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Case Report

Ovarian steroid cell tumor associated with von Hippel-Lindau syndrome: a report of two cases and literature review

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Abstract: Steroid cell tumor (SCT) is a rare sex cord-stromal tumor accounting for only 0.1% of ovarian tumors. Steroid cell tumor, not otherwise specified (SCT, NOS) is of uncertain lineage and is the most common among the three subtypes of SCT. Patients often present with endocrine abnormalities. Von Hippel-Lindau (VHL) syndrome is an autosomal dominant disorder resulting from inactivating gene deletions, frameshifts, and missense mutations of the VHL gene. VHL syndrome can involve multiple organs and clinically is subclassified into type 1 and type 2 based on the risk of pheochromocytoma (PCC). The association of VHL syndrome with genital tract tumors is rare, and here we report two cases of SCT, NOS in patients with VHL disease. The first case is a 19-year old female with VHL and prior resection of bilateral cerebellar hemangioblastomas. During the radiological surveillance, she was found to have multiple small enhancing foci in the cerebellar hemispheres and a stable small enhancing focus in the T6 cord with associated edema, likely reflecting a small hemangioblastoma. She had long history of irregular menses and ultrasound of pelvis found a large right ovarian mass. Cystectomy specimen showed a 6.4 cm well-circumscribed lesion with yellow cut surface. Histologic examination and immunohistochemical staining confirmed the diagnosis of SCT, NOS. The second patient is a 39-year-old female with VHL, previous surgery for retinal hemangioblastomatosis and cerebellar hemangioblastoma, history of abnormal uterine bleeding and elevated testosterone. CT of abdomen and pelvis revealed bilateral multiple cystic and solid renal lesions and a large left ovarian complex cyst. Bilateral partial nephrectomy showed multiple renal cysts and clear cell renal cell carcinomas (RCCs). Left salpingo-oophorectomy showed a 7 cm lesion with yellow-orange cut surface and features consistent with SCT, NOS. Review of the previously reported VHL SCT cases (not including the current two cases) indicated a probable link between VHL syndrome and SCT.

Keywords: Ovarian steroid cell tumor, von Hippel-Lindau syndrome, histological examination, immunohistochemistry

Introduction

Von Hippel-Lindau (VHL) syndrome is a neoplastic disease commonly associated with inactivating gene deletions, frameshifts, or missense mutations of the tumor suppressor gene VHL. The familial form is predominant, and patients often inherit a germline mutation of the VHL gene from affected parents, gain somatic inactivation of the normal allele in special types of cells, and are prone to tumor formation [1-3]. Approximately 20% of cases are the result of de novo mutations of the VHL gene without known family history. VHL disease may involve multiple organ systems and the common VHL-associated tumors are hemangioblastoma, clear cell renal cell carcinoma (RCC), pheochromocytoma (PCC), paraganglioma, and pancreatic neuroendocrine tumor. VHL disease can be further classified as Type 1 or Type 2 depending on the risk of PCC. Type 1 has low risk of PCC but has a wide spectrum of different cancers. Type 2 disease has high risk of PCC and is sub-classified into 2A (with other typical VHL manifestations but low risk of RCC), type 2B (with high risk of RCC) and type 2C (with PCC

only). Clinical diagnosis of von Hippel-Lindau syndrome requires patients with family history, and a CNS haemangioblastoma, phaeochromocytoma, or clear cell renal carcinoma. Patients with no family history must have two or more CNS haemangioblastomas, or one CNS haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts).

Steroid cell tumor (SCT), formerly referred to as 'lipid' or 'lipoid' cell tumors, is one group of ovarian sex cord-stromal tumor accounting for only 0.1% of ovarian tumors and approximately 2% of sex-cord-stromal tumors [4]. SCTs are subdivided into tumors of known origin, including the stromal luteoma, the Leydig cell tumor, and tumors of uncertain lineage, or steroid cell tumors, NOS. The SCT NOS accounts for about 60% of ovarian SCTs. It is extremely uncommon that patients with VHL syndrome develop human genital tract tumor [5-7], and here we report two cases of ovarian SCT NOS in the context of VHL disease that we encountered during our practice over the past five years.

Case presentation

Case 1

A 19-year-old G0P0 female was transferred to our hospital for new patient care. She had a long history of menstrual irregularities since onset of menses at age 13. Her periods were irregular and usually lasted 20 days, and once for 30 days. She had no history of clotting or bleeding disorders. Severe abnormal uterine bleeding caused symptomatic anemia requiring transfusion with packed red blood cells. She had been on and off birth control for menstrual regulation.

The patient was diagnosed with von Hippel-Lindau (VHL) disease at another hospital and had suboccipital craniotomy for resection of bilateral cerebellar hemangioblastomas at age 16. She was on surveillance screening with yearly MRI. A recent MRI (two years after resection) showed stable multiple small enhancing foci in both cerebellar hemispheres, left more than right. Findings were in keeping with hemangioblastomas in the von Hippel-Lindau disease. There was also a stable small enhancing focus along the left dorsolateral aspect of the T6 cord with associated edema, likely reflecting a small hemangioblastoma. The patient was clinically asymptomatic, having no headaches and no complaints about her gait/mobility. Abdominal MRI showed no evidence of RCC or PCC.

Most recently, the patient was diagnosed with an ovarian cyst by ultrasound at another hospital and had no follow-up since then. Ultrasound of pelvis performed at our hospital showed the right ovary was moderately enlarged measuring 6.2 × 5.0 × 6.0 cm containing a heterogeneous mass, measuring 5.5 × 4.2 × 5.3 cm, most likely representing an ovarian dermoid. The left ovary measured 4.1 × 1.6 × 3.8 cm containing few follicles. The patient eventually underwent laparoscopic right ovarian cystectomy.

The right ovarian tumor was well-circumscribed and solid, measuring 6.4 × 4.6 × 3.6 cm. Serial sectioning revealed a yellow soft cut surface with no hemorrhage or necrosis (**Figure 1A**). Microscopically, the tumor cells were predominantly arranged in a diffuse pattern with focal large nests separated by a delicate vascular network and well-delineated from the surrounding ovarian stroma (**Figure 1B** and **1C**). Under high-magnification, the tumor cells were polygonal with distinct borders, abundant clear to foamy/spongy cytoplasm and small ovoid nuclei with no conspicuous nucleoli. No mitotic figures, areas of necrosis or hemorrhage were present. This bland clear cell morphology raised a differential diagnoses including clear cell RCC and adrenal-derived lesion. Immunohistochemical staining revealed the tumor cells were positive for calretinin (focal, **Figure 1D**), inhibin alpha (**Figure 1E**), pan-cytokeratin AE1/AE3 (patchy), and CAM5.2 (focal), while negative for CD10, Pax8, CEA, CK7, synaptophysin, chromogranin and S-100 protein (data not shown), confirming the diagnosis of steroid cell tumor, not otherwise specified [8].

Case 2

A 37-year old female was referred to our hospital for further management of multiple bilateral solid and cystic renal lesions which were identified on renal ultrasound consistent with RCC. She was found to have renal lesions since she was 30 years old and was followed for years. The patient had retinal hemangioblastomatosis and originally presented with ocular symptoms as a young teenager (at around 12-14 years old). Over many years she had numerous sur-

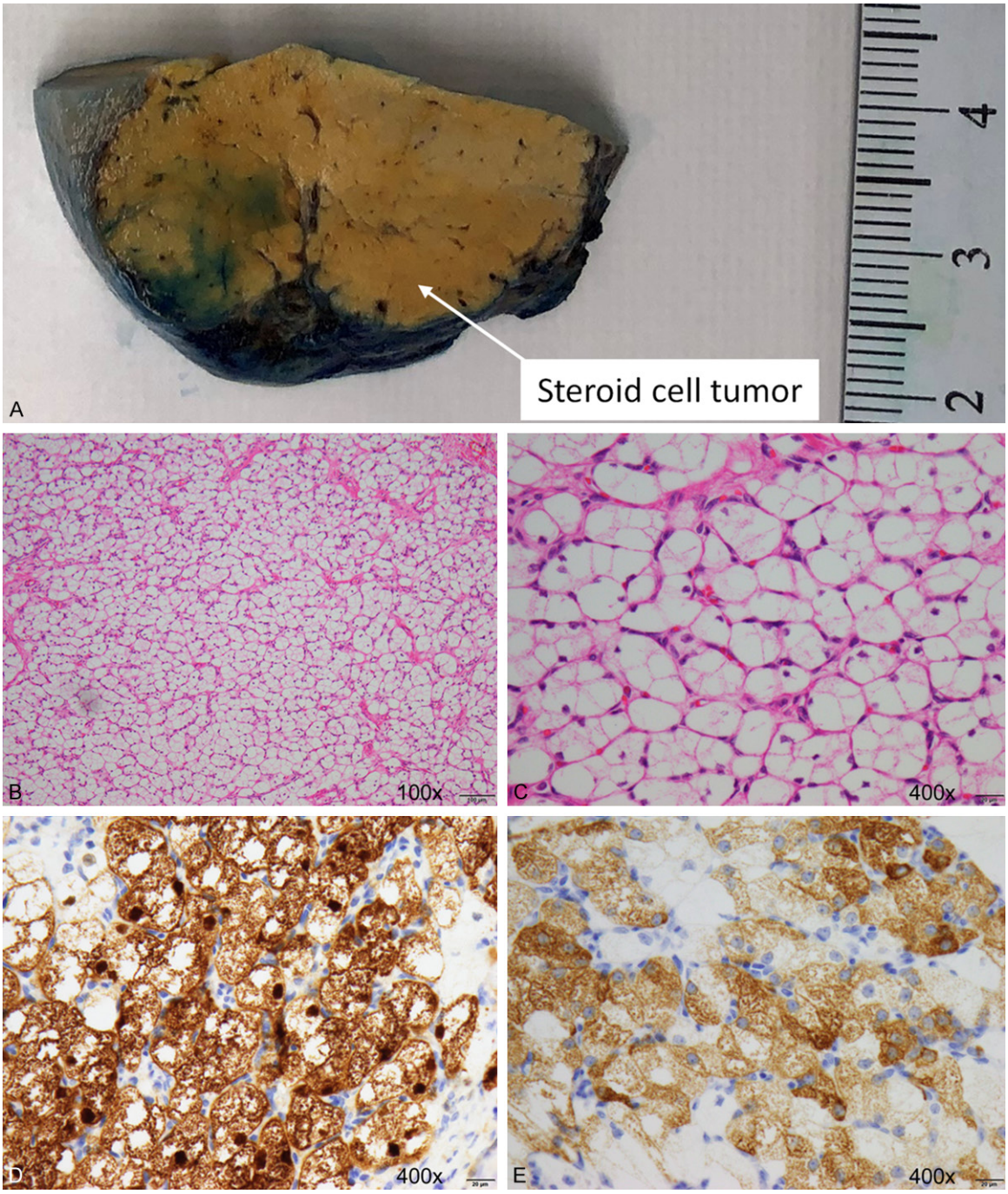

Figure 1. Steroid cell tumor from case 1. Macroscopic picture of tumor (A), ruler unit: cm. Microscopic features of the tumor (B. H&E, 100 ×, scale bar: 100 μm; C. H&E, 400 ×, scale bar: 20 μm). Immunohistochemical stains show the tumor cells are positive for calretinin (D. 400 ×, scale bar: 20 μm) and inhibin (E. 400 ×, scale bar: 20 μm).

geries, and eventually became blind in her late 20 s. She had resection of cerebellar hemangioblastomas twice in her early 20 s, and was diagnosed with VHL disease. Upon presentation to our hospital this time, she also had abnormal uterine bleeding and further work-up showed elevated total free testosterone (127 ng/dL). TSH, FSH, LH, CMP were normal. Pelvic ultrasound showed a normal right ovary and a 7.6 × 7.4 × 6.9 cm complex left ovarian cyst. She was recommended to have partial nephrectomy for nephron preservation. At the age of

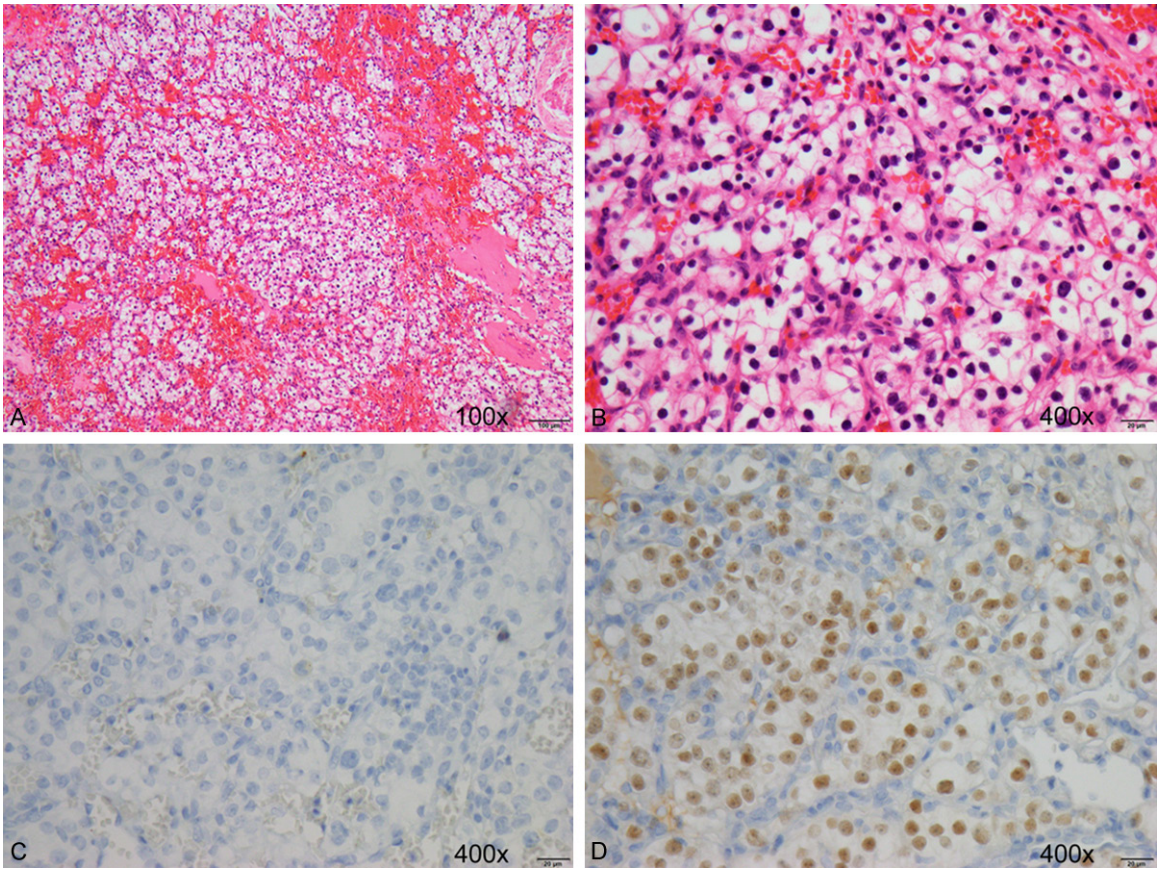

Figure 2. Clear cell renal cell carcinoma from case 2. Histologic features of the tumor (A. 100 ×, scale bar: 100 μm; B. 400 ×, scale bar: 20 μm). Immunohistochemical stains show the tumor cells are negative for inhibin (C. 400 ×, scale bar: 20 μm) and positive for Pax8 (D. 400 ×, scale bar: 20 μm).

39, she decided to have bilateral partial nephrectomy and left salpingo-oophorectomy.

The partial nephrectomy specimen showed bilateral multiple cystic and solid lesions. Histologically, multiple solid and cystic clear cell RCCs (WHO/ISUP grade 2) were identified with the largest lesion measuring up to 6.7 cm. Some of the cystic lesions were benign renal cysts. **Figure 2A** and **2B** shows the typical histological features of one of the solid clear cell RCC. Immunohistochemical staining showed an immunophenotype typical of clear cell RCC (positive for Pax8 (**Figure 2D**), CD10 and RCC and negative for inhibin (**Figure 2C**)). Chromosomal microarray analysis (CMA) disclosed that the RCC had chromosome 3p deletion. The salpingo-oophorectomy specimen had a 7 × 5.5 × 5.5 cm nodular mass occupying the entire left ovary with yellow-orange firm lobulated cut surface. Microscopically, the tumor cells were ovoid to polygonal with clear cytoplasm in some areas and eosinophilic cytoplasm in others (**Figure 3A** and **3B**). The nuclei were mostly ovoid with focal nuclear membrane irregularities and some had small distinct nucleoli. Necrosis or significant mitotic activity were not identified. The tumor cells were positive for inhibin (**Figure 3C**) and negative for Pax8 (**Figure 3D**), AE1/AE3, CD10 and RCC (data not shown). This immunophenotype ruled out metastatic RCC and therefore a diagnosis of sex cord stromal tumor of ovary was rendered. The patient's testosterone level normalized following the surgical excision of the lesion.

Discussion

The association of VHL disease with genital tract neoplasms is rare, nevertheless, clear cell papillary cystadenomas of mesosalpinx and broad ligament in the female genital tract, and epididymis in the male genital tract have been reported in the context of VHL disease [5-7]. In

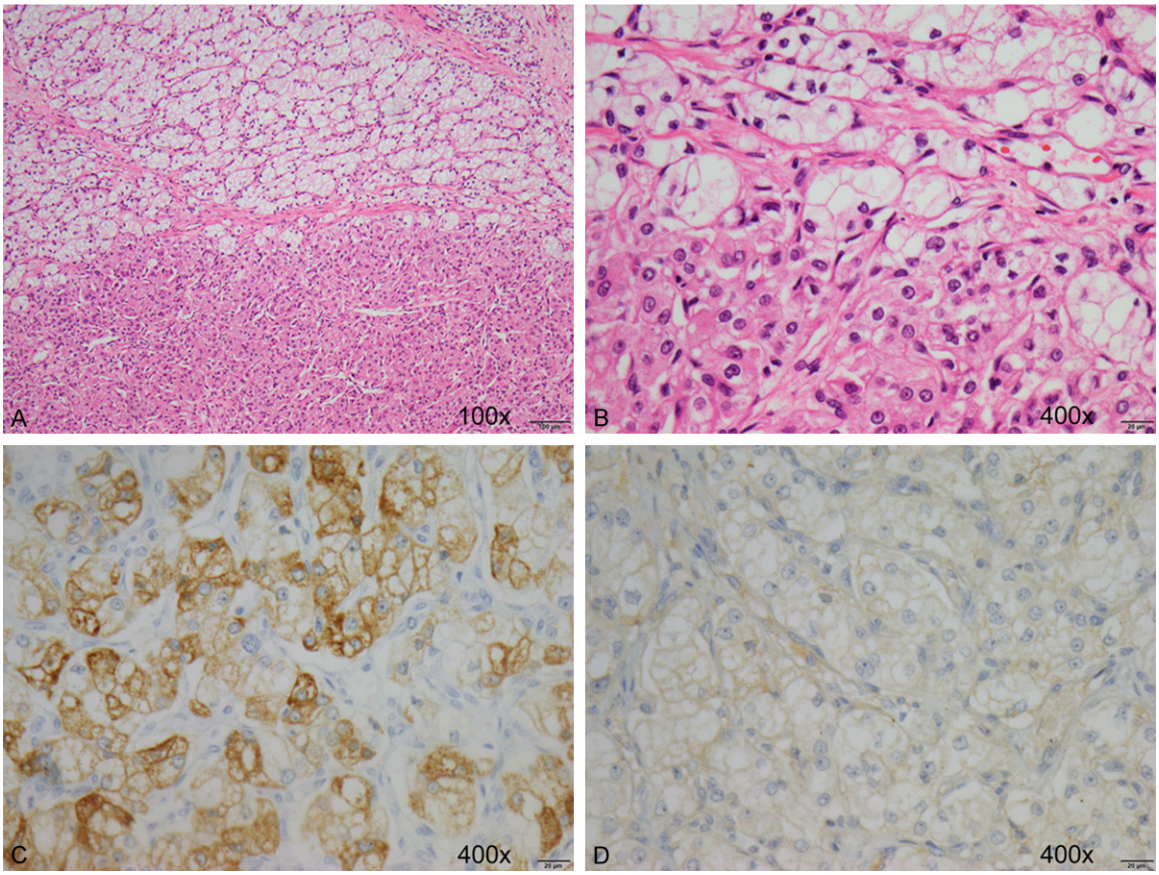

Figure 3. Steroid cell tumor from case 2. Histologic features of the tumor (A. 100 ×, scale bar: 100 μm; B. 400 ×, scale bar: 20 μm). Immunohistochemical stains show the tumor cells are positive for inhibin (C. 400 ×, scale bar: 20 μm) and negative for Pax8 (D. 400 ×, scale bar: 20 μm).

a large-scale analysis of genotype-phenotype relations of VHL tumor suppressor, the genital tract neoplasm associated VHL mutations were about 1.1% of all disease (mostly neoplasm) related VHL mutations, as compared to 36.91% contributed by renal cell carcinoma and renal cysts, the phenotypes with the most VHL mutations [9]. Interestingly, these mutations are commonly located on surfaces B and C of pVHL which together form the β-domain of pVHL containing the hypoxia-inducible factor 1α (HIF-1α) binding site. HIF-1α dependent pathways play crucial roles in pVHL functions including angiogenesis, chemotaxis, cell cycle progression, proliferation, survival, apoptosis, senescence, and transcriptional regulation [1]. This suggests a possible role of the VHL-HIF-1 interaction in genital tract tumorigenesis.

SCT, NOS accounts for less than 0.1% of ovarian tumors and its occurrence in association with VHL syndrome is very rare. Searching through the literature, we found only 6 previously reported cases of ovarian steroid cell tumor in patients with VHL syndrome [10-12]. The mean age at diagnosis among these patients (including the current two cases) was 27 years (varying from 16 to 46 years old), younger than that of non-VHL SCT (mean 43 years). As with other familial diseases, perhaps VHL aberration facilitates the development of SCT in these patients. Consistent with non-VHL SCT patients, these patients often have elevated serum testosterone levels (6/8 patients), and clinically present with hirsutism (4/8 patients). The most common clinical manifestation though, is irregular menses including abnormal uterine bleeding, amenorrhea, and infertility (8/8 patients). With the exception of one patient who had bilateral tumors, VHL SCT appears to show no preference for the laterality of tumor (4 on the right and 3 on the left). Half of the patients had underlying type 2 VHL disease due to the presence of PCC and the other

half had type 1 including the current two cases. Five of eight patients had cervical, cerebellar, and/or retinal hemangioblastoma, which is the most common tumor in VHL syndrome. Clear cell RCC and pancreatic neuroendocrine tumor occur at similar frequency among the patients (each occurred in 3/8 patients).

Features associated with malignant behavior of SCT, NOS include a size of ≥7 cm (78% malignant); ≥2 mitotic figures/10 high power field (92% malignant); necrosis (86% malignant); hemorrhage (77% malignant); and grade 2 or 3 nuclear atypia (64% malignant) [4]. The sizes of the seven VHL SCT tumors found in six of eight patients varied from 2.3 cm to 7 cm with a mean of approximately 5 cm. None of the tumors showed histological features meeting the criteria of malignant SCT.

In summary, we here report two SCT, NOS cases in the context of VHL disease. Considering the earlier age of SCT, NOS occurring in eight VHL patients, it may be worthwhile to explore the role of molecular pathogenesis of VHL in the tumorigenesis of SCT, NOS in future studies.

Disclosure of conflict of interest

None.

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