

CASE REPORT

A Benign Cause of Obstructive Jaundice with von Hippel-Lindau Disease. A Case Report and Review of the Literature

Joseph Boujaoude¹, Elia Samaha¹, Khalil Honein¹, Roger Noun²,
Bassam Abboud², Claude Ghorra³, Raymond Sayegh¹

Departments of ¹Gastroenterology, ²General Surgery, and ³Pathology;
Hotel-Dieu de France Hospital, Saint-Joseph University. Beirut, Lebanon

ABSTRACT

Context Von Hippel-Lindau disease is a genetic disorder characterized by neoplasms with multiple organ involvement, the pancreas being involved in about half of the cases. Conservative treatment is indicated because the disease is usually asymptomatic with long-term follow-up.

Case report We herein present the case of a 64-year-old man with von Hippel-Lindau disease who presented with obstructive jaundice which resulted as being caused by a fibro-cystic pancreatic nodule. In addition, we reviewed the literature concerning pancreatic involvement in von Hippel-Lindau disease with emphasis on their presentation, type of lesions and appropriate management, especially in cases with obstructive jaundice.

Conclusion Conservative management is advocated in the majority of VHL disease patients with pancreatic involvement, but surgery is sometimes required, especially when patients are symptomatic (obstructive jaundice, upper gastrointestinal bleed).

INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disorder with high penetrance and variable expression. It includes neoplasms with multiple organ involvement, the most common organ

involved being the central nervous system but renal and pancreatic diseases are also frequent. Pancreatic involvement in VHL disease was observed in 0.05 to 77.2% [1,2], and found in all types of VHL disease [3]. The most common pancreatic lesion is a simple cyst, but other lesions can also be found: serous cystadenomas, neuroendocrine tumors, adenocarcinomas, hemangioblastomas and renal cell cancer metastases [2, 4]. Patients with VHL disease often present for neurological disorders, and the pancreatic involvement is most often found during routine screening. Obstructive jaundice due to VHL disease is a very rare finding. We present a new case complicated by obstructive jaundice and treated by surgery, and a brief review of the literature about reported cases of VHL disease with obstructive jaundice using a MEDLINE search.

CASE REPORT

A 64-year-old male patient, with unremarkable gastrointestinal history, was admitted to our hospital after a three-day history of abdominal pain, fever and jaundice, along with dark urine and light colored stools. He had a personal history of two cerebral hemangioblastomas operated on at the age of 20 and 53 years, and a positive familial history of cerebral hemangioblastomas. Physical examination showed stable hemodynamic parameters, a low-grade fever

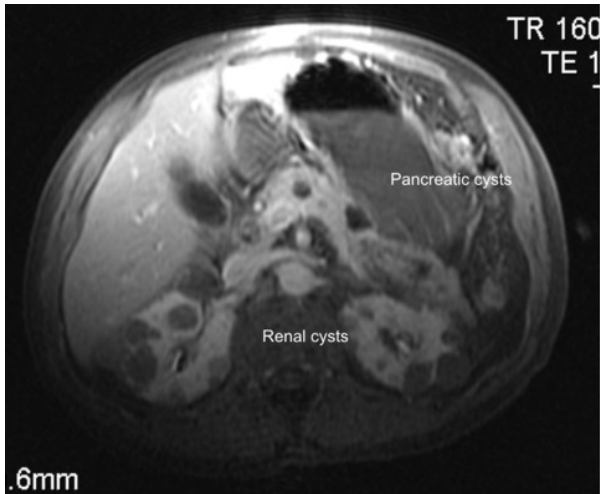


Figure 1. MRI showed multiple cysts in the kidney and the pancreas.

and generalized cutaneo-conjunctival jaundice. The abdomen was unremarkable with negative Murphy sign, no organomegaly and no palpable mass. Blood tests showed a normal complete blood count and liver function tests were: AST 6-times the upper reference limit (URL), ALT 5.5 URL, alkaline phosphatase 2 URL, GGT 28 URL, total bilirubin 6 URL (predominantly direct), amylase 1.5 URL and lipase 2.5 URL. HBV and HCV serology was negative. Abdominal ultrasound revealed a normally distended non-lithiasic gallbladder, dilated intrahepatic and extrahepatic bile ducts, along with multiple

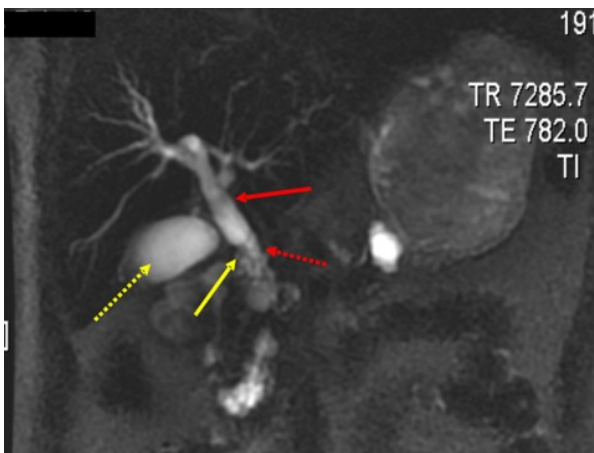


Figure 2. A slide of MRCP: the yellow arrow indicates the extrinsic nodule compressing the common bile duct, the red arrow indicates the dilated common bile duct and the red arrow shows the level of the stenosis at the middle portion of the common bile duct.

pancreatic and renal cysts. Abdominal MRI with MRCP revealed multiple simple renal and pancreatic cysts (Figures 1 and 2). Intrahepatic and extrahepatic bile duct dilations were seen along with a stenotic region in the mid-common bile duct. EUS showed a homogenous pancreatic gland which contained multiple cysts; the largest one was located in the isthmus and showed an intramural nodule which was compressing the common bile duct (Figure 3). The ERCP probe was unsuccessful in passing through the stenosis. A cholangiogram by means of percutaneous drainage was done prior to surgery to decompress the common bile duct and relieve the cholangitis. A Whipple procedure was eventually carried out (Figure 4). Histopathology showed fibro-cystic dystrophy of the pancreatic gland compatible with the diagnosis of VHL disease of the pancreas (Figure 5). Based on these clinical and pathological findings (hemangioblastomas of the central nervous system, visceral manifestations compatible with VHL disease (renal and pancreatic cysts), a positive familial history of hemangioblastomas and a compatible histopathological examination), the final diagnosis was that of type 1 VHL disease—with obstructive jaundice caused by a pancreatic pseudotumorous fibrotic lesion compressing the common bile duct.

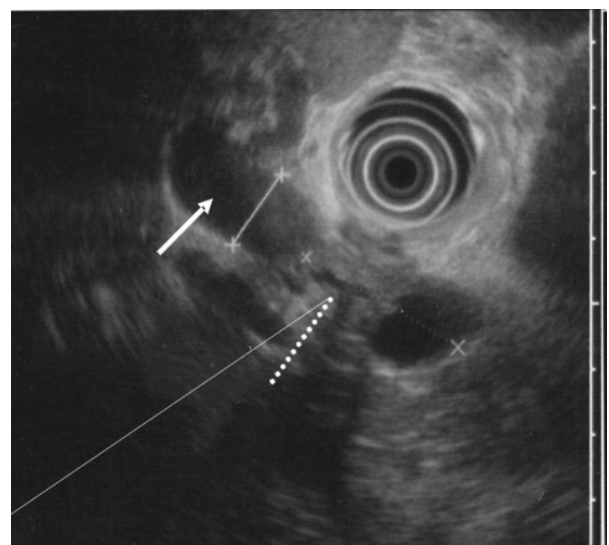


Figure 3. EUS confirmed the stenosis at the middle portion of the common bile duct and showed a nodule at this level, extrinsically compressing the common bile duct.

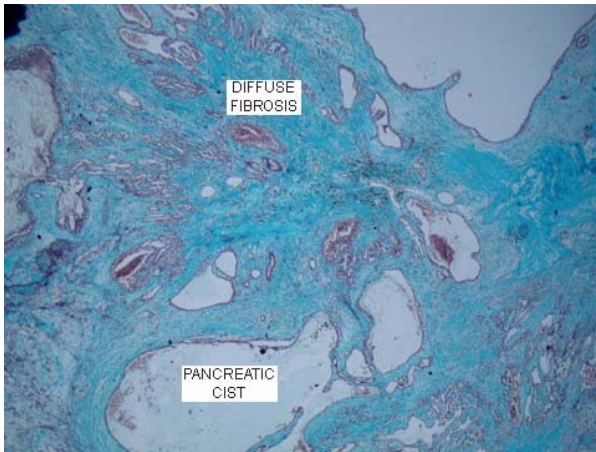


Figure 4. The histology study of the totality of the pancreatic specimen and the region of the stenosis, demonstrates diffuse fibrosis.

DISCUSSION

VHL disease is an autosomal dominant genetic disorder associated with various tumors and cysts characterized by multiple organ involvement including the central nervous system, the retina, the kidneys, the adrenal glands and the pancreas [3]. The VHL tumor suppressor gene, which is located on chromosome 3p25-26, is responsible for this disease. This tumor suppressor gene comprises 3 exons and encodes for a 213 amino acid protein called the pVHL, composed of 2 domains and responsible for the ligation of the hypoxia inducible factor (HIF) under normoxic conditions. With the loss of the functional VHL protein, a high level of non-degraded HIF causes increased transcription of VEGF, PDGF and TGF- α . These findings explain cell growth and the development of microvascular vessels and accelerated tumoral growth [3].

The major tumors and cysts associated with VHL disease are hemangioblastomas in the central nervous system, retinal hemangioblastomas, pheochromocytomas, renal cell carcinoma, renal cysts, and pancreatic involvement including simple cysts, serous cystadenomas, neuroendocrine tumors, adenocarcinomas, hemangioblastomas and renal cell cancer metastasis [2, 4].

Pancreatic involvement in VHL disease is a relatively frequent finding being present in approximately one-third to three-fourths of

patients with a mean incidence of approximately 50% [1, 2]. The largest review included 275 reported cases in 7 studies with an incidence of 32.7% of pancreatic lesions [1]. Another French series reported a total of 158 patients in which the pancreas was involved in 77.2% [2].

Clinical classification of VHL disease comprises two types: type 1 includes patients without pheochromocytoma and type 2 includes patients with pheochromocytoma [3]. VHL disease type 2 is further classified into three categories: type 2A, type 2B and type 2C. Type 2A does not include renal cell carcinoma, type 2C manifests only with pheochromocytoma, and type 2B includes all the other tumors [3]. Pancreatic involvement can be seen in all types of VHL disease. In our case, no evidence of pheochromocytoma was present and therefore it was considered as type 1 VHL disease.

In VHL disease, the clinical presentation of patients with pancreatic lesions ranges from asymptomatic disease (30-70%) to non-specific symptoms such as abdominal pain, obstructive jaundice or upper gastrointestinal bleeding [1, 2]. Management of pancreatic lesions in VHL disease is not well standardized. Neumann *et al.* [5] suggested conservative treatment with long-term follow-up because the disease is usually asymptomatic. In the review of Cheng *et al.* [1], pancreatic lesions were found in 90 patients; 73 had cystic lesions and 17 had solid tumors including 14 neuroendocrine

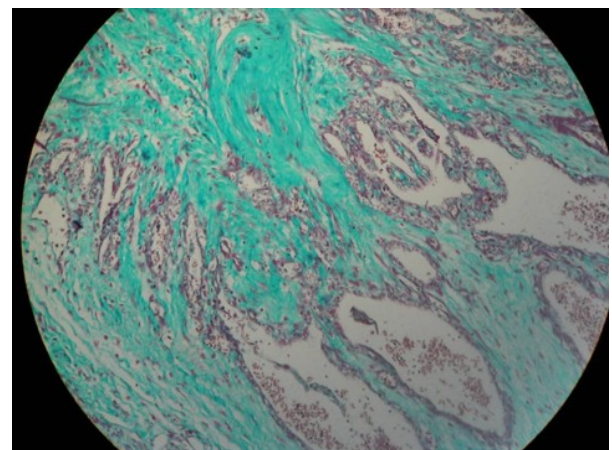


Figure 5. Histopathology showed fibro-cystic dystrophy of the pancreatic gland.

tumors and 8 malignant lesions. The global management was conservative in most of the patients, and surgery was done only in symptomatic patients or to exclude malignant lesions when confronted with a solid mass (neuroendocrine tumor, adenocarcinoma). Furthermore, in the Hammel *et al.* [2] study, only 10 out of 122 patients (8.2%) required specific treatment; 4 were medically managed with chemotherapy, cyst drainage or symptomatic management, and 6 surgical procedures were done for neuroendocrine tumors, including 4 duodenopancreatectomies (Whipple procedure) and 2 left pancreatectomies.

However, serious complications can occur, such as upper gastrointestinal bleeding and obstructive jaundice, especially when the lesion grows to invade the surrounding structures [1]. To date, there are 11 reported cases of VHL disease complicated with obstructive jaundice in the literature [1, 6, 7, 8, 9, 10, 11, 12]. Nine of them were caused by extrinsic compression of the common bile duct, also by a pancreatic cyst (serous cystadenoma or simple cyst) [1, 8, 9, 10, 11], and two by a neuroendocrine tumor [6, 7]. There was one case which had intrinsic stenosis caused by a neuroendocrine tumor of the common bile duct [12]. The management of these cases was mainly surgical; out of 5 cases, there were 3 reported pancreatectomies (the two patients who had neuroendocrine tumors and one patient who had a cystadenoma), one biliary bypass in a patient with a cystadenoma and one endoscopic management with biliary stent placement in a patient who had a simple cyst compressing the common bile duct. The management of the other five cases is not well-described. The particularity in our case was the presence of a nodular lesion apparent at EUS which resulted as being a pseudo-tumor lesion composed of fibro-cystic dystrophy at histopathology, compressing the common bile duct and causing cholangitis; therefore, a surgical approach using a duodenopancreatectomy was the most appropriate in this case to relieve the obstruction and to exclude malignancy.

In conclusion, conservative management is advocated in the majority of VHL disease patients with pancreatic involvement, but surgery is sometimes required, especially when patients are symptomatic (obstructive jaundice, upper gastrointestinal bleed). The management of obstructive jaundice in VHL disease depends largely on the cause of the obstruction and the operability of the lesion. Solid tumors including neuroendocrine tumors must be removed whenever possible and the obstruction relieved; otherwise, a symptomatic treatment is advocated to alleviate the obstruction and can include surgical biliary bypass or endoscopic biliary stent placement.

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Keywords Fibrosis; Hippel-Lindau Disease; Jaundice

Abbreviations URL: upper reference limit; VHL: von Hippel-Lindau

Conflict of interest The authors have no potential conflicts of interest

Correspondence

Joseph Boujaoude
Department of Gastroenterology
Hotel-Dieu de France Hospital
Saint-Joseph University
Achrafieh, Adib Eshak street
Beirut
Lebanon
Phone: +961-03.704.890
Fax: +961-1.615.295
E-mail: jbouj@hotmail.com

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