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Pancreatic manifestations in von Hippel–Lindau disease: A case report

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ABSTRACT

INTRODUCTION: Pancreatic manifestations in Von Hippel–Lindau (VHL) disease can present as a multitude of forms, and their management can be challenging.
PRESENTATION OF THE CASE: A 66-year-old woman presented with increasing abdominal girth without other associated symptoms of nausea, vomiting, abdominal pain, weight-loss, and jaundice. Her medical and surgical histories were significant for type II diabetes, cerebral tumor resection, bilateral nephrectomies, and laser photocoagulation of retinal hemangiomas. Computed tomography (CT) of the abdomen showed a massive multi-cystic lesion in the pancreas and the patient was referred to our hepatopancreatic biliary center.
DISCUSSION: The findings on the subsequent cross-sectional MRI imaging signified pancreatic manifestations in VHL disease.
CONCLUSION: The management of VHL disease-associated benign pancreatic cystic lesions involves interval monitoring with cross-sectional imaging for malignant changes/development.

1. Introduction

Von Hippel–Lindau (VHL) disease is a rare autosomal dominantly inherited familial syndrome with an incidence of 2–3 cases per 100,000 population [1]. Approximately 65–75% of patients with VHL as a component of multi-visceral tumors have some form of pancreatic lesions (cystic and solid tumors) [2]. The incidence of pancreatic lesions among the VHL population varies considerably among different kindred. An incidence rate of 37% in Hawaiian VHL kindred was reported compared with 0% in Newfoundland VHL kindred [1]. The pancreatic lesions can be benign or malignant, can produce symptoms due to the mass effect or hormonal activity, can present as recurrent multifocal lesions, or be associated with lesions involving several organs simultaneously. Thus, it is of paramount importance to understand the management of various pancreatic manifestations of VHL.

2. Case report

A 66-year old woman presented for the evaluation of increasing abdominal girth with no other associated symptoms of abdominal pain, weight-loss, and jaundice. We report her case in line with CARE criteria [3]. Her medical and surgical histories included type II diabetes mellitus, dyslipidemia, osteoporosis, cerebral tumor resection in 1976 and 1981, laser photocoagulation of retinal hemangiomas, bilateral nephrectomies in 1998 for renal cell carcinoma, and a living unrelated renal transplant in 2000. Her family history was significant for paternal demise from renal cell carcinoma and two other family members who had cerebral tumors resected. Abdominal examination was significant for distension with a non-tender abdominal mass most profoundly palpable in the epigastrium. Magnetic resonance imaging of the abdomen showed major replacement of the pancreas with a multiloculated cystic lesion (Fig. 1). Imaging findings showed the disease to be extensive, with a multitude of pancreatic cystic lesions—simple cysts, serous cystadenomas without cystic characteristics concerning carcinoma, or the presence of solid tumors. The tumor markers CA 19-9 and chromogranin A were within the normal range. Hence, monitoring with serial cross-sectional imaging studies was recommended for this patient for changes in the cystic characteristics concerning carcinoma or the development of solid lesions. Since the diagnosis, patient has been followed up at our hepatobiliary pancreatic center every six months with cross-sectional imagining for any changes in the existing lesions and for development of any further new lesions.

3. Discussion

Described independently in 1911 by Hippel and in 1926 by Lindau [4], VHL disease is a rare autosomal dominantly inherited multisystem disease that is characterized by neoplastic lesions of the central nervous system (CNS) and various visceral organs due to loss of the VHL tumor suppression gene on the short arm of chro-

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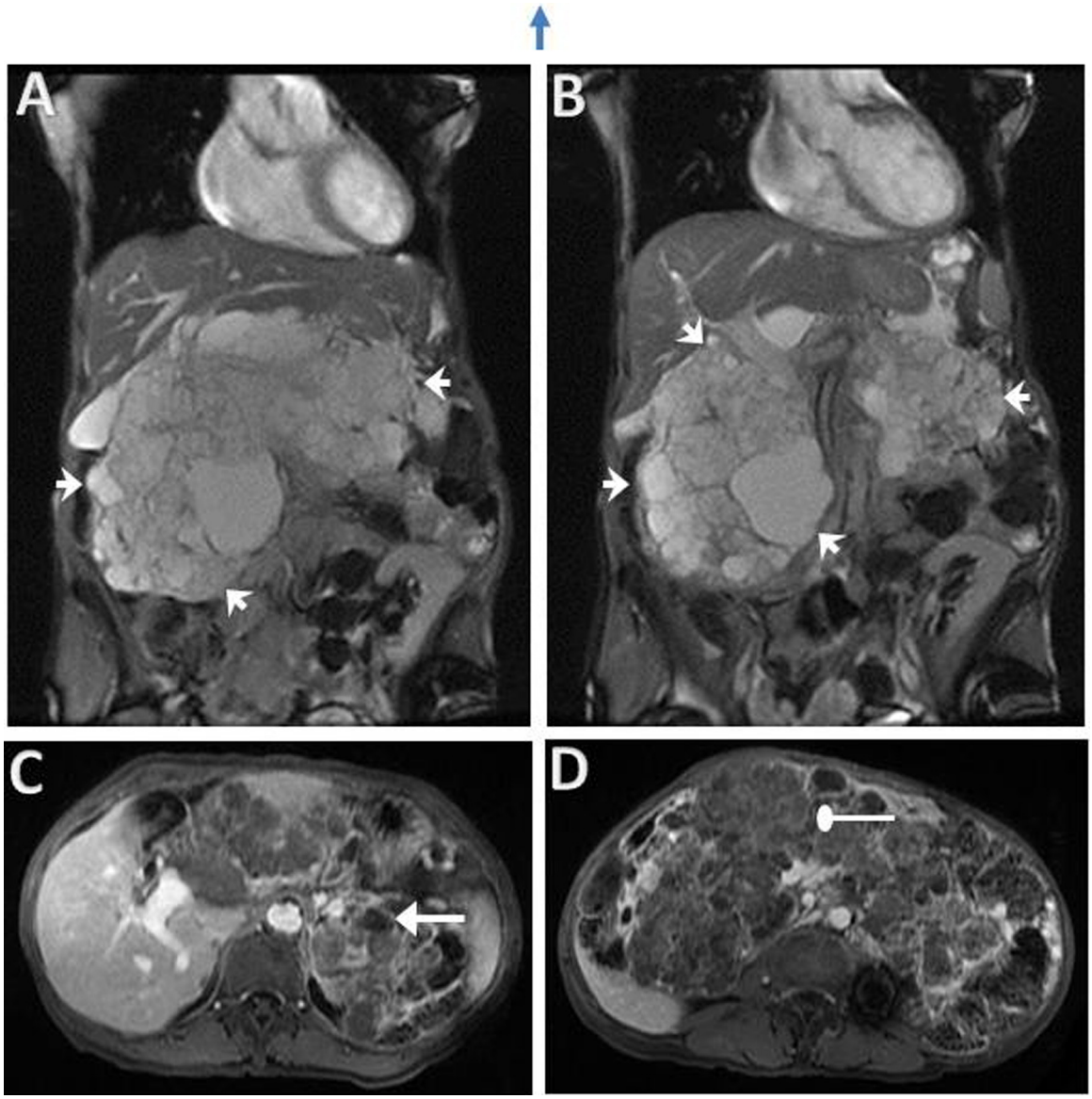

Fig. 1. Magnetic resonance imaging of abdomen (panel A–D). Arrow head: multiple pancreatic cysts; single arrow: benign simple cysts; oval arrow: serous cystadenomas.

mosome 3. The prevalence of VHL disease has been reported to be 1 in 1,000,000 families [5]. Patients with VHL disease are found to have retinal angiomas, renal cell carcinomas, pheochromocytomas, CNS hemangioblastomas, tumors of the inner ear and epididymis, cystic lesions of the ovaries, and cystic and endocrine tumors of the pancreas. The clinical diagnostic criteria, as proposed in 1964 by Melmon and Rosen for VHL disease, are as follows: (i) greater than one CNS hemangioblastoma; (ii) CNS hemangioblastoma in combination with visceral manifestation of VHL disease; and (iii) any manifestation and a known family history of VHL disease [6].

Approximately 7.6% of patients with VHL disease might present with pancreatic manifestations alone. The manifestations of pancreatic lesions in VHL disease can present as a cystic and/or solid lesion. Combined lesions are reported in 11.5% of patients with VHL disease [7]. The solid lesions are most often neuroendocrine tumors, and the cystic lesions are most often simple cysts and serous cystadenomas [5], as presented in this case.

Pancreatic neuroendocrine tumors (pNETs) are found in 5–17% of VHL disease patients [8]. Often of islet cell tumor origin and often found in women (66%) at a median age of 38 years, 17–25% of pNETs have metastasized at the time of diagnosis [9]. On the other hand, most cystic manifestations of VHL disease are benign, but differentiation of these lesions from premalignant cystic lesions, such as intraductal papillary mucinous neoplasms or mucinous cystadenomas is mandatory. Because renal cell carcinoma is one of the components of VHL disease, metastatic lesions to the pancreas should also be considered in the differential diagnosis [4].

Most of the pancreatic lesions in VHL disease are asymptomatic. When symptomatic, they often present with vague symptoms of epigastric pain, diarrhea [9], dyspepsia [7], and obstructive jaundice. Most often, these patients present initially with neurological symptoms associated with VHL disease due to involvement of the CNS [10] rather than symptoms associated with pancreas involvement. This case highlights the importance of evaluating VHL patients for abdominal pathology despite most patients being asymptomatic.

Imaging is of paramount importance as a tool to identify and differentiate benign lesions from malignant tumors, and for any transformation of lesions from baseline characteristics. MRI is the preferred imaging study for the absence of radiation and with respect to the current literature recommendation for annual surveillance of the abdominal manifestation. Characteris-

tic MRI findings differ depending on the lesion. Pancreatic cysts appear hypointense on T1-weighted images and hyperintense on T2-weighted images without enhancement on post-gadolinium images. Pancreatic microcystic serous cystadenomas appear as circumscribed encapsulated masses, hypointense on T1-weighted images and hyperintense on T2-weighted images, with radial septa and a peripheral wall that enhance in post-gadolinium images, and with a central fibrous scar. Macrocystic serous cystadenomas appear as fluid filled lesions with the septa and peripheral wall that do not enhance in the post-gadolinium images. Neuroendocrine tumors show intense and early enhancement in post-gadolinium images [11].

The management of pancreatic lesions is dependent on the symptomology and findings on cross-sectional imaging. Although most patients present with no pancreatic symptoms, the pancreatic lesions should be assessed prior to any surgical intervention that a patient might undergo due to associated neoplasms of other visceral structures. The treatment strategy for the management of pancreatic lesions can be challenging, because they might present as multiple lesions or develop recurrent lesions that might jeopardize the functional adequacy of the remnant pancreas. Most neuroendocrine tumors are hormonally non-functional but require resection due to the metastatic risk to distant organs (11–20%) or local invasiveness [2]. Current recommendations for the treatment of pNETs in VHL disease is based on the prognostic factors of tumor size ($\geq$3 cm), mutation in exon 3, and the tumor doubling time ($\leq$500 d). Having two or three of these criteria requires surgical resection, while having one or no criteria involves monitoring by cross-sectional imaging (CT/MRI) every 6–12 months or 2–3 years, respectively [12]. Most cystic lesions are asymptomatic, but might cause endocrine and/or exocrine insufficiency and need to be differentiated from lesions with a malignant potential or those that are malignant. Lesions that are malignant or suspicious of malignancy, or those that cannot be distinguished from benign lesions or causing symptoms due to compression on adjacent organs, require operative resection [5]. Intervention might be warranted if these lesions cause compression on the intestine or bile duct

4. Conclusion

VHL disease is a familial disease characterized by neoplasms of various visceral organs including pancreas. The pancreatic manifestation of VHL disease can present as a cystic, solid, or combined lesion. The management is complex because of the challenge in the differentiation of benign cystic lesions from malignant lesions, potential for malignant transformation, and development of solid lesions. The treatment strategy can be complex because of its multifocal presentation and recurrence of the pathology threatening the functional adequacy of the remnant pancreas. Cross-sectional monitoring of benign lesions, and resection of solid or malignant lesions or lesions with a mass effect, is recommended.

Conflicts of interest

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Ethical approval

Not applicable.

Consent

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Author contribution

Authors Ayloo and Molinari contributed equally in writing the paper.

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