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CLINICAL, GENETIC AND RADIOGRAPHIC ANALYSIS OF 108 PATIENTS WITH VON HIPPEL-LINDAU DISEASE (vHL) MANIFESTED BY PANCREATIC NEUROENDOCRINE TUMORS (PNETs)

Joseph A. Blansfield, MD¹, Lynda Choyke, DPM², Shane Y. Morita, MD¹, Peter L. Choyke, MD³, James F. Pingpank, MD¹, H. Richard Alexander, MD¹, Geoffrey Seidel, RN¹, Yvonne Shutack, RN¹, Nargiza Yuldasheva, RN¹, Michelle Eugeni, RN¹, David L. Bartlett, MD¹, Gladys M. Glenn, MD, PhD², Lindsay Middleton, RN², W. Marston Linehan, MD², Steven K. Libutti, MD¹

¹:Tumor Angiogenesis Section, Surgery Branch, National Cancer Institute, NIH

²:Urologic Oncology Branch, National Cancer Institute, NIH

³:Molecular Imaging Program, National Cancer Institute, NIH

Abstract

BACKGROUND—vHL is an autosomal dominant syndrome associated with tumors in multiple organs including the pancreas. Here we report on the largest single center experience with vHL PNETs.

METHODS—Between 12/88 and 11/06, 633 patients with vHL were evaluated and those with PNETs were enrolled on a prospective protocol.

RESULTS—One hundred eight vHL patients had PNETs (17%). Nine had metastatic disease (8.3%) from their PNET. Patients with lesions >3 cm (n=25) were more likely to develop metastases than patients with lesions ≤3 cm (n=83) (p<0.0046). Thirty-nine patients underwent resection. Germ line sequencing showed that 78% (7/9) of patients with metastases had exon 3 mutations compared with 46% (32/98) of patients without metastases (p<0.01). Tumor doubling time (TDT) was calculated for the largest PNET. The group with metastases had an average TDT of 337 days (range: 180 to 463) compared with 2628 days (range: 103 to 9614) for those without metastases (p<0.0001).

CONCLUSIONS—By implementing a system of selective surgical resection based on defined criteria, vHL patients with PNETs can be safely managed. For patients with small primary lesions

Address correspondence and reprint requests to: Steven K. Libutti, M.D., Head, Tumor Angiogenesis Section, Surgery Branch, National Cancer Institute, NIH, 10 Center Drive, CRC 4W-5940, Bethesda, MD 20892, Telephone: 301-496-5049, libuttis@mail.nih.gov, Fax: 301-402-1788.

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(<3 cm), without a mutation of exon 3 and slow TDT (>500 days), a non-operative approach may be appropriate for these non-functional tumors.

INTRODUCTION

Von Hippel-Lindau disease (vHL) is an autosomal dominant syndrome which predisposes individuals to a variety of tumors. VHL is associated with tumors in a variety of organs including the kidney (renal cell carcinoma), adrenal (pheochromocytoma), central nervous system (hemangioblastoma), the eye (retinal angioma), the inner ear (endolymphatic sac tumor), the epididymis (epididymal cystadenoma) as well as the pancreas (cystic and solid lesions).

Most of the pancreas lesions associated with vHL are cystic or serous cystadenomas. These cystic lesions can occur as a single lesion or as multiple lesions and can occur in 17–56% of patients with vHL.^{1,2} These lesions have no malignant potential but can replace enough of the pancreas to cause endocrine or exocrine insufficiency of the pancreas or cause compression of the intestine or the bile duct. VHL is also linked to neuroendocrine tumors of the pancreas (PNETs). These lesions, which are always nonfunctional, can be malignant. PNETs have been previously reported to be present in 12–17% of patients with vHL and these tumors behave in a malignant fashion in up to 17% of patients.^{3,4} An association between PNETs and pheochromocytoma has been reported.⁵

PNETs remain an uncommon cause of death, even in patients with vHL, but do have the capacity to metastasize in certain instances. Up until now, size of the primary PNET has been the only predictor of malignant potential. The purpose of this study was to attempt to better understand the pathologic condition and behavior of solid pancreatic neoplasms associated with vHL in order to further elucidate a diagnostic and management strategy for these patients. This strategy's goal is to minimize the risk of metastatic disease from pancreatic neuroendocrine tumors while maximizing the preservation of pancreatic function and minimizing an individual patient's risk from surgery and unnecessary testing.

PATIENTS AND METHODS

From December 1988 through November 2006, 633 patients with vHL were evaluated by a multidisciplinary team at the National Institutes of Health. These patients were treated on a National Cancer Institute Institutional Review Board approved protocol. Patients underwent a comprehensive evaluation including a complete history and physical examination, and directed imaging studies that included ultrasonography, computed tomography (CT) scanning, magnetic resonance imaging (MRI), and laboratory studies (including serum chemistries). Each patient was evaluated by a team of medical professionals which included internists, endocrine surgeons, urological surgeons, otolaryngologists, neurosurgeons, genetic counselors, and audiologists. Follow up on patients is complete through March 2007.

The diagnosis of PNET was made either by pathologic analysis of tissue specimens or by characteristic radiographic appearance on CT and MRI.^{3,6,7} Metastasis in this group of patients was defined as an imageable visceral (lung, liver, etc.), bony, soft tissue or lymph node lesion radiologically consistent with or biopsy confirmed to be a neuroendocrine

tumor. VHL germline mutations were determined by quantitative Southern blotting to detect gene rearrangements, and complete gene sequencing as described previously.⁸ Tumor doubling time was obtained by measuring the longest diameter of the largest pancreatic lesion at baseline and on at least one subsequent CT scan for each patient. If more than 2 sequential scans were measured then the doubling times over these time points were averaged to obtain a doubling time for the patient's lesion. The formula used for tumor doubling time was $T_i \times \log 2 / 3 \times \log (D_i/D_o)$ where T_i was the time interval, D_i was the initial diameter and D_o was the final diameter. Statistical analysis was performed on GraphPad InStat software to calculate two sided p values using Fisher's exact test.

The decision to perform a surgical resection of a neuroendocrine tumor of the pancreas was based on criteria outlined previously.^{3,9} Tumors were resected if the lesion was greater than 3 cm in diameter (or greater than 2cm if located in the head of the pancreas), and if there was no evidence of metastatic disease associated with the PNET, or if the patient was undergoing a laparotomy for the management of another pathological manifestation of vHL and a pancreatic resection could be done with minimal morbidity. If a patient's tumor did not meet these criteria the patient was followed prospectively with serial radiologic scans of the abdomen.

RESULTS

One hundred eight patients with PNETs have been identified out of 633 with vHL screened (17%). Patient demographics are outlined in Table I. The male to female ratio was 1:1.12 and the mean age at diagnosis of the PNET was 38 years (range, 16–68 years). The majority of patients (76 patients, 70%) had a single lesion in the pancreas. Serum hormone testing has been performed on all one hundred eight patients. This testing included serum levels of insulin, glucagon, pancreatic polypeptide and vasoactive intestinal peptide. No patient had a functional tumor by hormone levels or by symptoms. The median follow up time for this patient population was 52.5 months (range: 2–189 months).

Thirty-nine patients have had definitive surgical treatment for their disease to date. These patients have undergone a variety of pancreatic procedures dictated by the number and location of their pancreatic lesions as well as the proximity of the lesion to the pancreatic duct. These results are summarized in Table II. Thirty-five patients are being prospectively followed, one patient has died from complications due to metastases from their PNET, one patient died peri-operatively and two patients have died of other causes related to their vHL. In our series of thirty-nine patients, we had one patient who died in the perioperative period (2% mortality rate) most likely due to an underlying cardiac condition. In this group of thirty-nine patients our operative morbidity rate was twenty-eight percent (11 patients out of 39). The most common complication in this population was pancreatic fistula seen in five patients (13%), followed by infectious complications in 3 patients (8%).

One hundred seven patients have undergone genetic testing for germline mutation analysis. A majority of patients had missense mutations (54%), while 30 patients had deletions (27%), and 9 patients each had frameshift or nonsense mutations (8% each). Of the patients with specific exon mutations, exon 3 was most commonly involved (39 patients out of 77, 50%).

Exon 3 was also more commonly involved in patients with metastatic disease (7 out of 9 patients, 78%) compared with patients without metastatic disease (32 patients out of 98, 46%). This difference was statistically significant ($p<0.01$).

There have been nine patients in our series with metastatic disease confirmed from their pancreatic neuroendocrine tumors. In all nine of our patients with metastatic disease, imaging and confirmatory biopsy were consistent with distant spread of the disease. Two out of the nine patients have died due to complications from their PNET metastases. Table III summarizes some of the differences in the patients who have metastatic disease compared to the patients without metastatic disease. Sixty-seven percent of patients with metastatic disease (6 patients out of 9) compared with nineteen percent of patient without metastatic disease (19 patients out of 99) had primary lesions which were greater than three centimeters in diameter ($p<0.0046$)(See Figure 1). As stated previously exon 3 mutations were more prevalent in patients with metastatic disease. Tumor doubling times were measured in the patients with and without metastatic disease. In 9 out of 9 patients with metastatic disease and 54 out of 99 patients without metastatic disease at least two sequential CT scans were available to compute a doubling time. The mean doubling time of the primary PNET for patients with metastatic disease was 337 days (range, 180 to 463 days). The mean doubling time of the primary PNET for patients without metastatic disease was 2628 days (range, 103 to 9614 days). The difference in the doubling time was statistically significant ($p<0.0001$). Figure 2 shows graphically the rate of growth of each individual patient's largest primary tumor.

Table IV stratifies patients by the three criteria which were associated with metastatic disease. Of the nine patients with metastatic disease, all nine had at least 2 of these criteria. Of the patients who do not have metastases, only five patients out of fifty-four have two criteria present and the remaining 49 have either one or no high risk criteria present.

DISCUSSION

Patients with the vHL mutation can develop a variety of tumors affecting a variety of organs. They are prone to kidney tumors (renal cell carcinomas), adrenal tumors (pheochromocytomas), epididymal tumors (cystadenomas), central nervous system tumors (hemangioblastomas), retinal tumors (angiomas), inner ear tumors (endolymphatic sac tumors), and pancreatic tumors (neuroendocrine tumors). Because of the number of organs involved, and the number of lesions which can be present, the management of these patients can become quite complex. Lesions associated with the pancreas have traditionally been managed surgically due to their potential for malignancy. However, surgical management of these patients is not without morbidity and mortality. Since these lesions are non-functional, resection must be predicated on a potential benefit due to a reduction in the risk of metastasis and therefore a positive impact on survival.

Until now, our group has based its management strategy on the size of the primary lesion. After following these 108 patients closely over a median of 52.5 months of follow-up we have found that the size of the primary lesion, presence of an exon 3 mutation, and tumor doubling time can all be used as prognostic indicators for metastatic disease in patients with

vHL who present with PNETs. Because none of our patients had functioning tumors, serum hormone levels are not a good indicator for the presence of a PNET and we recommend patients undergo serum hormone testing only in the unlikely event that they have symptoms.

Based on these prospective findings, a more rational management for the follow-up of these patients can be based on these three criteria: 1) tumor size greater than or equal to three centimeters, 2) presence of a mutation in exon three, and 3) tumor doubling time less than 500 days. If the patient has none of these criteria we feel the likelihood of the patient's lesion resulting in metastatic disease is very low and the patient can be followed with a history and physical examination and radiologic scans on a two to three year cycle. If the patient has one criterion present the patient should be followed more closely every six months to a year to detect the manifestation of a second criterion. If the patient has two or three criteria the patient should be considered for surgical management of his or her lesion because of the higher likelihood of future malignancy from their PNET. Figure 3 summarizes these recommendations.

We believe that this strategy will help us better identify those patients at a higher risk of developing metastatic disease from their PNET and therefore those patients who may benefit from surgical intervention. It is important to put the overall risk of metastatic disease from a PNET in a patient with vHL into proper perspective. Of the 633 patients with confirmed vHL that we have screened at the NIH over the past 18 years, only 108 (17%) have been found to have PNETs (all non-functional) and only 9 (1.4%) have developed metastatic disease. This is in contrast to more common lesions such as renal cell carcinoma which can occur in up to forty-five percent of patients and when left untreated can lead to death from metastases in 13–42% of patients.^{10, 11} Therefore, renal lesions have a much higher impact on survival than do PNETs. To routinely resect all PNETs in patients with vHL would be to subject these patients to unnecessary morbidity and mortality. By using the criteria we propose, all 9 patients who developed metastases in our series would have been identified as well as several additional patients at possible risk. As important, many patients at lower metastatic risk would be spared the risks of surgery. The ultimate impact of this approach on the management of these patients and on the reduction of metastatic risk will only be known as we continue to follow these patients.

CONCLUSIONS

By implementing a system of selective surgical resection based on defined criteria, vHL patients with PNETs can be safely managed. For patients with small primary lesions (<3 cm), without a mutation of exon 3 and slow tumor doubling times (>500 days), a non-operative approach may be appropriate for these non-functional tumors.

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Figure 1:

Scatterplot of the tumor diameters of primary PNETs comparing patients with and without metastatic disease. Sixty-seven percent of patients with metastatic disease (6 patients out of 9) compared with nineteen percent of patient without metastatic disease (19 patients out of 99) had primary lesions which were greater than three centimeters in diameter ($p < 0.0046$).

Figure 2:

The rate of growth of the diameter of the primary PNET in patients with vHL. The dashed lines are growth rates for individuals who had metastatic disease. The solid lines are growth rates for individuals without metastases.

Figure 3:
Treatment and follow-up recommendations for patients with PNETs.

Table I.**Demographics**

Patients with vHL Screened	
December 1988 to November 1, 2006	633
Patients with PNET	
	108 (17%)
Male:Female	51:57
Mean age (y)	38 (range 16–68)
No. of pancreatic tumors per patient	
N=1	76
N>1	32
No. of Patients Resected	39
No. of Patients with Metastatic Disease	9

Table II.**Solid Pancreatic Tumors in vHL: Surgical Management in 39 Patients**

Enucleation	16/39	41%
Distal Pancreatectomy	14/39	36%
Laparoscopic Resection	2/39	5%
Whipple Resection	11/39	28%
Total Pancreatectomy	2/39	5%

* Some patients had more than one procedure performed at the same setting

Table III.

Comparison of Patients with and without metastatic disease from PNETs

	Metastatic Disease Present (Total)	Metastatic Disease Absent (Total)	P value
Male (Total)	2 (9)	49 (99)	<0.16
Size >3	6 (9)	19 (99)	<0.0046
>1 Primary Lesion	5 (9)	27(99)	<0.12
Location of Primary in the Head of Pancreas	8 (9)	75 (99)	<0.15
Exon 3 Mutation Present	7 (9)	32 (99)	<0.01
Mean doubling time (range)	337 days (9) (180–463)	2628 days (54) (103–9614)	<0.0001

Table IV.

Comparison of patients with or without metastatic disease from PNETs in the setting of vHL

No. of Criteria Met	No. of Pts with Metastatic Disease	No. of Pts. without Metastatic Disease
0 out of 3	0	29
1 out of 3	0	20
2 out of 3	3	5
3 out of 3	6	0

Criteria: 1) Exon 3 mutation, 2) Diameter of pancreatic lesion ≥ 3 cm, 3) Doubling time <500 days