A Case of von Hippel-Lindau Disease with Aortic Valve Insufficiency

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Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disorder caused by a germline mutation of the VHL gene. It is a multi-systemic disorder that is predisposed to benign or malignant tumors of visceral organs such as hemangioblastoma of the central nervous system, renal cell carcinoma, retinal angioma and pheochromocytoma. We report herein a case of VHL disease that initially manifested with aortic valve insufficiency.

Key Words: von Hippel-Lindau disease, Aortic valve insufficiency

INTRODUCTION

Von Hippel-Lindau (VHL) disease is a rare genetic disease causing multisystemic hereditary neoplastic syndrome. It is most commonly complicated with cerebellar hemangioblastoma, retinal angioma, renal cell carcinoma (RCC), and pheochromocytoma.1 Both the VHL disease and aortic valve insufficiency (AI) are uncommon diseases with reported incidence of AI from 0% to 33% within the general population.2 The concurrent development of both AI and VHL disease is considered extremely rare. We report a case of the VHL disease that was initially manifested with typical symptoms of AI.

CASE

A 24-year-old female has been presented with progressive dyspnea and chest discomfort for the past 6 months. She was previously in a healthy condition with normal exercise capacity until the incidental diagnosis of hypertension two years before the presentation. After the diagnosis of hypertension, she had not been treated nor had any further symptoms. Transthoracic echocardiography at the local clinic revealed significant AI and she was transferred for further evaluations. On presentation, vital signs showed the following: blood pressure of 150/70 mm Hg, pulse rate of 76/min, respiratory rate of 18/min and body temperature of 36.5°C. Heartbeats were regular and a high-pitched, decrescendo, grade III/VI diastolic murmur was audible at left lower sternal border. Her height was 172 cm, weighing 42 kg and her father died of metastatic RCC at 43 years old. Initial electrocardiogram was unremarkable and the routine blood chemistry also did not show any abnormalities. Transthoracic echocardiography disclosed severe AI with regurgitant volume of 68 cc per beat and regurgitant fraction of 54%. Left ventricle (LV) ejection fraction was approximately 50% and a diastolic internal dimension of LV was 60 mm (Fig. 1).

Surgical correction was planned for the management of AI. However, the chest discomfort was paroxysmal and accompanied with palpitation and sweating. Hormonal tests from collected urine were performed to exclude pheochromocytoma and 24 hours urinary vanillylmandelic acid and metanephrine was increased to 12.9 mg/day and 3.9 mg/day respectively. Following the abdominal contrast, enhanced computed tomography revealed not only both adrenal pheochromocytoma (Fig. 2A) but also multifocal masses in liver and...
Fig. 1. Aortic valve insufficiency in transthoracic echocardiography. Parasternal long axis (A) and 3-chamber view (B) shows severe regurgitation of blood through the aortic valve. The estimated regurgitation volume was 68 cc and the regurgitation fraction was 54%.

Fig. 2. Multifocal tumors in VHL disease. Contrast enhanced computed tomography shows well-enhanced both adrenal pheochromocytomas (A, white arrows), strong enhancing hepatic hemangioma in S2 segment of liver (B, white arrow) and right renal cell carcinoma (C, white arrow). T2 weighted brain magnetic resonance images show hemangioblastoma with peritumoral edema in cortical area of right cerebellum (D, white arrow).

Fig. 3. Microscopic findings. The extracted aortic valve shows infiltration of lymphocytes with focal necrotic changes. There is no evidence of rheumatic valve disease (H&E stain, ×10).

Setting aside the RCC history of her father, VHL disease was diagnosed with her hemangioma and multifocal visceral kidney. A small enhancing mass in S2 segment of the liver was compatible with hemangioma (Fig. 2B) and both hypervascular renal masses were compatible with RCC (Fig. 2C). Multifocally developed uncommon tumors suggested the VHL disease. Magnetic resonance imaging (MRI) of the brain showed hemangioblastoma with ill-defined high signals in right cerebellum cortical area (Fig. 2D). In the ophthalmologic examination, left ptosis bulbi and right retinal hemangioma were being observed.

Setting aside the RCC history of her father, VHL disease was diagnosed with her hemangioma and multifocal visceral tumors. And the genetic study identified missense germline mutation of the eightieth codon and the sequencing of three exons of VHL gene by polymerase chain reaction.

A laparoscopic bilateral adrenalectomy with bilateral renal biopsies was followed by aortic valve replacement without any complications. Intraoperative renal biopsy revealed clear cell type RCC in the left kidney whereas biopsy from the right kidney showed no evidence of malignancy. Three fragments of the extracted aortic valves were thickened and retracted with focal yellowish degenerative changes showing chronic inflammation without evidence of rheumatic valve disease (Fig. 3).

The patient is being followed up periodically with abdominal computed tomography scans, which monitors the size of her renal mass. Until now, no neurological deficit has been detected.

**DISCUSSION**

VHL disease is an autosomal dominant cancer syndrome resulting from the mutation of the VHL gene, which is responsible for the proteolytic degradation of the hypoxia inducible factor (HIF) transcriptional complex. Abnormal or absent VHL protein function can disrupt tumor suppressions indirectly through HIF-mediated effects or directly through VHL-mediated effects, or both. Altered tumor suppressive