Pancreatic Involvement in von Hippel–Lindau Disease

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Background & Aims: **Pancreatic involvement in von Hippel–Lindau (VHL) disease, a genetic disorder with a dominant mode of inheritance affecting various organs, has rarely been studied. We assessed the prevalence, type of lesions, natural history, and impact of pancreatic involvement in patients with VHL.** ***Methods:*** **A total of 158 consecutive patients from 94 families with VHL disease were studied in a prospective French collaborative study. All patients underwent systematic screening for VHL lesions, including computerized tomography (CT) scanning of the pancreas reviewed by an experienced radiologist. Clinical data, investigations, and treatments performed were also reviewed.** ***Results:*** **Pancreatic involvement was observed in 122 patients (77.2%) and included true cysts (91.1%), serous cystadenomas (12.3%), neuroendocrine tumors (12.3%), or combined lesions (11.5%). The pancreas was the only organ affected in 7.6% of patients. Patients with pancreatic lesions had fewer pheochromocytomas than those without (14/122 vs. 16/36; $P < 0.0001$), and patients with neuroendocrine pancreatic tumors had renal involvement less often than those without (8/99 vs. 6/20; $P = 0.013$). None of the patients with neuroendocrine tumors had symptoms of hormonal hypersecretion. Pancreatic lesions evolved in half of patients but required specific treatment in only 10 (8.2%) when they were symptomatic or for the resection of large neuroendocrine tumors.** ***Conclusions:*** **Pancreatic involvement is seen in most patients with VHL disease. Although symptoms are rare, specific treatment of pancreatic lesions is required in selected patients, mainly those with neuroendocrine tumors.**

Von Hippel–Lindau (VHL) disease is characterized by dominant autosomal predisposition to develop hemangioblastomas of the retina and central nervous system (CNS), renal cell carcinoma, pheochromocytoma, and endolymphatic sac tumors with marked phenotypic variability.[1] The VHL protein, bound to elongin C, elongin B, Cul2, and Rbx1, degrades α subunits of hypoxia-inducible factor in an oxygen-dependent manner. Lack of degradation of this factor caused by absence of the VHL protein results in uncontrolled production of factors promoting formation of blood vessels such as vascular endothelial growth factor (VEGF).[2] Germline mutations in the VHL gene are extremely heterogeneous and are distributed widely throughout the coding sequence.[1,3] They are now identifiable in virtually all families with VHL.[3]

Various pancreatic lesions—including pancreatic cysts or serous cystadenomas,[4–10] neuroendocrine tumors (NET),[7,8,11–13] adenocarcinomas,[4] hemangioblastomas,[14] and renal cell cancer metastasis[15]—have been described in patients with VHL. The frequency of pancreatic involvement in the largest series of VHL patients studied by imaging methods varied from 17% to 56%.[5–7] Pancreatic lesions were formerly thought to have no clinical relevance because they tended to be the least symptomatic of the VHL lesions.[1] However, cystic lesions may compress neighboring organs,[10,16] and NET may metastasize.[7,11,12] In addition, lesions that are unique to the pancreas may confirm a diagnosis of VHL disease in relatives of affected patients in the absence of detectable mutations.[1]

The aims of this study were to assess the prevalence, types of lesions, and natural history of pancreatic involvement and their impact on the treatment of patients with VHL.

Abbreviations used in this paper: CNS, central nervous system; CT, computerized tomography; NET, neuroendocrine tumor(s); VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau.

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Patients and Methods

Patient Selection

All French patients with VHL disease were registered in a database. Clinical history, results of tests, and treatment modalities were recorded. This study prospectively analyzed VHL patients beginning in 1996 by a group of multidisciplinary French practitioners involved in the care of patients with this disorder. The criteria used to confirm the diagnosis of VHL disease have been published previously.[3,4] Briefly, a diagnosis was made in patients with a first-degree relative with VHL disease who had at least 1 lesion typical of the disease: hemangioblastoma of the CNS or retina, pheochromocytoma, renal cyst or carcinoma, or pancreatic cyst or tumor. In the absence of a clear family history (cryptic cases), the presence of at least 2 VHL lesions, including 1 hemangioblastoma of the CNS or the retina, was required. All but 6 patients underwent complete screening for VHL lesions, including ophtalmologic examination, magnetic resonance imaging of the CNS, measurement of blood pressure and urinary metanephrins, and adrenal, renal, and pancreatic imaging by computerized tomography (CT) scanning with contrast enhancement.

Patients' ages at diagnosis of VHL disease and at documentation of pancreatic and extrapancreatic associated lesions were noted. A thorough record-based genealogic survey was performed for each patient. Symptoms possibly related to pancreatic lesions (abdominal pain, vomiting, jaundice, weight loss, diarrhea, or flushes) were also recorded.

Imaging Data

All patients in this series underwent CT scanning of the pancreatic region, which is known to be the most accurate imaging procedure for this purpose, at least once.[17] All examinations were reviewed by a radiologist who was experienced in pancreatic imaging and blind to the patients' clinical data. The following features were systematically collected: location, number, and type of pancreatic lesions (solid or cystic); size; density and calcifications; enhancement after contrast injection; wall (thickness, regularity, and limitations); peripancreatic organ compression; main pancreatic duct or biliary tree enlargement; and features of portal hypertension. When there were multiple lesions of the same type (i.e., numerous cysts or multiple NETs), the largest lesion was taken into account to calculate the mean diameter. Peripancreatic extension, lymph node involvement, or distant intra-abdominal metastases were assessed in cases of solid pancreatic tumors.

Criteria used at CT to determine the diagnosis of cystic lesions were as follows: true cysts (solitary or multiple) in lesions with a low-density cystic component and serous cystadenoma in well-limited cystic tumors, according to the criteria of Johnson et al.[18] These radiologic criteria are known to be accurate for this purpose and because of the low accuracy of fine-needle aspiration in the diagnosis of these lesions[19] and the potential morbidity of this procedure, we did not obtain pancreatic tissue by biopsy in patients who did not undergo surgery. The diagnosis of NET was confirmed histologically in patients undergoing surgery or endoscopic biopsies. In patients who did not undergo biopsies, the diagnosis was made when well-limited solid lesions strongly and homogeneously enhanced after contrast injection on CT and were confirmed by an additional procedure (endoscopic ultrasonography with characteristic NET features, i.e., homogeneous hypoechoic pattern with or without calcifications and peripheral rim enhancement, or positive somatostatin receptor scintigraphy). In addition, the absence of a history of invasive renal cancer was verified to exclude the possibility of pancreatic metastases.

The natural history of pancreatic lesions was assessed in 58 patients who underwent systematic screening (yearly abdominal CT scanning and other procedures to detect extrapancreatic VHL lesions) before the study began. To assess the course of pancreatic lesions in those in whom follow-up imaging was available, we considered modifications in lesions significant when there was a change in the perpendicular diameter of more than 25% (increase or decrease) and/or the presence of new lesions.

Other Investigations

Biochemical data (serum pancreatic enzyme levels, liver function tests, and blood glucose levels) were also recorded. These data were registered at the onset of the study, and not all parameters were available at follow-up. In patients with suspected NET on CT scanning, additional appropriate investigations were performed (serum and urinary peptide levels, somatostatin receptor scintigraphy, and endoscopic ultrasonography).

Surgical and histopathologic data were recorded in all patients who underwent pancreatic surgery.

Results

Population Characteristics

A total of 158 patients (65 male and 93 female) from 94 families were studied. Mutations in the VHL gene were identified in 74% of the probands studied (Olschwang et al.[20] and unpublished data). Mean age was 36 years (range, 13–80 years). Diagnostic modalities of VHL, based on symptoms (and primary system involvement) or systematic screening, are shown in Table 1. In 42 patients, the diagnosis of VHL disease was based on

Table 1. Circumstances of Diagnosis of VHL Disease in the 158 Patients Studied

	Patients [n (%)]
Neurologic symptoms	59 (37)
Ophthalmologic symptoms	27 (17)
Hypertension	15 (9)
Renal symptoms	6 (4)
Pancreatic symptoms	3 (2)
Systematic screening	42 (27)
Fortuitous diagnosis	6 (4)

Table 2. Description of Lesions in the 122 VHL Patients With Pancreatic Involvement

Pancreatic lesions	n (%)[a]	Female (%)	Mean age (yr)	Size[b] (mm) [mean (range)]	Localization		
					Head-neck	Body-tail	Disseminated
Single cysts	16 (10.1)	8 (50)	36	10 (4–30)	5	10	—
Multiple cysts	96 (60.8)	60 (62)	34	26 (5–90)	4	15	77
Serous cystadenomas	15 (9.5)	12 (80)	47	45 (20–170)	6	6	3
NET	15 (9.5)	10 (66)	38	36 (10–100)	9	5	1
None	36 (22.8)	20 (56)	36	—	—	—	—

[a]Overall total is >100% because of combinations of differents types of lesions in several patients.
[b]Median size of lesions. When multiple lesions were present, the largest one was taken into account for analysis.

systematic screening in a familial context. In 6 patients, the diagnosis was made by chance during abdominal imaging for an unrelated cause (n = 5) or pregnancy (n = 1).

Morphologic Data

Pancreatic involvement was present in 122 of 158 patients (77.2%). The pancreas was the only organ affected in 12 patients (7.6%) who underwent complete screening. The sex ratio and patients' age did not differ in the presence or absence of pancreatic involvement (Table 2). Of the 122 patients with pancreatic involvement, 112 (91.1%) had isolated or multiple cysts, 15 (12.3%) had NET, and 15 (12.3%) had serous cystadenomas. Seventeen patients (11.5%) had a combination of different lesions, including 2 types in 14 patients (multiple cysts and NET, n = 8; multiple cysts and serous cystadenomas, n = 6) and 3 types in 3 patients (multiple cysts, serous cystadenomas, and NET). The distribution, size, and location of pancreatic lesions are shown in Table 2. Calcifications were seen in 3 patients with solitary cysts (19%), 39 with multiple cysts (41%), 3 with NET (20%), and 8 with serous cystadenomas (53%). In patients with multiple cysts, the number of calcifications included 1 in 21 patients, 2 or 3 in 13 patients, and 4 or more in 5 patients. None of the cystic lesions in this series had radiologic features suggesting malignancy (i.e., thick or irregular capsule and/or intracystic vegetations).

Histologic confirmation was obtained in 10 patients with suspected NET (examination of resected specimen, n = 8; duodenal biopsy of an invasive tumor, n = 1; or intraoperative biopsy, n = 1). Immunohistochemical analysis showed positive staining with both anti–chromogranin A and anti-synaptophysin antibodies in all cases. Among the 5 patients without histologic confirmation, 4 patients underwent endoscopic ultrasonographic examination, and their tumors had characteristic NET features (see Patients and Methods) of small size (<2 cm in diameter). In 1 of them, fine-needle aspiration was performed but the sample was noninformative (i.e., hemorrhagic). In the 3 remaining patients, either the tumors were very small or the anatomic conditions were not favorable and prevented safe needle aspiration. Results of somatostatin receptor scintigraphy were negative in these patients. Finally, 1 patient with a tumor that was highly suggestive of NET on CT scanning refused further investigations.

Compression of the main pancreatic duct or neighboring organs was found in 23 patients (18.8%): 4 patients had compression of the main pancreatic duct by cysts (n = 3) or NET (n = 1); 12 had mesenterico–portal venous system compression caused by multiple cysts (n = 8), serous cystadenoma (n = 3), or NET (n = 1); and 3 had subsequent segmental portal hypertension. Otherwise, asymptomatic compression of the biliary tract (n = 3) or the duodenum (n = 3) caused by multiple cysts or serous cystadenoma was observed. Finally, 1 patient had compression of the stomach by a large pancreatic cyst.

Biochemical Data of VHL Patients With Pancreatic Involvement

During the study period, diabetes mellitus was present in 3 patients: 1 with mild pancreatic involvement, including 4 infracentimetric cysts; 1 in whom the pancreas was entirely replaced by cysts; and 1 in whom the pancreas was replaced by a panglandular cystadenoma. None of the 15 patients with NET had clinical symptoms of hormonal hypersecretion. Among 5 of those who underwent complete clinical, biochemical, and imaging investigations, 2 had increased somatostatin serum levels (8 and 20 times the upper limit of normal values [N], respectively) and 1 with liver metastases had a slightly high neuron-specific enolase level (1,2 N). A mild increase in several serum peptides values (thyrocalcitonin, 4 N; adrenocorticotrophin, 4 N; glucagon, 2 N; somatosta-

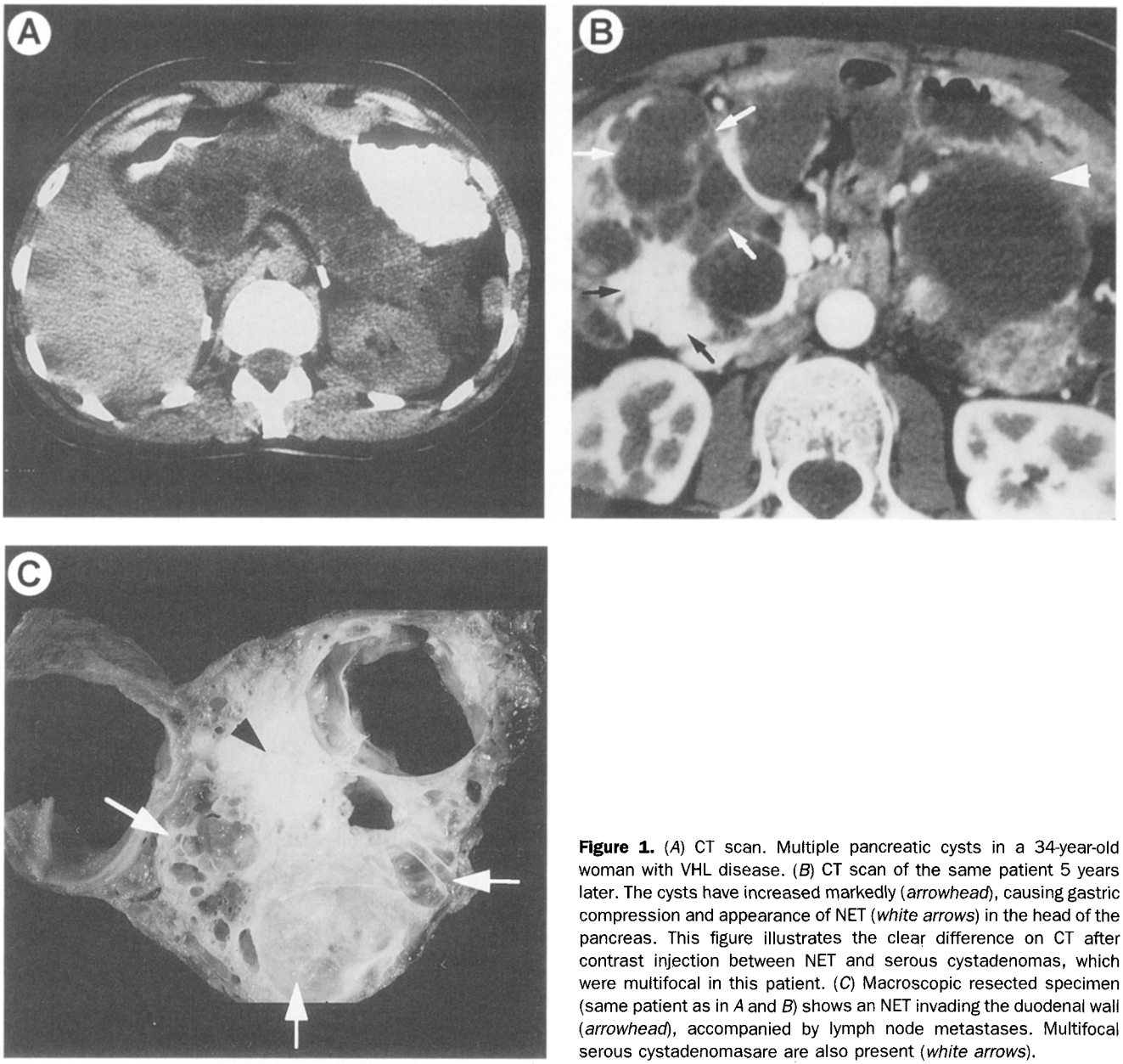

Figure 1. (*A*) CT scan. Multiple pancreatic cysts in a 34-year-old woman with VHL disease. (*B*) CT scan of the same patient 5 years later. The cysts have increased markedly (*arrowhead*), causing gastric compression and appearance of NET (*white arrows*) in the head of the pancreas. This figure illustrates the clear difference on CT after contrast injection between NET and serous cystadenomas, which were multifocal in this patient. (*C*) Macroscopic resected specimen (same patient as in *A* and *B*) shows an NET invading the duodenal wall (*arrowhead*), accompanied by lymph node metastases. Multifocal serous cystadenomasare are also present (*white arrows*).

tin, 4 N) was found in a patient with renal insufficiency requiring chronic dialysis.

Course of Pancreatic Lesions

Repeated CT examination was available in 58 patients with a median of 30 months of follow-up (range, 12–108 months). Overall, changes occurred in pancreatic lesions over time in 48% of patients, with most lesions increasing in size. One of the 9 patients (11%) without pancreatic lesions at the initial assessment developed multiple cysts at 30 months of follow-up. Among the 36 patients with pancreatic cysts (isolated, n = 6; multiple, n = 30), lesion modification occurred in 20 (66%; increase, n = 17; decrease, n = 3) and calcifications appeared in 6. The size of lesions increased in 2 (29%) of the 7 patients with serous cystadenomas. A dramatic example is shown in Figure 1.

Retrospective analysis of CT performed 72 and 78 months before entry into the study showed that the tumor was already visible in 2 of 15 patients with NET. In 1 patient, the tumor size was stable until surgery (patient 9; Table 3). In the other patient, there was a metastatic course (patient 4; Table 3 and Figure 2). In 4 other patients, NET appeared within a follow-up period of 12–63 months. Three of these patients underwent surgical resection (patients 3, 7, and 8; Table 3). The remaining patient received palliative care (patient 5).

Table 3. Description of the 10 Patients With VHL Disease Who Required Medical or Surgical Treatment for Pancreatic Lesions

Patient	Sex/ age (*yr*)	Symptoms	Pancreatic lesions implicated/site	VHL lesions other than pancreatic	Treatment and course
1	F/43	Abdominal pain revealing VHL disease	Cyst/body	Hb CNS and retina	Cyst drainage (radiological) Disappearance of symptoms
2	F/54	Necrotizing pancreatitis revealing VHL disease	Cysts/body	Hb CNS + retina RCC	Medical management for pancreatitis + nephrectomy; died at 16 mo (metastatic progression RCC)
3	F/34	Abdominal pain	Cyst/body	Hb CNS + retina Renal cysts/pheo	Cyst marsupialization + duodenopancreatectomy to treat NET (head)
4	M/34	Abdominal pain	NET/head Duodenal invasion Liver metastases	Hb CNS + retina	Chemotherapy Renal cysts/pheo
5	F/42	Abdominal pain	NET/head Metastatic	Hb CNS + retina RCC/pheo	Chemotherapy; died at 12 mo of metastatic progression
6	F/24	Abdominal pain revealing NET	NET/body	Hb CNS + retina	Left pancreatectomy, with no evidence of relapse after 6 mo
7	M/26	Abdominal pain revealing NET	NET/body	Hb CNS + retina	Duodenopancreatectomy; well after 2 mo
8	F/28	Asymptomatic	NET/head	Hb CNS/pheo	Duodenopancreatectomy; well after 21 mo
9	M/38	Asymptomatic	NET/body	Hb CNS + retina RCC/pheo	Left pancreatectomy; well after 19 mo
10	M/47	Asymptomatic	NET/head	Hb retina RCC	Duodenopancreatectomy; well after 6 mo

RCC, renal cell carcinoma; pheo, pheochromocytoma; Hb, hemangioblastoma.

Clinical Characteristics and Treatment of Patients With Pancreatic Lesions

Ten patients with pancreatic involvement (8.2%) required medical or surgical management of their lesions (Table 3). Seven of them (5.7%) had symptoms requiring treatment, and 3 patients underwent pancreatic resection for large NET. Pancreatic lesions revealed VHL disease in 2 patients (patients 1 and 2; Table 3). The first had diffuse upper abdominal pain attributed to a large pancreatic cyst (Figure 3). Symptoms improved after fine-needle aspiration. Cystic fluid analysis showed the following: amylase, 4 U/mL; carcinoembryonic antigen

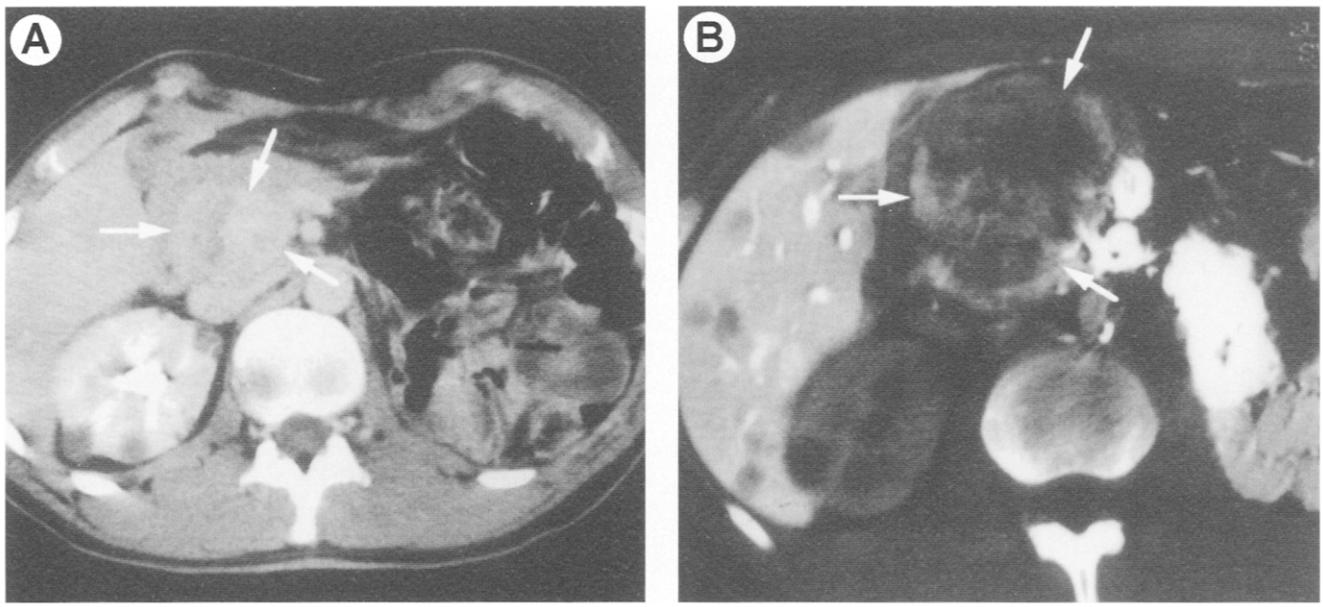

Figure 2. (*A*) Suspicion of a vascularized tumor in the head of the pancreas (*arrows*) in a 27-year-old patient with VHL disease. Intraoperative biopsy results were negative. (*B*) CT portography in the same patient 6 years later shows significant progression of the pancreatic tumor (*arrows*) and multiple liver metastases. The diagnosis of NET was established after analysis of endoscopic biopsy specimens obtained from a large ulcer of the second part of duodenum resulting from tumor extension.

(CA), 1 ng/mL; Ca 19.9, 273 U/mL; Ca 72.4, 3 U/mL. A complete examination showed a solid tumor of the left kidney as well as CNS and retinal hemangioblastomas. Screening performed in the patient's son revealed pancreatic and renal cysts. The second patient, whose history has been previously reported in part,[21] had acute necrotizing pancreatitis caused by cysts compressing the main pancreatic duct. She had no family history of VHL disease. Investigations performed showed multiple CNS hemangioblastomas and renal clear-cell carcinoma. The treatment and clinical course of this patient are shown in Table 3. In addition, 5 other patients became symptomatic during follow-up (patients 3–7; Table 3). An example of a dramatic progression in pancreatic lesions resulting in symptoms (patient 3) is shown in Figure 1*A* and *B* and Table 3. Cyst fluid analysis of this patient showed the following: amylase, 6 U/mL; lipase, 25 U/mL; carcinoembryonic antigen, 0; carbohydrate antigen 19.9, 400 U/mL; and Ca 72.4, 3 U/mL. Histologic examination of the resected specimen showed bifocal NET of the pancreatic head that extended to the duodenal wall and 2 peritumoral metastatic lymph nodes, as well as multifocal serous cystadenomas (Figure 1*C*). Three other patients (patients 4–6) became symptomatic because of progression of an NET (Figure 2*A* and *B* and Table 3). A further 3 patients (patients 8–10) underwent elective resection of NET >3 cm in diameter to prevent the development of metastases. Histology of the resected specimen showed multiple NET in 2 specimens, 1 of which had multiple adenomas suggesting nesidioblastosis. An example of histologic analysis showing the multicentricity of NET (patient 10) is shown in Figure 4. Peritumoral lymph node metastases were present in 2 cases. The treatment and clinical course of these patients are summarized in Table 3.

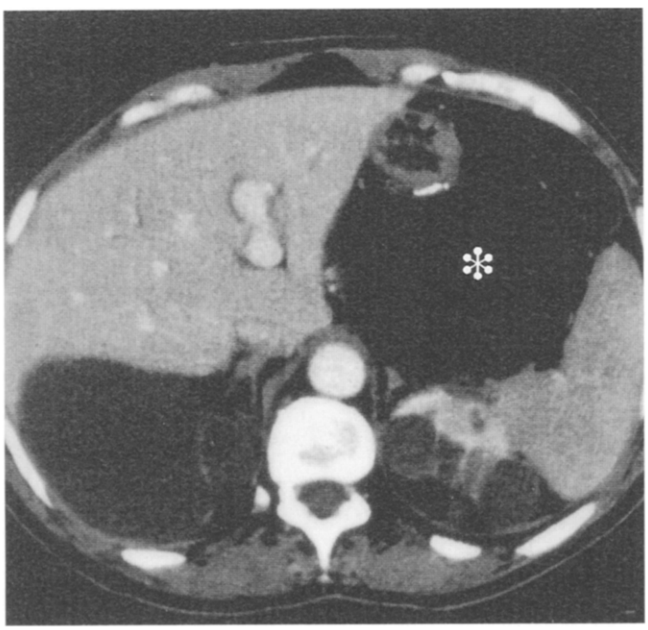

Figure 3. CT scan (after contrast injection) showing a large cyst of the pancreas (*) resulting in abdominal pain, leading to a diagnosis of VHL disease. A left renal tumor was also present.

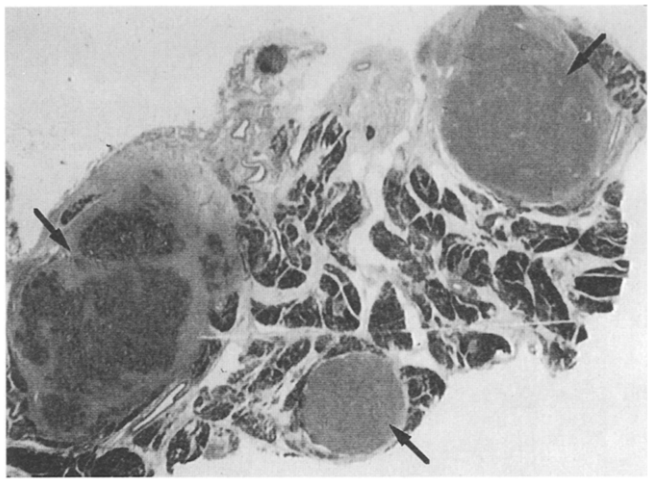

Figure 4. Example of histologic analysis (original magnification 3×) of a resected specimen showing the multicentricity of NETs in a patient with VHL. Adenomas of various size are indicated by *black arrows*.

Extrapancreatic Involvement With VHL Lesions

Among the 158 patients studied, associated extrapancreatic lesions included hemangioblastomas of the CNS (120 cases; 76.4%) or retina (90 cases; 57%); renal cysts or carcinomas (123 cases; 79.9%); and pheochromocytoma (30 cases; 19.1%). Table 4 shows the combination of pancreatic and extrapancreatic lesions. The presence of pancreatic lesions was associated with fewer pheochromocytomas than the absence of pancreatic lesions (14/122 vs. 16/36; $P < 0.0001$), and NET correlated negatively with renal involvement (8/99 vs. 6/20; $P = 0.013$).

Discussion

In previous reports, the frequency of pancreatic involvement in VHL disease has varied from 0% to 72%, with a mean incidence of approximately 50% when the largest series are pooled.[5–7] In our study, the prevalence of pancreatic involvement was higher (77%) and similar to that reported in an autopsy series of 29 patients with VHL disease reported by Horton et al.[16] Bias in the recruitment in our study favoring inclusion of patients with pancreatic lesions is unlikely because all but 3 patients were seen first by nongastroenterology specialists. Moreover, the prevalence of extrapancreatic VHL

Table 4. Other VHL Lesions According to Pancreatic Involvement in the 158 Patients Studied

	Other VHL lesions			
	Hemangioblastomas			
Pancreatic lesions	CNS (%)	Retina (%)	Kidney cysts/tumors (%)	Pheochromocytoma (%)
Single cysts	88	65	82	24
Multiple cysts	78	55	84	9
NET	64	64	57[a]	29
Serous cystadenomas	64	79	93	21
None	69	64	67	44[b]
Total	84	68	78	22

[a] $P = 0.013$.
[b] $P < 0.0001$.

lesions corresponded to that reported in the literature.[1,4] Systematic examination of all patients by CT scanning reviewed by an experienced radiologist optimized the detection of small pancreatic lesions,[5,6] particularly isolated cysts. Genetic factors may also influence the estimation of pancreatic involvement in VHL patients. For example, Neumann et al.[7] reported a 17% prevalence of pancreatic involvement in a series of 66 patients. After the 22 families from their series were genotyped, a common founder effect mutation at codon 98 of the VHL gene (Tyr98His) was identified.[22] The latter is known to be associated with a VHL phenotype in which pheochromocytomas are frequent but renal and pancreatic lesions are less frequent.[3] In contrast, patients in our series were from 94 different families originating from several regions in France and had various types of mutations in the VHL gene (Centeno et al.[19] and unpublished data).

Our study confirms that most pancreatic lesions in VHL disease are asymptomatic and are discovered during systematic screening of family members with VHL.[5–7] However, lesion size was found to increase in approximately half of the patients during follow-up. Compression of the main pancreatic duct or neighboring organs occurred in almost 20% of patients. Acute pancreatitis caused by stenosis of the main pancreatic duct by cysts has been described.[23] One patient in our study had pancreatitis leading to a diagnosis of VHL disease at an unusually advanced age, and 2 others had abdominal pain because of NET compressing the main pancreatic duct. Digestive, biliary, or venous compression in patients with VHL disease is not rare, but determining its potential clinical impact requires longitudinal follow-up. VHL disease was discovered by chance in 6% of patients during abdominal imaging performed for unrelated reasons. Thus, the possibility of VHL disease should be considered when the pancreatic lesions outlined above are discovered. The diagnosis of isolated pancreatic involvement, as illustrated in 12 VHL patients studied in our present study, can be a key factor in establishing the diagnosis in collaterals of VHL patients when the VHL gene mutation has not been identified.[1]

This large series gives an idea of the prevalence and the type of lesions that may occur in pancreatic involvement of VHL disease. We confirm that true cysts are the most predominant lesion. Hyperproduction of VEGF, also known as vascular permeability factor, may favor pancreatic and/or renal cyst formation in VHL patients.[2] Multiple pancreatic cysts are highly suggestive of VHL disease, although they can be found in other genetic disorders. These lesions occur in up to 10% of patients with polycystic kidney disease[24] and in the rare Ivemark[25] and Gruber[26] syndromes. We did not assess pancreatic exocrine function, but no patients with multiple cysts or panglandular cystadenomas had obvious malabsorption symptoms. The risk of diabetes mellitus is also probably low, even when the pancreatic parenchyma is completely replaced with cysts.[27]

We found that isolated cysts represented 15% of pancreatic lesions. Despite the presence of small cysts at autopsy,[28] congenital solitary cysts represent a very small proportion of cystic pancreatic lesions.[29] The differential diagnosis between these purely benign cysts and potentially or frankly malignant cystic lesions of the pancreas (i.e., cystic NET, mucinous cystadenoma, or cystadenocarcinoma) is not problematic because the former have not been described in VHL disease, and none of the cystic lesions in this series had radiologic features suggesting malignancy (i.e., thick or irregular capsule and/or intracystic vegetations). Pseudocysts are rare, especially in the absence of pancreatitis and in normal-sized pancreatic ducts. Calcifications, observed in 40% of VHL patients with pancreatic cysts, are thin and peripheral and differ from those in chronic pancreatitis.[30] The low levels of pancreatic enzymes and tumor markers found in the cystic fluid of 2 patients in this study clearly differ from those reported in mucinous cystadenomas and pseudo-

cysts.[31] Finally, isolated cysts in VHL patients may be serous cystadenomas in a rare macrocystic form.[32]

Serous cystadenomas are rare pancreatic exocrine tumors that occur at an unusually high frequency in patients with VHL disease.[5–8,10,33,34] They accounted for nearly 10% of pancreatic lesions in this series, and their prevalence may even have been underestimated because of the difficulty in distinguishing this tumor from a cluster of multiple small true cysts in VHL disease. In practice, however, differentiation between the 2 does not modify the therapeutic approach.[5,6] We and others[33] have suggested that serous cystadenomas in panglandular and/or multiple forms, or encountered in many family members, are specific to VHL disease. Despite previous reports of jaundice from common bile duct compression caused by a serous cystadenoma in VHL disease,[10] this complication was not observed in our series.

The frequency of NET in VHL patients in our study corresponds to the 10%–17% prevalence reported by other investigators.[6,13] The differential diagnosis between NET and other vascular tumors of the pancreas in VHL is limited.[5] Rare cases of pancreatic hemangioblastomas have been reported, but immunohistochemistry was not performed to exclude the possibility of NET in these lesions.[14] Only 1 case of pancreatic metastasis from renal cancer has been reported, despite the high frequency of the latter in VHL disease.[15] Finally, NET can be difficult to distinguish on CT scans from a solid form of vascularized serous cystadenomas.[5,13] Somatostatin receptor scintigraphy and endoscopic ultrasonography with possible tumor fine-needle aspiration biopsy may help in the preoperative distinction.[35] An isolated NET can represent the only lesion of VHL disease.[36] We and others have shown that NETs in VHL patients are often multiple and disseminated throughout the pancreas, making therapeutic decisions difficult. This form of presentation, associated with a high prevalence of pheochromocytoma, suggests multiple endocrine neoplasia. However, the lower prevalence of NET in VHL, the rarity of hormone-secreting tumors, and the lack of demonstrable multiple adenomas and nesidioblastosis did not support this possibility.[12] Our results could suggest the necessity of re-evaluating the relationship between VHL and multiple endocrine neoplasia because symptomatic hormone hypersecretion, especially somatostatin, is not rare in VHL patients with NET, as shown in our study and others,[11,37,38] and nesidioblastosis adjacent to NET was found on histologic examination of a resected pancreatic specimen in 1 patient in this series. There is a risk of malignant transformation of NET in VHL patients, and metastatic progression has been shown to occur in 25% of cases.[4,7,11,13] Five patients in our series underwent surgery to treat symptomatic NET or to prevent metastatic progression in large lesions. All NET >3 cm in diameter were highly aggressive tumors, as shown by invasion of the duodenum and lymph nodes or liver metastases. Therapeutic decisions in VHL patients with pancreatic NET can be a problem because the presence of multiple, various-sized NET makes surgical resection difficult and because these patients are often simultaneously affected by various life-threatening tumors of the CNS, adrenal glands, or kidneys that require priority treatment. Because the number of patients who underwent surgical resection for NET in our series is limited, we cannot draw definite conclusions on the management of these lesions. However, our results on tumor aggressiveness in NET >3 cm support those recently reported by other investigators who suggest that these large lesions should be resected whenever possible.[13]

Despite earlier reports associating pancreatic adenocarcinoma with VHL,[4] no cases were observed in the present study. Moreover, in a VHL patient with both pancreatic adenocarcinoma and NET, Lubensky et al.[12] found preservation of genetic heterozygosity in the former lesion and deletion of the nonmutated allele in the latter. Generally, the risk of adenocarcinoma in VHL patients appears to be similar to that in the general population.

In conclusion, pancreatic involvement occurs in most patients with VHL disease. Although symptoms are rare, medical or surgical treatment is required in selected patients with pancreatic lesions. The occurrence of pancreatic NET in patients with VHL disease requires careful evaluation because of their potential malignancy and the difficulties of therapeutic decision making.

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