicating VHL disease. Direct sequencing of the VHL gene showed a heterozygous duplication at codon 384 (c.384dup), which is predicted to cause a frameshift of the reading frame (p.Leu129Serfs*3). This was a novel pathogenic variant VHL gene. We carried out the surveillance protocol for VHL disease-associated tumors, and found a hemangioblastoma in the medulla of the brainstem. We are reporting an 11-year-old female patient of VHL disease with brainstem hemangioblastoma who could be suspected and diagnosed of VHL disease in asymptomatic state due to incidentally found multiple pancreatic cysts.

Key Words: Von Hippel-Lindau disease, Pancreatic cyst, Hemangioblastoma

Introduction

Von Hippel-Lindau (VHL) disease is a rare autosomal dominantly inherited familial cancer-predisposition syndrome with an incidence of 1 in 36,000 live births. VHL disease is caused by a germline mutation of VHL tumor-suppression gene located on chromosome 3p25-26 [1]. The VHL gene mutation predisposes patients to development of multiple cysts and tumors in various organs [2]. The most commonly reported cysts and tumors in VHL disease are cerebellar and spinal hemangioblastomas (HBs, 60-80%), retinal angiomas or capillary HBs, pancreatic neuroendocrine tumors (PNETs, 20%), pancreatic cysts (75%), clear-cell renal-cell carcinoma (RCC, 24-45%), renal cysts (38%), pheochromocytoma (20%), and endolymphatic sac tumors (ELSTs, 10-15%) [2-5]. Cerebellar HB usually presents at early adulthood and causes in-
creased intracranial pressure, and spinal cord HB causes proprioception abnormalities and disturbances of gait and bladder function. Approximately 25% of VHL disease with cerebellar HBs also have retinal angiomas, which can cause retinal detachments and loss of visual acuity. Although central nervous system (CNS) and retinal HBs contribute to morbidity, RCCs are the most common cause of death, causing 50% of death in VHL disease [5].

Although 80% of VHL disease are autosomal dominantly inherited from an affected parent, 20% of VHL disease cases are a de novo gene mutation without family history [6]. VHL disease-associated tumors usually present clinically in early adulthood, third to fourth decade, and more than 90% of penetrance is presented by the age of 65 [7,8]. Early diagnosis of VHL disease and regular follow-up with appropriate evaluations according to surveillance guidelines for VHL disease are necessary to identify pathologic lesions that may be treated at an early stage [5].

Herein, we are reporting a genetically confirmed case of VHL disease with brainstem HB in an 11-year-old girl without a family history who could be suspected and diagnosed of VHL disease in asymptomatic state due to incidentally found multiple pancreatic cysts.

**Case Report**

An 11-year-old girl was admitted with prolonged fever lasting for more than 10 days, sore throat, and cervical lymphadenopathy. She did not have a past medical history of admission or family history of cysts or malignancy.

On admission, she had a fever (temperature up to 38.5°C), and physical examination showed throat injection with palatine tonsillar hypertrophy, multiple cervical lymph-node enlargement on both neck levels II and III with a size smaller than 1.5 cm. Other physical examination findings including a neurologic examination were normal.

Initial CBC showed WBC 3,750/µL, Hb 13.7 g/dL, platelet 293,000/µL, absolute neutrophil count 2.088/µL, revealing mild leukopenia. Blood chemistry showed elevation in liver enzymes, including aspartate aminotransferase (AST, 111 IU/L), alanine aminotransferase (ALT, 208 IU/L), and lactate dehydrogenase (LDH, 412 IU/L), but amylase (75 U/L) and lipase (16 U/L) were normal. For the work-up of fever and hepatitis, C-reactive protein and cultures in blood, urine, cerebrospinal fluid, and throat were all negative. Virus studies and immunologic studies yielded negative results.

Neck ultrasonography (USG) was done for cervical lymph-node enlargement, and she was diagnosed as having benign reactive cervical lymphadenitis. Hepatobiliary USG was done, and multiple pancreatic cysts and mild fatty liver were observed (Fig. 1). For further evaluation of the pancreatic cysts, we did magnetic resonance cholangiopancreatography (MRCP), which showed multiple cystic lesions involving the whole pancreas, with cyst sizes up to 1.6 cm, but no neuroendocrine tumors of the pancreas, other tumors, or renal cysts were observed (Fig. 2). The MRCP finding implied an association of a genetic disorder, such as VHL disease. Therefore, VHL tumor-suppressor gene direct sequencing analysis and related tumor markers, including serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) studies were performed. Her CEA and CA 19-9 level were normal. Sequence analysis for the VHL gene showed heterozygous for duplication at codon 384 (c.384dup) in exon 2 of the VHL gene on chromosome 3p25.3, which is predicted to cause a frameshift of the reading frame (p.Leu129Serfs*3) (Fig. 3). This variant was assessed as a novel pathogenic variant based on the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines: PVS1 (a frameshift variant that leads to a truncated protein) and PM2 (absent from controls in the Exome Aggregation Consortium and Genome Aggregation Database), and PP4 (highly specific patient phenotype) [9].

The fever subsided after 16 days, and a follow-up laboratory examination showed improvement in leukopenia, AST, ALT, and LDH level before discharge on the 9th day of hospitalization, which was finally normalized 4 months later at our outpatient clinic. After genetic confirmation as VHL disease, we did sur-
Fig. 1. Hepatobiliary ultrasonography showing (A) mild fatty liver with possibly focal fat sparing zones and (B-D) a few anechoic lesions in pancreas, size up to 1.4 cm, implicating multiple pancreatic cysts (arrows).

Fig. 2. Magnetic resonance cholangiopancreatography (MRCP) showing multiple cystic lesions involving whole pancreas, with cyst size up to 1.6 cm, without definite evidence of mural nodule or direct communication of the main pancreatic duct (arrow). This MRCP finding of multiple pancreatic cysts implicates the association of genetic disorder such as von Hippel-Lindau disease in this patient. There were no anatomical variation of biliary tree or cysts in both kidneys.

Discussion

The VHL gene is a tumor-suppressor gene located on chromosome 3p25-26, which is composed of 3 exons encoding 2 isoforms of protein, pVHL [5,10]. VHL disease is classified as type 1 and type 2 with different genotype-phenotype manifestation. Type 1 VHL results from a loss-of-function mutation, such as truncation mutation of the VHL gene, and is characterized by rare development of pheochromocytoma. Type 2 VHL results from a missense mutation of the VHL gene and is characterized by development of pheochromocytoma. Type 2 VHL is further subdivided into type 2A VHL without RCC development, type 2B VHL with RCC development, and type 2C VHL with only pheochromocytoma development. From the VHL gene mutation type, our case with a truncation mutation of the VHL gene can be classified as type 1 VHL [11].

The mean age of initial tumor diagnosis in VHL disease is 26 years (range 1-70 years) [7], but different tumors develop typically at different mean ages. Cerebellar HBs are diagnosed in the 3rd decade (at a mean age of 29 years), and brainstem and spinal HBs develop rarely in year and considered surgical excision if symptoms developed or size of the HB increases.
the younger population (less than 40 years of age), but in multiple location. RCCs are diagnosed in the 4th decade, but can be as early as at 16 years of age, presenting with hematuria, flank pain, or a palpable mass. Pheochromocytomas are diagnosed at a mean age of 28 years, presenting with secondary hypertension or stroke. Pancreatic lesions in VHL disease are diverse, including simple cysts within pancreatic parenchyma, serous cystadenomas, and PNETs. Simple pancreatic cysts are benign and typically asymptomatic, but surgical treatment is indicated when they are symptomatic because of compression or obstruction.

Surveillance guidelines have been developed by the VHL disease Family Alliance and are recommended for VHL disease patients diagnosed by VHL gene analysis and for patients’ family members who have not undergone VHL gene analysis. In individuals diagnosed with the VHL gene mutation, there should be a yearly assessment of neurologic status, visual acuity and ophthalmologic status, hearing, and blood pressure. After the age of 5 years, there should be laboratory screening for pheochromocytoma every year, hearing evaluation every 2 years, and contrast-enhanced MRI for CNS and spine every 2 years. Contrast-enhanced MRI for CNS with thin cuts of the internal auditory canal is necessary to evaluate the ELST for symptomatic patients. After the age of 16 years, there should be abdominal USG yearly to identify visceral lesions, and MRI of the abdomen and entire neural axis every 2 years.

Our patient could be suspected and genetically diagnosed as VHL disease because of incidentally found multiple pancreatic cysts by abdominal USG and MRCP. By using the surveillance protocol for VHL disease-associated tumors, we could diagnose brainstem HB before progression. We plan to conduct a VHL gene analysis and surveillance protocol for VHL disease-associated tumors.
in other family members of the patient and carry out regular follow-up surveillance in our patient.

In one previous study of 55 VHL disease in Korea, there were 7 pediatric cases genetically diagnosed at age of 10 to 18 years [13]. Amongst 7 pediatric patients, 4 patients manifested as CNS HB and either pancreatic cysts or tumor, or renal or hepatic cyst, and 3 patients manifested as either retinal or CNS HB [13]. In another study of 26 VHL disease in Korea, there were 3 pediatric cases genetically diagnosed at age of 12, 11 and 14 years [14]. Amongst 3 pediatric patients, 12 year old male patient with family history manifested with CNS HB, RCC, pancreatic lesion and renal cyst, 11 year old male patient manifested with symptomatic CNS HB, pancreatic and renal cysts, and 14 year old male patient manifested with symptomatic pancreatic cysts and retinal HB [14]. In our 11-year-old VHL disease case without family history, multiple pancreatic cysts found incidentally in asymptomatic state became a clue to VHL disease. When there is symptomatic or asymptomatic multiple pancreatic cysts with or without renal or hepatic cysts, VHL disease must be suspected and surveillance protocol for VHL disease-associated tumors is recommended.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

References