Von Hippel-Lindau (VHL) disease is an autosomal dominant inherited tumor syndrome characterized by heterogeneous tumors derived from different organs. VHL is caused by germline mutations in the VHL tumor suppressor gene located on chromosome 3p25-26. The VHL tumor suppressor gene has three exons and encodes 213 amino acid protein, called pVHL, composed of two domains and is responsible for the ligation of hypoxia inducible factor (HIF) under normoxic conditions. The loss of functional VHL protein contributes to tumorigenesis. VHL tumors are most frequently derived from the kidneys, adrenal gland, central nervous system, eyes, inner ear, epididymis and pancreas. We herein describe the case of a 64-year-old man carrying the VHL gene mutation affected by simultaneous colon adenocarcinoma, renal clear cell carcinoma and adrenal pheochromocytoma.

Key words: VHL, colon adenocarcinoma, pheochromocytoma, clear cell renal carcinoma

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(10.1 g/dL), neutrophilic leukocytosis (WBCs: 13,400 and 80% neutrophils), a serum creatinine level of 1.5 mg/dL and normal urine findings (cytology was negative). Abdominal ultrasound disclosed multiple hepatic cysts and an 8.6x7.5 cm mass in the third medium segment of the left kidney. An abdominal CT scan confirmed the presence of an 8x7 cm solid tumor with areas of colliquative necrosis in the upper pole of the left kidney (Fig. 1). The scans also showed distension of the colon with concomitant wall thickening, indicating possible neoplasia. Colonoscopy revealed a small polyp in the rectum-sigmoid junction, and a subsequent histological exam confirmed a diagnosis of adenocarcinoma.

The patient was scheduled for surgery to resect both tumors, which were later successfully ablated using left hemicolectomy and left radical nephrectomy (Fig. 2). In the left colon, there was a polypoid-annular tumor (size: 5x3x2 cm) partially stenosing the lumen. Macroscopically, the tumor had invaded the intestinal wall involving the muscularis propria (T2) and exhibited intra and peritumoral inflammatory infiltrates. Nine examined regional lymph nodes were found to be free of metastasis (N0). The proximal and distal margins of the resection were free of tumor infiltration. A subsequent histological examination confirmed the typical features of colon adenocarcinoma (pT2, pN0, M0: stage I G 2, Dukes A).

A histologic examination of the kidney revealed renal clear cell carcinoma (pT2, pN0, pMx; stage II). The patient’s postoperative course was uneventful and he was discharged 12 days after surgery without any complications during the follow-up. His blood pressure was well-controlled with antihypertensive therapy (calcium antagonists). Fundoscopy revealed no vascular abnormalities of the retina.

In February 2004, an abdominal CT scan revealed an adrenal lesion in the right adrenal gland and multiple hepatic cysts in the right kidney and liver. Endocrinological examinations disclosed the following data: urinary vanillylmandelic acid: 14.4 μg/day (normal value: 1-10), urinary metanephrines excretion: 420.1 μg/day (normal value: 20-320), urinary free cortisol excretion: 78 μg/day (normal value: 20-140), urinary aldosterone excretion: 10 μg/day (normal value: 2.8-30), plasma chromogranin A: 145 ng/mL (normal value: <90), plasma cortisol: 12 μg/dL (normal value: 5.6-23), plasma aldosterone: 114 pg/mL (normal value: 7.5-150) and dehydroepiandrosterone sulfate (DHEAS): 132 μg/dL (normal value: 120-360). Metaiodobenzylguanidine (MIBG) scintigraphy displayed high levels of accumulation in the right adrenal gland (Fig. 3). Based on the endocrinological results and radiographic findings, we diagnosed the patient with right adrenal pheochromocytoma. Before receiving specific therapy with alpha-adrenergic receptor blockade (doxazosin) and plasma expansion, the patient underwent laparotomic right adrenalectomy. Histologically, the resected right adrenal gland exhibited proliferation of polygonal tumor cells with cytoplasm arranged in cuts, demonstrating a Zell band appearance, bound by a delicate fibrovascular stroma. There was no convincing evidence of malignancy, and most of the tumor cells were positive for chromogranin A. The final diagnosis was right adrenal pheochromocytoma.

With regard to the patient’s clinical history, we suspected VHL disease. Subsequently, a PCR-SSCP sequencing analysis of the VHL gene revealed a mutation in exon 1 at the
Following adrenalectomy, the patient underwent evaluations with office visits using fundoscopy, abdomen and scrotal ultrasound, cerebral MRI and a laboratory workup every six months. The patient remained under active observation without disease progression until February 2008, when total body positron emission tomography (PET)-CT revealed the presence of several metastatic sites (both lungs, a 12×10 mm right sovraclaveare lymphadenopathy and a 32×12 mm lesions at the mediastinum) (Fig. 5). An agobiospy and cytologic broncholavage showed lymphocytes and epithelial cells with voluminous clear cytoplasm and large nuclei with prominent nucleoli, confirming the presence of metastatic lesions of clear cell renal carcinoma.

Following an oncologic evaluation, we decided to administer a chemotherapy infusion consisting of: gemcitabine (1,200 mg/mq) and vinorelbine (25 mg/mq) on days 1 and 15 every 28 days; IL-2 (18,000 U.I. aerosol administration) daily from Monday to Friday for three weeks every four weeks. Two months later, CT imaging showed stable disease (SD) at the pulmonary and adenopathic sites; therefore, the above treatment was continued for another two cycles.

In July 2008, CT imaging revealed progression of the pulmonary disease; thus, second-line therapy with vinblastine (10 mg e.v. every three weeks) was administered (eight cycles). SD was confirmed on CT scans obtained at the end of four cycles of chemotherapy. The patient remained largely asymptomatic, and his blood pressure was well-controlled with calcium antagonists.

After one year (April 2009), a new CT scan revealed hepatic metastases and worsening of the mediastinal adenopathy and pulmonary metastases (Fig. 6).

Therefore, third-line chemotherapy with multi-target TKI (sorafenib: 800 mg/day continuously) was initiated in June 2009; however, due to severe toxicity (hand-foot syndrome, G3) the treatment was immediately interrupted and an mTOR inhibitor (everolimus: 10 mg daily) was provided. The treatment was well tolerated, leading to only G1 hyper-
cholesterolemia and G1 hypertriglyceridemia, which were controlled with specific therapies.

The laboratory data were as follows: erythrocyte sedimentation rate (ESR): 80 mm/h (normal value: <20), PCR: 5 mg/dL (normal value: <0.8), Hb 15: gr/dL, WBC: 6,590 μL, RBC: 5.31×10^6/μL, platelet count (PLT): 185×10^9/μL, creatinine: 1.33 mg/dL (normal value: 0.7-1.2), calcium: 9.3 mg/dL, sodium: 139 mEq/L, potassium: 4.28 mEq/L, urinary metanephrines excretion: 60 μg/24 hours and urinary free cortisol excretion: 71.2 μg/24 hours.

At the beginning of July 2010, a new CT scan showed SD at various metastatic sites with minimal pleural effusion. The patient remained asymptomatic until the end of the month, when he was admitted to the hospital for severe dyspnea, fatigue and lower limb edema. A chest X-ray revealed significant congestion and pulmonary edema. The patient died a few days later.

Discussion

VHL disease (OMIN No: 193300) is a rare autosomal dominant genetic disease, with a prevalence ranging between 1 in 34,000 and 1 in 85,000. It is characterized by tumors and cysts throughout the entire body including the cerebellum, retina, kidneys, adrenal gland and pancreas. Renal cell carcinoma is the primary tumor of VHL, present in up to 75% of patients 60 years of age (6). The renal tumors are mostly the clear cell subtype and can be bilateral and multifocal. Pheochromocytoma arises in up to 24% of VHL patients, with a mean age of 27 years at presentation (6). VHL-associated pheochromocytoma can be multiple, bilateral or extra-adrenal and is malignant in 5% of cases (7).

It has been reported that there are three phenotypes of VHL: type 1 (hemangioblastoma), type 2A (hemangioblastoma + pheochromocytoma) and type 2B (hemangioblastoma + pheochromocytoma + renal cell carcinoma) (8).

In this case report, we observed the coexistence of two primary tumors at diagnosis: colon adenocarcinoma and clear cell renal adenocarcinoma. Later, the case became complicated by adrenal pheochromocytoma. A Medline search of the literature from 1996 to the present revealed no previous documentation of VHL presenting as colon adenocarcinoma and renal carcinoma followed by adrenal pheochromocytoma.

In the general population, the incidence of synchronous primary malignancies of the kidneys and colon is difficult to assess. Some authors have reported synchronous asymptomatic renal and colon carcinoma (9, 10); however, the etiology is complex, including both genetic and environmental risk factors. Regarding the genetic factors, synchronous colon and renal primary neoplasms have been described in patients with Lynch II syndrome (a hereditary non-polyposis colorectal cancer with malignant tumors) (11). In our patient, the genetic alteration was a CCT>CTT VHL gene mutation (Fig. 4).

The VHL gene has three exons and encodes a 4.7 Kb messenger RNA (mRNA) that is largely expressed in both fetal and adult tissues. The expression of the VHL gene is not restricted to the organs affected in VHL disease (12). Individuals with VHL disease carry one wild-type VHL allele and one inactivated VHL allele. Therefore, VHL patients are VHL heterozygotes. Inactivation of the VHL tumor suppressor gene is an early, causal event in the development of neoplasms.

Several studies conducted before 1996 demonstrated that the inactivation of tumor suppressor genes 5q, 17p, 18q and 8p is implicated in the development of colon carcinoma. In 1996, Zhuang et al. analyzed VHL gene alterations (chromosome 3p) in sporadic human colon carcinomas and adenomas using modified microdissection techniques (polymerase chain reaction, PCR). Allelic loss of the VHL gene was detected in seven of 11 (64% patients) who underwent colectomy, whereas no allelic loss was found in patients who underwent colectomy for adenoma, suggesting that VHL gene mutations frequently occur in patients with colon carcinoma (13). In this case report, the histopathological features of colon carcinoma associated with the VHL mutations did not differ from those of sporadic colon carcinoma.

Following the loss of functional VHL proteins, a high level of non-degraded HIF causes increased transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-alpha. These findings explain the cell growth and development of microvascular vessels and accelerated tumoral growth (14).

In particular, the mutation of the VHL gene is responsible for proteolytic degradation of the HIF transcriptional complex. During hypoxia, the HIF transcriptional complex promotes the expression of growth factors, and the loss of the VHL function results in uncontrolled HIF activity and overexpression of VEGF and PDGF, leading to several carcinomas, as well as the development of hemangioblastomas in the retina and central nervous system (CNS), pheochromocytomas and cystic lesions in various organs (15, 16). Recently, the level of HIF, a key modulator of the transcriptional response to hypoxia, was found to be increased in patients with colon cancer. In fact, Xue and colleagues (17) found that intestinal epithelium-specific dysfunction of the VHL gene results in constitutive HIF signaling in mice, while an increased HIF expression augmented colon tumorigenesis in an Apcmin/− intestinal tumor model. These effects were ameliorated in the mice with double dysfunction of pVHL and HIF. The authors considered that chronic increases in the expression of HIF in the colon initiate protumorigenic signaling, which may have important implications for the development of preventive and therapeutic strategies for treating colon cancer.

Regarding the progression from colorectal adenoma to carcinoma, increased oxygen and nutrient demands must be met by the formation of new capillaries from preexisting vasculature (18). Therefore, VEGF plays an important role, and the VEGF levels are regulated by HIF, which is nor-
mally rapidly degraded in the presence of oxygen (a process requiring the VHL tumor suppressor) (19, 20). Patients with VHL disease develop highly vascularized lesions and tumors secreting high levels of VEGF (21). Giles and colleagues (22) observed upregulated levels of VHL in early colorectal lesions obtained from sporadic and familiar adenomatous polyposis patients, in correlation with increased levels of HIF and VEGF. In conclusion, these data offer evidence suggesting that secretion leading to VHL downregulation provides a proangiogenic impulse for colorectal cancer development.

The authors state that they have no Conflict of Interest (COI).

References