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Original contribution

PAX8 expression in sporadic hemangioblastoma of the kidney supports a primary renal cell lineage: implications for differential diagnosis

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Abstract Hemangioblastoma is a benign, morphologically distinctive neoplasm of disputed histogenesis that typically occurs in the central nervous system either in the setting of von Hippel-Lindau disease or more often sporadically. Extraneural hemangioblastoma is exceptional and raises a challenging differential diagnosis. Herein, we report a primary renal hemangioblastoma occurring in 51-year-old woman without stigmata of von Hippel-Lindau disease. Histologically, the tumor was composed of sheets of polygonal epithelioid stromal cells with ample pale or eosinophilic, vacuolated cytoplasm in an arborizing capillary network. Tumor cells showed variable nuclear pleomorphism, intranuclear cytoplasmic invaginations, scattered hyaline globules, and psammoma-like calcifications. Some areas showed branching hemangiopericytoma-like vessels with tumor cells radiating from the wall, while other areas were edematous and hyalinized with sparse stromal cells and abundant reticular vessels. Immunohistochemically, the tumor cells reacted strongly and diffusely with antibodies to PAX8, CD10, α-inhibin, S100 protein, neuron-specific enolase, and vimentin, and they showed focal positivity with antibodies to epithelial membrane antigen and AE1/AE3. Tumor cells were negative for CK7, CK8/18, RCC antigen, synaptophysin, chromogranin, c-kit, D2-40, HMB45, melan-A, cathepsin K, SMA, desmin, CD31, CD34, and estrogen and progesterone receptors. Positive immunoreactivity for PAX8 is unexpected and contrasts to central nervous system (CNS) hemangioblastomas, which are essentially always negative for PAX8. This novel finding adds support to the hypothesis that the immunoprofile of extraneural hemangioblastoma varies with site of origin, perhaps as a result of tumor cell lineage and retention of organ-specific markers or acquisition of site-specific antigens due to local factors.

1. Introduction

Hemangioblastoma, also referred to as capillary hemangioblastoma, is a distinctive benign neoplasm of uncertain

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histogenesis that typically occurs in the central nervous system (CNS) [1,2]. Most tumors arise sporadically, although approximately 25% are associated with von Hippel-Lindau (VHL) disease, a hereditary tumor predisposition syndrome with autosomal dominant inheritance [1,3]. Histologically, hemangioblastoma is characterized by the presence of vacuolated tumor cells, referred to as stromal cells, closely associated with an elaborate network of capillary-sized blood vessels. Based on the prominence of the stromal cell component, hemangioblastomas have been subdivided into two variants: reticular and cellular [1,2]. Cytologic features of the stromal cells are characteristically bland; however, they can occasionally exhibit nuclear pleomorphism mimicking malignancy [2], particularly in the cellular variant. Hemangioblastoma occurs most frequently in the cerebellum and less commonly at other sites in the central neuraxis such as the brainstem, spinal cord, nerve roots, retina, and supratentorial compartment [1,2]. Examples of hemangioblastoma developing in sites outside the CNS are exceptional and have been reported in small series and case reports, including liver, lung, pancreas, adrenal gland, urinary bladder, kidney, skin, soft tissue, and bone, many of which are associated with one or more stigmata of VHL disease [4,5]. Sporadic hemangioblastoma occurring outside the CNS is much rarer. In the kidney, only seven cases of sporadic hemangioblastoma have been published in the English literature [4-9], typically posing a challenging differential diagnosis [5]. In this article, we report a case of primary renal hemangioblastoma occurring in a patient without evidence of VHL disease and review the literature to better delineate the clinicopathologic features and differential diagnosis of this rare renal tumor.

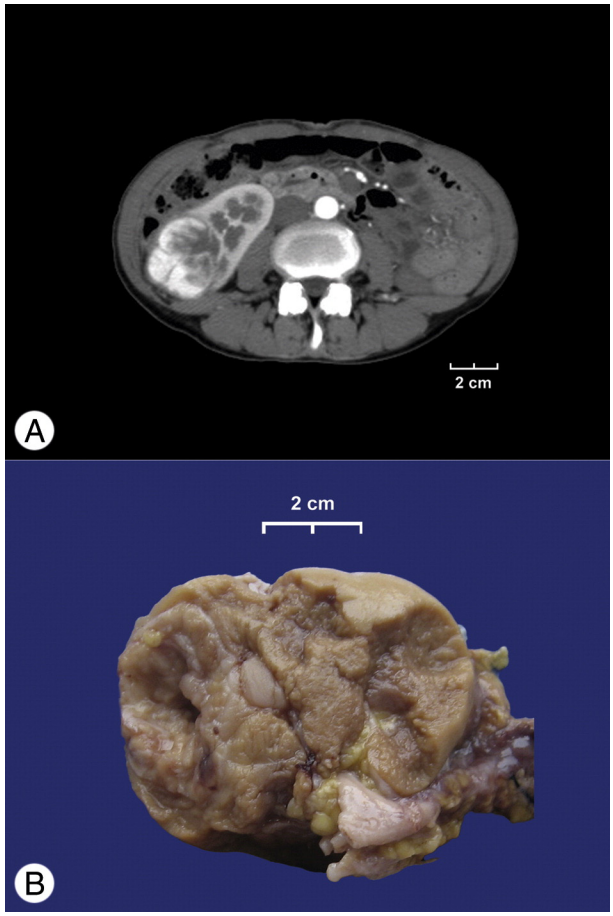

Fig. 1 Renal hemangioblastoma. A, Abdominal computed tomography demonstrates a solid, lobulated, heterogeneously enhancing mass located in the lower pole of the right kidney. B, Gross appearance of the tumor shows a gray-to-brown solid mass with heterogeneous fibrotic areas.

2. Case presentation

A 51-year-old woman presented with recurrent right-sided lumbar abdominal pain of 1-year duration. She denied gross hematuria, weight loss, change in appetite, or neurological symptoms. Physical examination revealed a small palpable mass in the right hypochondriac region that was mobile, smooth, and solid. Computed tomography demonstrated a 5.5 × 4.5 cm well defined, lobulated, heterogeneously enhancing solid mass, located in the lower pole of the right kidney (Fig. 1A). The contralateral kidney, other internal organs, and CNS demonstrated no abnormalities. Blood cell counts including hemoglobin level were within normal limits. The patient's past medical history was significant for early-stage gastric cancer managed with curative subtotal gastrectomy 10 years before surgery for her renal tumor. Family history included a brother with "renal cancer" who underwent radical nephrectomy; however, the pathologic specimen was unavailable for review for comparison and confirmation of diagnosis. Otherwise, the patient and immediate family had no clinical signs to indicate VHL disease. Given the suspicion for renal cell carcinoma (RCC), the patient underwent laparoscopic right radical nephrectomy. Her recovery was uneventful, and there was no evidence of local recurrence or metastasis from the renal tumor 12 months after surgery.

3. Methods

The resection specimen was fixed in 10% buffered formalin. Tissue sections were routinely processed and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using the avidin-biotin complex immunoperoxidase technique with a panel of commercially available primary antibodies to the following antigens: epithelial membrane antigen (EMA; E29, Dako, Carpinteria, CA), cytokeratin AE1/AE3 (AE1/3, Dako), cytokeratin 7 (CK7; OV-TL12/30, Dako), cytokeratin 8/18 (CAM5.2, Dako), vimentin (V9, Dako), CD10 (56C6, Dako), RCC marker; gp200, Dako), PAX8 (BCL2; Biocare, Concord, CA), α-inhibin (R1, Dako), S100 protein (polyclonal, Dako), neuron specific enolase (NSE; polyclonal, Dako), synaptophysin (polyclonal, Dako), chromogranin A (polyclonal, Dako), CD31 (JC/70A, Dako), CD34