

Case Report

Sporadic hemangioblastoma of the kidney with PAX2 and focal CD10 expression: report of a case

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Abstract: In this study, we presented an additional case of renal hemangioblastoma, which demonstrates PAX2 and focal CD10 expression. Histologically, the tumor consisted of sheets of oval or polygonal cells and a prominent vascular network. The tumor cells varied in size, and possessed pale or eosinophilic cytoplasm that sometimes contained sharply delineated fine vacuoles. The tumor cell nuclei with inconspicuous nucleoli showed moderate nuclear atypia and pleomorphism. Focal areas of stromal hyalinization and sclerosis were detected. On account of its strong or moderate immunoreactivity for the α -inhibin, S100, NSE, and EGFR, the diagnosis of renal hemangioblastoma was established. For further evidence of *VHL* deficiency, the tumor was subjected to *VHL* sequence analysis of all three exons and fluorescence in situ hybridization (FISH) detection for chromosome 3p deletion. None of the *VHL* gene mutations and chromosome 3p deletion was detected in the tumor. Because of several shared morphological and immunophenotypic features, renal hemangioblastoma may be underrecognized and should be included in the differential diagnosis of primary renal tumors, in particular clear cell renal cell carcinoma. The unexpected positive staining of PAX2 and CD10 in renal hemangioblastoma should be particular concerned. Using a combination of immunoprofile may be helpful to the differential diagnosis of these renal tumors.

Keywords: Kidney, hemangioblastoma, PAX2, CD10, von-Hippel-Lindau (VHL), fluorescence in situ hybridization (FISH), molecular genetics, differential diagnosis

Introduction

Hemangioblastomas are rare benign tumors of uncertain histogenesis that can arise sporadically or in association with von-Hippel-Lindau (VHL) disease [1]. VHL disease is an autosomal dominant disorder, which predisposes the patients to clear cell neoplasm of various organs, such as the central nervous system, kidney, adrenals, pancreas, and epididymis [2, 3]. Hemangioblastomas typically arises within the central nervous system (CNS), predominantly in the cerebellum, but may occasionally in extraneural sites such as bone, soft tissue, skin, liver, lung, pancreas and kidney [1, 4]. A few reports of sporadic hemangioblastoma have been previously described outside the CNS, including only 8 cases in the kidney [1, 5-10]. In the present study, we report the ninth case of such rare tumors with PAX2 and focal

CD10 expression, which may be underrecognized because of its resemblance with several common renal tumor types, in particular clear cell renal cell carcinoma (RCC).

Case report

Clinical history

A 57-year-old female with no significant past medical history was found to have a 3 × 2 cm sized mass in the upper pole of the right kidney on a computed tomography (CT) scan done for an unrelated reason. A malignant tumor was suspected and a radical nephrectomy was performed, showing a 3 × 2.5 × 2 cm well-encapsulated brownish-white tumor with some hemorrhagic areas. There was no familial history or clinical evidences of VHL disease. Currently, the patient was alive without tumor recurrence or metastasis with 6 months of follow-up.

Sporadic renal hemangioblastoma

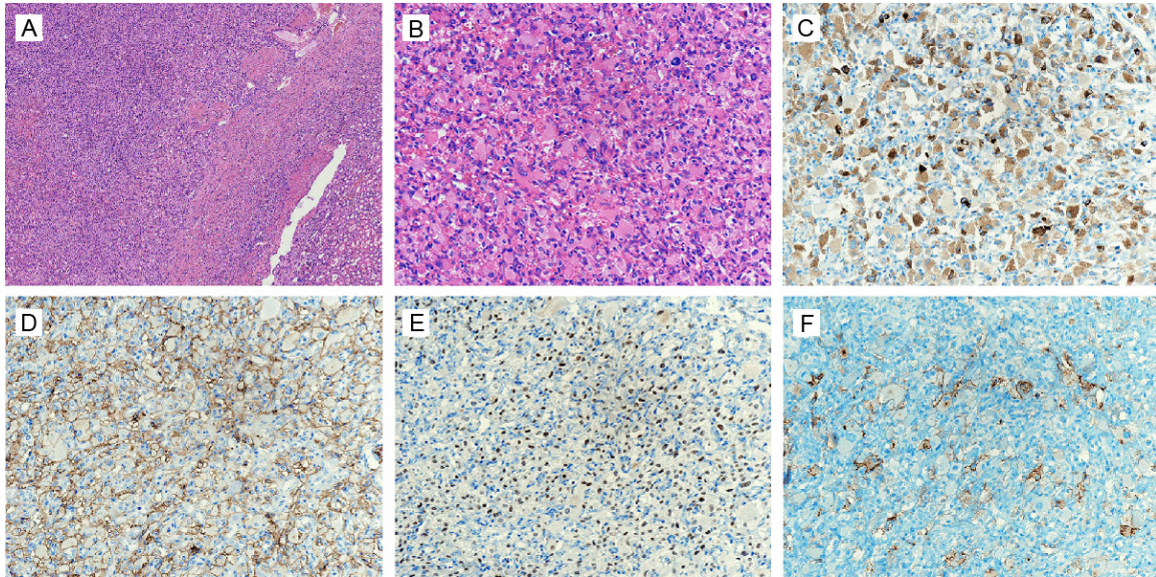


Figure 1. A: The tumor at left field was well circumscribed from the renal parenchyma by a fibrous capsule. (original magnification, $\times 40$). B: The tumor consisted of sheets of oval or polygonal cells and a prominent vascular network. The tumor cells varied in size, and possessed pale or eosinophilic cytoplasm that sometimes contained sharply delineated fine vacuoles. The tumor cell nuclei with inconspicuous nucleoli showed moderate nuclear atypia and pleomorphism. (original magnification, $\times 200$). The tumor moderately to strongly expresses a-inhibin (C), CA9 (D), and PAX2 (E) and focally expresses CD10 (F) (original magnification, $\times 200$).

Histopathological and immunohistochemical findings

Morphologically, the tumor consisted of sheets of oval or polygonal cells and a prominent vascular network. The tumor cells varied in size, and possessed pale or eosinophilic cytoplasm that sometimes contained sharply delineated fine vacuoles. The tumor cell nuclei with inconspicuous nucleoli showed moderate nuclear atypia and pleomorphism. Neither mitotic figures nor necrosis was present. Focal areas of stromal hyalinization and sclerosis were detected (**Figure 1A** and **1B**).

Immunoreaction was performed using the labelled streptavidin–biotin method and overnight incubation as previously described [11, 12]. Immunohistochemically, the tumor cells demonstrated moderately (2+) or strongly (3+) positive staining for a-inhibin, S100, NSE, EGFR, CA9, HIF-1 α , and PAX2 but negative for CKpan, HMB45, Melan A, SMA, CD68, D2-40, TFE3, and TFE3. Focal membranous staining was noted for CD10. The presence of Ki-67 protein demonstrated a low proliferation rate, with few Ki-67-positive nuclei (**Figure 1C-F**).

Molecular analysis

VHL sequence analysis of all three exons of *VHL* gene and fluorescence in situ hybridization (FISH) detection for chromosome 3p deletion were performed as recently described [13, 14]. *VHL* gene mutations and chromosome 3p deletion were not detected in the tumor.

Discussion

In this study, we reported an additional case of sporadic hemangioblastoma of the kidney with PAX2 and focal CD10 expression. Histologically, the tumor consisted of sheets of oval or polygonal cells and a prominent vascular network. The tumor cells varied in size, and possessed pale or eosinophilic cytoplasm that sometimes contained sharply delineated fine vacuoles. The tumor cell nuclei with inconspicuous nucleoli showed moderate nuclear atypia and pleomorphism. Focal areas of stromal hyalinization and sclerosis were detected. On account of its strong or moderate immunoreactivity for the a-inhibin, S100, NSE, and EGFR, the diagnosis of renal hemangioblastoma was established [15-17].

Sporadic renal hemangioblastoma

Hemangioblastoma is a benign tumor, which typically occurs within the central nervous system. Extraneural hemangioblastoma, including kidney are extremely rare [1]. In fact, renal hemangioblastoma may be underdiagnosed or misclassified as other renal tumors such as epithelioid angiomyolipoma, schwannoma, in particular clear cell RCC as it shares several morphologic and immunophenotypic features [5, 6]. The diagnosis should be based not only on morphology itself but also on immunophenotypic findings. Some immunohistochemical markers such as α -inhibin, S100, NSE, EGFR, PAX8, PAX2 and CD10 have been shown to be helpful in the differential diagnosis of these tumors [1, 5-10]. Many studies have suggested the immunoprofile of PAX8, PAX2, α -inhibin, and CD10 is a helpful combination for distinguishing between a hemangioblastoma and a metastatic clear cell RCC since α -inhibin usually demonstrates positive staining in hemangioblastoma while is steadily negative in clear cell RCC, on the contrary, PAX8, PAX2, and CD10 are usually positive in clear cell RCC but negative in hemangioblastoma [15-17]. Of interest, PAX2 and focal CD10 expression were observed in our present case. PAX2 is a transcription factor that is normally expressed by cells of the nephric, thyroid, and Mullerian duct lineage and has been regarded as one of the RCC markers [17]. CD10 usually demonstrates positive staining in clear cell RCC and stains glomerular cells and proximal convoluted tubules, participating in the regulation of water and sodium metabolism, in the normal kidney [9]. Thus, our results support the earlier hypothesis that the hemangioblastoma has the capacity to express variable lines of differentiation depending on its site of origin, as previously suggested by other authors [1]. Therefore, caution should be exercised when interpreting the differential efficacy of these reagents on specific locations.

Hemangioblastoma can arise sporadically or in association with von-Hippel-Lindau (VHL) disease [1]. VHL disease is an autosomal dominant disorder, which predisposes the patients to clear cell neoplasm of various organs, such as the central nervous system, kidney, adrenals, pancreas, and epididymis [2]. The *VHL* tumor suppressor gene mapped on the short arm of chromosome 3 (3p26-p25) is consistent with Knudson's two hit hypothesis that indicates tumor suppressor gene inactivation by two genetic alterations results in the develop-

ment of tumors. For inherited cancer syndrome, the first hit is an inherited germline mutation, the second hit is a somatic DNA alteration acquired during the patient's lifetime [2]. The *VHL* gene product protein is important in the regulation of hypoxia inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF), whereas Loss of function of the *VHL* gene ultimately leads to overexpression of a variety of proteins that are targets of the HIF pathway including HIF-1 α , glucose transporter-1 (GLUT-1), and CA9 [18]. CA9 is one of the better-known HIF targets and has been shown to be useful as an immunohistochemical marker of clear cell RCC [18]. For further evidence of *VHL* deficiency, the tumor was subjected to *VHL* sequence analysis of all three exons and FISH detection for chromosome 3p deletion. In fact, we did not find any *VHL* gene mutations and chromosome 3p deletion in the sample. However, the strong expression of HIF-1 α and CA9 provide supporting evidence that the genetic defect of *VHL* has relevance to pathogenesis. Other events, such as hypermethylation or point mutations of the promoter might cause allelic loss of function of the *VHL* gene.

In conclusion, we presented an additional case of renal hemangioblastoma, which demonstrates PAX2 and focal CD10 expression. Because of several shared morphological and immunophenotypic features, renal hemangioblastoma may be underrecognized and should be included in the differential diagnosis of primary renal tumors, in particular clear cell RCC. The unexpected positive staining of PAX2 and CD10 in renal hemangioblastoma should be particular concerned. Using a combination of immunoprofile may be helpful to the differential diagnosis of these renal tumors.

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Disclosure of conflict of interest

None.

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