CASE REPORT

Late Recurrence after Surgical Resection of a Pancreatic Tumor in von Hippel-Lindau Disease

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ABSTRACT

Context Patients with von Hippel-Lindau syndrome, a dominantly inherited familial cancer syndrome, develop a variety of tumors in different organ systems which make the clinical management of these patients complex. **Case report** The long clinical history of a 45-year-old woman started at 22 years of age when she had surgery for a right adrenal pheochromocytoma. Two years later, a pancreaticoduodenectomy was performed to remove a pancreatic mass which turned out to be a pancreatic neuroendocrine tumor. After a long period of relative wellness, 21 years after the surgical resection of her primary pancreatic neuroendocrine tumor, abdominal lymph node metastases of pancreatic neuroendocrine origin occurred. In fact, three abdominal nodules were removed by laparoscopic surgery, and the histological examination showed well-differentiated neuroendocrine tumors with similar immunohistochemical characteristics and Ki67 below 1%. Considering the patient's clinical history, an inherited cause was postulated and multiple endocrine neoplasia type 1 was first investigated, but the result was negative. Then, a missense mutation in exon 3 of the VHL gene (ACT>ATT; Thr157Ile) was found. **Conclusion** Although no local and/or distant tumor recurrences are usually reported in radically operated on von Hippel-Lindau pancreatic neuroendocrine tumor patients after a median time of five years of follow-up, the present patient had a recurrence after a very long period of time, suggesting that a pancreatic neuroendocrine tumor associated with von Hippel-Lindau syndrome may behave more aggressively than that has previously been described, thus requiring a life-long follow-up.

INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal dominant disease caused by a germline mutation of the VHL gene, a tumor suppressor gene located on the short arm of chromosome 3 (3p25-26) which regulates hypoxia-induced cell proliferation and angiogenesis [1]. VHL syndrome is associated with neoplasms in different organs such as the kidney (25-60%), adrenal gland (10-20%), central nervous system (44-72%), eye (25-60%), inner ear (10-25%), epididymis (25-60%) and pancreas (35-77%) [2]. Benign serous cysts represent the most frequent pancreatic involvement, but 5-10% of VHL patients develop pancreatic neuroendocrine tumors (PNETs), which are usually single and non-functional, having malignant behavior in up to 17% of patients, even if PNETs represent an infrequent cause of death in patients with VHL. Although PNETs develop in patients with VHL, no evidence of mutations in the VHL gene in sporadic PNETs has been reported, suggesting an unknown indirect role of the VHL gene in the pathogenesis of PNETs.

No specific genotype-phenotype correlations have been clearly defined for PNETs in VHL patients, even though a concomitant pheochromocytoma has frequently been observed (40% of VHL patients having PNETs). The majority of studies have evaluated the PNET tumor phenotype in VHL patients only at the time of the diagnosis, and less is known about the tumoral disease after long-term follow-up [3, 4]. Indeed, data on long-term PNET behavior, after radical excision of the primary tumor, are virtually absent.

CASE REPORT

A 45-year-old woman, who had been affected for several years by intermittent abdominal pain, was admitted to our outpatient service. She presented with a long clinical history which started at 22 years of age when she had surgery for an occasionally diagnosed right adrenal mass of 40 mm in diameter which histological examination revealed to be a pheochromocytoma. Two years later, a pancreatic head mass, with a diameter of 50 mm, was visualized by routine ultrasound examination and confirmed by computed tomography (CT) in the absence of any specific symptoms. In order to achieve a radical tumor excision, a pancreaticoduodenectomy was performed. After the operation, she had a long period of relative wellness, with only occasional diarrhea and/or mild abdominal pain. The patient was able to have a normal pregnancy and delivery.

Almost four years ago, the patients presented at our hospital for the first time due to an episode of acute
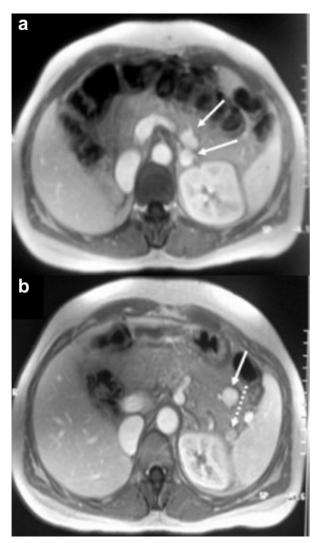
Figure 1. Abdominal MR arterial phase scan images. **a.** Tumor nodules close to the celiac artery (arrows). **b.** Tumor nodule close to the spleen (arrow), the accessory spleen (broken arrow).

hypertensive crisis; thus she was screened for pheochromocytoma. Twenty-four-hour collection urinary vanillyl mandelic acid (VMA; 6 mg/24 h, reference range: 1-11 mg/24 h) and metanephrine evaluation (120 µg/24 h, reference range: 0-300 µg/24 h) revealed normal values. Twenty-four-hour blood pressure monitoring also revealed normal values. Abdominal magnetic resonance (MR) imaging showed the presence of four abdominal nodules, two close to the spleen (8 and 12 mm in diameter), and two close to the celiac artery (both 15 mm in diameter) (Figure 1). A homogeneous adrenal nodule of 15 mm of diameter was also described.

The growth of the nodules was closely monitored every six months. In addition, a histological examination of the pancreatic lesion previously removed by a pancreaticoduodenectomy was revised, confirming the previous diagnosis of pheochromocytoma and a well-differentiated pancreatic non-functioning endocrine tumor of uncertain behavior, according to the World Health Organization (WHO) 2000 criteria [5]. In particular, the immunostaining of a pheochromocytoma revealed the presence of positivity for chromogranin A and S-100 protein, and the pancreatic neuroendocrine tumor cells were positive for chromogranin A and synaptophysin, with a low mitotic index (Ki67 less than 1%) and absence of neuro and/or vascular invasion.

An MRI examination, 12, months later, demonstrated a 25% increase in three out of the four abdominal nodules while the adrenal nodule remained unchanged. However, repeated VMA and metanephrine determinations were within the reference range and a scintigraphy with [123]I 3-iodobenzylguanidine (MIBG) did not reveal any uptake by the lesions, as is typically described in a non-functioning adrenal mass. In order to have a reliable pathological diagnosis, a laparoscopic surgical excision of the abdominal nodules was performed. Although utilization of a laparoscopic technique in such a case may generally be debatable, in the present case, it represented a rational and feasible choice due to the particular expertise in abdominal laparoscopic surgery in our institution. Nonetheless, complete informed consent was obtained from the patient before the procedure. All four previously detected nodules were successfully removed. At histological examination, three out of the four nodules were characterized as well-differentiated neuroendocrine tumors with similar immunohistochemical characteristics, chromogranin A and synaptophysin positive, and Ki67 below 1%. The fourth nodule turned out to be an accessory spleen.

Considering the patient's clinical history, a hereditary endocrine syndrome was suspected. Multiple endocrine neoplasia (MEN) syndrome type 1 was first investigated. DNA analysis only demonstrated a polymorphism in exon 9 (418 GAC>GAT) of the MEN1 gene. Subsequently, a missense mutation in exon 3 of the VHL gene (ACT>ATT; Thr157Ile) was found. Genetic analysis was also performed on the

relatives of our index patient (including her daughter) and only one 55-year-old brother presented the same mutation, with no clinical signs of VHL disease.

DISCUSSION

In recent years, due to the wider availability of genetic studies and the progress in imaging techniques, VHL disease is more frequently being diagnosed, and the assessment of its associated diseases better characterized. The clinical history of the present case, which spans more than 20 years, is also representative of the previous difficulties in correctly interpreting apparently unrelated diseases such as pheochromocytoma and pancreatic neuroendocrine tumors.

Although no specific genotype-phenotype association has been shown for PNETs occurring in VHL disease, the clinical and genetic aspects of the present case are in agreement with most of the PNET-VHL mutated features previously described in large studies. In fact, our patient presented a well differentiated functionally inactive PNET and a pheochromocytoma, carrying an exon 3 VHL gene missense mutation. The particular feature of the present case is represented by the very late (after 250 months) occurrence of lymph node metastases. Indeed, that particular behavior differentiates the present PNET from the similar sporadic form of pancreatic endocrine tumors, and could suggest a more aggressive disease course in PNET patients harboring the VHL gene mutation [6]. In this regard, PNETs in VHL patients are nowadays better recognized and managed, representing the second most common inherited cause of endocrine pancreatic tumor after MEN1.

In the present case, in line with the recently reported guidelines, surgical treatment of the primary pancreatic tumor has been shown to be a valid therapeutic choice. In fact, according to the aforementioned guidelines, surgical resection is indicated when at least two of the following criteria are met: a primary PNET greater than 30 mm (20 mm if located in the head of the pancreas), a mutation in exon 3 or a tumor doubling time greater than 500 days [4, 7].

Unusually enough, in the present case, we did not observe the occurrence of hepatic metastases, although the primary pancreatic tumor was 50 mm in diameter. In fact, two large studies demonstrated that hepatic metastases are very likely when the primary tumor is greater than 30 mm [4, 8].

The vast majority of VHL-related PNETs are non-functioning tumors with a slow growing pattern. In fact, small PNET lesions, left voluntarily in place, have not shown any progression after up to ten years of follow-up [4]. Moreover, no local and/or distant tumor recurrences have been reported in radically operated on VHL PNET patients after a median time of five years of follow-up [4, 9]. These data suggest a careful revision of surgical indications in such patients, especially nowadays, when an accurate and cost-

effective imaging method such as endoscopic ultrasound has become available in most centers.

Systemic chemotherapy, usually using streptozocin and doxorubicin, is indicated only in patients with a well-differentiated VHL PNET which is rapidly progressive on CT scan comparisons but scarce, if any, results have been observed [7]. However, recent advances in the understanding of neuroendocrine tumorigenesis have provided important insights into the molecular targets for the development of specific therapies. Specifically, VHL protein is involved in angiogenesis, binding and inducing degradation to hypoxia-induced factor 1-alpha (HIF-1-alpha). Since PNETs consistently express HIF-1-alpha, the deregulation of this vascular factor may be involved in their tumorigenesis. Specific treatment to inhibit HIFs is not available at the moment, but inhibitors of VEGF-receptor kinase, which is up-regulated by non-degraded HIF-1-alpha, are yielding promising results in the treatment of VHL-related renal cell carcinomas; however, very few data are available on VHL PNETs [10]. In conclusion, similarly to other neuroendocrine tumors, the risk of malignancy in VHL PNETs seems to be directly proportional to primary tumor size and, in the absence of local or persistent disease, radical excision of the primary tumor could definitively cure the patient. Nonetheless, the case herein reported suggests that PNETs associated with VHL may behave more aggressively than has previously been described, and may require a life-long follow-up, thus fulfilling the definition of VHL as a "life-time disease".

Conflict of interest The authors have no potential conflicts of interest

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