

Von Hippel-Lindau disease involving pancreas and biliary system

A rare case report

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Abstract

Rationale: Von Hippel-Lindau (VHL) disease is a rare inherited, autosomal-dominant syndrome caused by heterozygous germline mutations in the VHL gene. VHL patients are prone to develop benign and malignant tumors and cysts in multiple organ systems involving kidneys, pancreas and central nervous system (CNS). The varied and complex clinical manifestations and radiological findings of VHL are of interest.

Patient concerns: We report a 38-year-old woman with a ten-year history of VHL disease involving both pancreas and biliary system. To the best of our knowledge, direct involvement of the biliary system in VHL disease has never been reported.

Diagnoses: The diagnosis was established via computed tomography scan and was confirmed by genetic testing.

Interventions: The patient chose to receive conservative treatment and was followed up by magnetic resonance cholangiopancreatography and magnetic resonance imaging examination.

Outcomes: Renal angiomas and cysts were found during follow-up and there were no evidence of malignant change of the pancreas and biliary system.

Lessons: We described the first case of VHL-associated choledochal cysts and may present new visceral manifestations of VHL disease. Gastroenterologists should be aware of the clinical presentations of this rare disease for early detection of its life-threatening manifestations.

Abbreviations: CA = carbohydrate antigen, CBD = common bile duct, CNS = central nervous system, CT = computed tomography, HIF = hypoxia inducible factor, PNET = pancreatic neuroendocrine tumors, VHL = Von Hippel-Lindau.

Keywords: choledochal cysts, heredity, polycystic pancreas, Von Hippel-Lindau

1. Introduction

Von Hippel-Lindau (VHL) disease is a rare hereditary multisystem neoplasia syndrome that results from a germline mutation in the VHL tumor suppressor gene located on chromosome 3p25.^[1] The incidence of VHL mutations is roughly 1 in 36,000 live births, and penetrance reaches 90% at 65 years of age.^[2] Approximately 20% of VHL cases have no apparent family history and appear to arise de novo. The affected patients mainly develop tumors of the central

nervous system (CNS), kidneys, adrenals, pancreas, and reproductive organ, and the median life expectancy of VHL patient is 49 years.^[2] The availability of a genetic test for detection of individuals carrying the defective gene would not only increase the accuracy and availability of presymptomatic diagnosis of VHL disease, but improve the clinical management of families with VHL disease, so as to reduce the complications of undetected disease which can sometimes be devastating.^[3]

2. Case presentation

A 38-year-old woman with a 10-year history of VHL disease was referred to our hospital for routine examination of the disease. Ten years ago, she experienced dyspeptic symptoms and a huge abdominal mass was palpated during physical examination. Computed tomography (CT) scan revealed multiple pancreatic cysts (Fig. 1A) and marked dilation of the extrahepatic common bile duct (CBD) (Fig. 1B, arrow). She denied any history of pancreatic diseases and had no signs suggesting previous pancreatitis, but has been suffering from diabetes for several years. Her family history was remarkable for polycystic pancreas in her mother who died of complications after resection of pituitary tumors. The diagnosis VHL disease was suspected and was finally confirmed by genetic testing. The patient refused surgical treatment at that time and was discharged after the symptom was relieved.

During the past 10 years, the patient suffered from intermittent abdominal pain and distension and was followed up annually by a standard protocol including laboratory tests and ultrasound or CT examination. This time, the patient complained jaundice of

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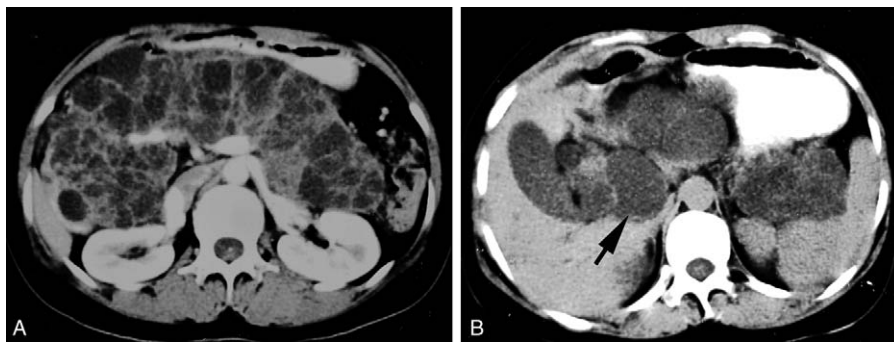


Figure 1. (A) CT scan revealed multiple pancreatic cysts. (B) Marked dilation of the extrahepatic biliary duct can be detected on CT scan (arrow). CT = computed tomography.

1 month duration and her laboratory tests revealed elevated serum level of glucose (19.6 mmol/L, normal range 3.9–6.1 mmol/L), total bilirubin (69 μ mol/L, normal range 1.7–21 μ mol/L), aspartate aminotransferase (92 U/L; normal range 5–37 U/L), alanine aminotransferase (137 U/L; normal range 5–40 U/L), gamma-glutamyl transpeptidase (1040 U/L; normal range 0–50 U/L), and alkaline phosphatase (498 U/L; normal range 40–130 U/L). Tumor markers of carbohydrate antigen (CA) 19-9, CA125, and carcinoembryonic antigen were all within normal values. Though CT scan demonstrated multiple calcifications in the pancreas, the size of pancreatic cysts was smaller than that of 10 years ago (Fig. 2A). Magnetic resonance cholangiopancreatography and magnetic resonance imaging also showed the Todani type IV choledochal cyst, as well as multiple cystic lesions in the pancreas (Fig. 2B and C). In addition, bilateral renal angiomas (Fig. 2C, arrows) and cysts, which were not found in previous examination, were also detected at this time. Because further examinations did not reveal involvements of other organs and there were no evidence of malignant change of these cystic lesions, the patient chose to receive conservative treatment and was followed up without evidence of deterioration.

The study was approved by the Ethic Committee of Qilu Hospital, Shandong University, performed in accordance with the approved guidelines, and informed consent was obtained from the patient.

3. Discussion

The first descriptions of the VHL disease were, respectively, reported by von Hippel and Lindau in 1911 and 1926. Melmon

and Rosen coined the current name of the disease and set out clinical criteria for its diagnosis in 1964. Nowadays, genetic testing for VHL is widely available and is generally regarded as the standard for diagnosis of VHL disease, as germline mutations in the VHL tumor-suppressor gene on chromosome 3 is reported to account for more than 95% of the VHL cases.^[4] The VHL tumor-suppressor gene encodes for the VHL protein, which is involved in the degradation of hypoxia inducible factor 1 α (HIF1 α) through ubiquitin-dependent proteolysis. In cases of VHL disease where the VHL gene is mutated, VHL protein does not bind to HIF1 α and activates the expression of a number of factors, including vascular endothelial growth factor, platelet-derived growth factor, erythropoietin, and transforming growth factor, which lead to angiogenesis and tumorigenesis.^[5,6]

Pancreatic lesions may develop in 35% to 77% of patients with VHL and most of them present as benign cysts mainly comprised of simple cysts or rarely serous cystadenomas.^[2] These lesions have no malignant potential and are usually managed conservatively with long-term follow-up. Positive and negative growing cysts may co-exist and can replace enough of the pancreas to cause endocrine or exocrine insufficiency of the pancreas. Pancreatic neuroendocrine tumors (PNET) have been reported to occur with an incidence of 17% in VHL patients. They are hormonally nonfunctional, often multiple, and are located throughout the pancreas.^[7] Although usually well circumscribed and confined to the pancreas, VHL-associated PNET can metastasize. The size of the tumor appears to be related to the risk of metastatic disease, and PNET with the size <1.5 cm is indicative of a benign nature.^[8] Resection is advocated for PNET >2 cm because malignant change or metastasis is more common

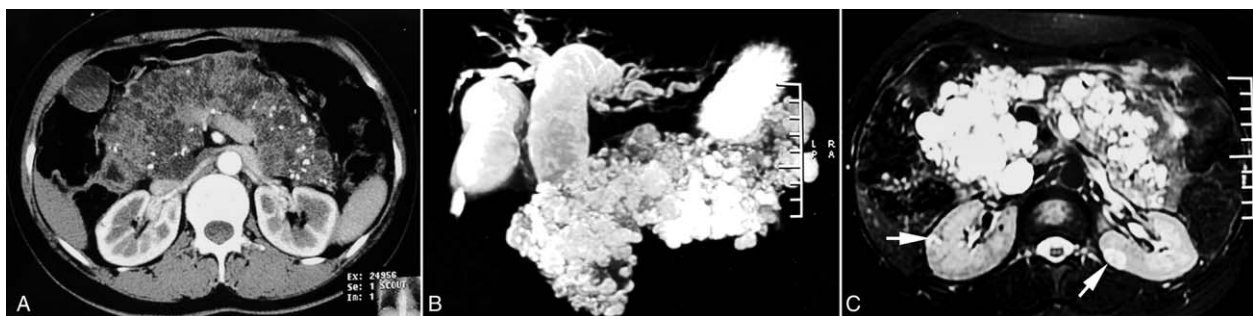


Figure 2. (A) Computed tomography scan demonstrated that the size of pancreatic cysts was smaller than that of 10 years ago, but there were multiple calcifications in the pancreas. (B) Magnetic resonance cholangiopancreatography showed the Todani type IV choledochal cyst, as well as multiple cystic lesions in the pancreas. (C) Magnetic resonance imaging detected bilateral renal angiomas (arrows) and cysts.

in such cases and remains an uncommon death cause of VHL disease.

Though bile duct obstruction due to pancreatic cysts compression has been previously described in several VHL cases, direct involvement of the biliary system in VHL disease has never been reported. The most widely accepted Todani classification describes 5 types of choledochal cysts. Type I cyst is the most common variety involving dilatation of a portion or entire CBD with normal intrahepatic duct; Type II is an isolated choledochal diverticulum; Type III consists of a bulbous dilation (more than 1 cm) of the distal CBD near the ampulla; Type IV is characterized by multiple dilations of the intrahepatic and extrahepatic bile ducts; and Type V (Caroli disease) is cystic dilatation of intrahepatic biliary ducts without extrahepatic duct disease.^[9,10] Our case presents the first case of VHL associated Type IV choledochal cysts.

Taylor et al performed a study of patients with an atypical manifestation of VHL, namely visceral cysts, followed in a Genetics Clinic. Cystic visceral lesions, such as renal cysts, pancreatic cysts, and epididymal cystadenoma, were detected in about 30% of VHL patients.^[11] However, owing to their relatively benign nature, cystic visceral lesions have received comparatively less attention in relation to their correlation with other phenotypic manifestations of VHL disease and genotypic associations. Whether choledochal cysts are visceral manifestations of VHL disease deserves further study.

The presence of cysts, unaccompanied by other more typical lesions such as retinal or cerebellar hemangioblastoma, may represent a major diagnostic problem, leading to errors in the assessment of disease status. Therefore, the majority of VHL patients are diagnosed by neurologists or neurosurgeons after the discovery of CNS tumors. However, pancreatic lesions may precede any other manifestation of VHL diseases by several years, and recognition permits earlier surveillance and detection for renal cell carcinoma and cerebellar hemangioblastomas, which are the major causes of death in affected patients. Since pancreatic involvement alone rarely arouses diagnostic suspicion of VHL disease, our case highlights the need for gastroenterologists to be

aware of its clinical presentations.^[2] A clinical presentation of multiple pancreatic cysts without previous pancreatic inflammatory episodes should suggest a diagnosis of VHL disease and lead to a genetic test.^[2] Once the diagnosis has been confirmed, all family members at risk must be screened immediately, and affected persons should undergo genetic counseling and rigorous follow-up to treat the life-threatening CNS and visceral manifestations of the disease.

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