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Case study

Unclassified hemangioma-like renal cell carcinoma: a potential diagnostic pitfall☆

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Summary Recently, rare renal cell carcinomas (RCCs) have been reported to closely mimic hemangioma; however, these have been largely recognizable as clear cell RCC. Conversely, true hemangiomas of the kidney are also increasingly recognized. We report a 62-year-old woman who underwent partial nephrectomy for a hemangioma-like RCC without appreciable clear cell morphology. Immunohistochemistry revealed luminal structures that stained positively for cytokeratin, cytokeratin 7, carbonic anhydrase IX, PAX8, and high-molecular-weight keratin, admixed with a CD34-positive, CD31-positive, and ERG-positive complex network of vessels. Staining was minimal for α-methyl-acyl-coA-racemase and EMA, and absent for GATA3, HMB45, melan-A, and cathepsin K. Fluorescence in situ hybridization revealed no *TFE3* or *TFEB* rearrangement, 3p deletion, or trisomy 7 or 17. This case adds to the spectrum of hemangioma-like RCC with differing morphology and immunophenotype. Further study will determine whether this represents a distinct entity or an unusual pattern of degenerative changes in an existing entity.

1. Introduction

Clear cell renal cell carcinoma with hemangioma-like degenerative changes can present a diagnostic dilemma [1]. Despite the kidney being a highly vascular organ, primary vascular tumors of this organ are actually rare [2], although recently the novel hemangioma subtype anastomosing hemangioma has been recognized to have more frequent occurrence in the kidney and genitourinary tract, among other sites [3,4]. In general, predominant sinusoidal-like vascularity in a renal mass would have a differential diagnosis that includes hemangioma (especially anastomosing hemangioma), hemangioma-like degenerative changes in renal cell carcinoma (usually clear cell type), or spontaneous regression of renal cell carcinoma. There are a few reports of clear cell renal cell carcinoma mimicking a hemangioma [1,5]; however, to our knowledge, non–clear cell hemangioma-like renal cell carcinoma has not been previously reported. In this article, we report a case of unclassified hemangioma-like renal cell carcinoma presenting in a 62-year-old woman.

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2. Materials and methods

2.1. Case report

A 62-year-old woman presented to the urology clinic with an incidentally detected asymptomatic left renal mass. The renal mass was under active monitoring for a 2-cm renal cyst, which progressed over 8 years into a solid mass. Computed tomography revealed a thick, enhancing capsule with a solid, enhancing central region suggestive of renal cell carcinoma. An elective partial nephrectomy was performed.

2.2. Methods

This study was approved by the Henry Ford Health System Institutional Review Board. Four-micrometer–thick sections were prepared from the specimen for hematoxylin and eosin staining and immunohistochemistry. Immunohistochemical staining was performed in a Dako Autolink-48 (Dako, Carpinteria, CA) with a cytokeratin antibody cocktail including keratin AE1/AE3 (polyclonal; Dako), MAK6 (clone UCD/PR 10.11 and KA-4; Life Technologies, Frederick, MD), CAM 5.2 (polyclonal; Becton Dickson, BD Biosciences, San Jose, CA), and high-molecular-weight cytokeratin (clone 34βE12; Dako), as well as individual antibodies against CD34 (polyclonal; Dako), PAX8 (clone BC12; Biocare Medical, Concord CA), EMA (clone E29; Dako), α-methyl-acyl-coA-racemase (AMACR) (clone 13H4;ThermoScientific, Fremont, CA), CD31 (polyclonal; Dako), carbonic anhydrase IX (polyclonal; Novocastra, Buffalo, IL), CK7 (polyclonal; Dako), HMB45 (polyclonal; Dako), melan-A (polyclonal; Dako), cathepsin K (clone 3F9; Leica/Novocastra, Buffalo, IL), ERG (polyclonal; Dako), high-molecular-weight cytokeratin (34βE12; Dako), and GATA3 (clone L50-823; Biocare Medical), with appropriately reacting positive and negative controls. Fluorescence in situ hybridization (FISH) was performed as described previously [6,7].

3. Results

At gross examination, the partial nephrectomy specimen contained a 2.6 × 2.5 × 2.5–cm well-circumscribed, encapsulated tan-brown hemorrhagic mass (Fig. 1). Microscopically, the morphological appearance was unusual with hemangioma-like features, extensive vascular component, fibrin accumulation, and hemorrhage. The areas with morphology suggestive of a renal epithelial component exhibited a tubulocystic appearance with flattened eosinophilic cells showing International Society of Urological Pathology modified Fuhrman nuclear grade 3. There were no sarcomatoid features or tumor necrosis other than zones of fibrin accumulation interpreted as hemorrhage. The tumor was limited to the kidney with negative surgical margins.

Immunohistochemistry (Fig. 2) revealed the presence of a renal epithelial component (PAX8+, keratin cocktail+, high-molecular-weight cytokeratin+, diffuse labeling CK7+, and carbonic anhydrase IX+, minimal EMA and minimal AMACR positive). CD31, CD34, and ERG labeled the extensive vascular component, although, histologically and on a single immunohistochemically stained slide, it was difficult to discriminate the vascular network from the epithelial component. Both components were negative for HMB45, melan-A, cathepsin K, and GATA3. FISH was negative for rearrangement of *TFE3* or *TFEB*, showed no chromosome 3p deletion, and revealed disomy for chromosomes 7 and 17.

4. Discussion

Rich vascularity and an extensive capillary network separating nests of neoplastic cells are commonly used as diagnostic clues for a diagnosis of clear cell renal cell carcinoma, and it has been noted recently that some cases may mimic hemangioma when the epithelial component is inconspicuous and the residual vascular network predominates [1,5], possibly resulting from degenerative changes. Conversely, hemangiomas can also occur in the kidney less frequently, potentially mimicking clear cell renal cell carcinoma [2,8,9]. In particular, anastomosing hemangioma is now recognized as a unique subtype of hemangioma, originally recognized in the ovary, kidney, and testis [3,4] and subsequently recognized at a number of other sites [10]. These tumors typically contain interconnecting thin-walled vascular channels, with a predominant lobular architecture. Although the complexity of this vascular component may raise concern for angiosarcoma, lack of cytologic atypia, mitotic activity, and endothelial multilayering, combined with the presence of some helpful clues, such as extramedullary hematopoiesis and hyaline globules, can lead to the correct diagnosis [3]. In the current case, immunohistochemical staining with CD31, CD34, and ERG labeled the extensive vascular component, largely obscuring the epithelial cells, and if such markers were used in isolation, this may have led to misdiagnosis. As such, some authors have recommended a low threshold for implementation of renal epithelial markers any time a primary renal vascular tumor is a consideration [5].

In contrast to prior reports of hemangioma-like renal cell carcinoma [1], the current case is unusual in that no readily appreciable low-grade clear cell renal cell carcinoma component was identifiable. Although the diffuse labeling for carbonic anhydrase IX would suggest clear cell renal cell carcinoma, the concurrent diffuse positivity for cytokeratin 7 and high-molecular-weight cytokeratin is unusual, and the lack of chromosome 3p loss by FISH did not provide additional support for classification as clear cell renal cell carcinoma. The combination of cytokeratin 7, high-molecular-weight cytokeratin, carbonic anhydrase IX, and minimal AMACR staining would raise consideration of the entity clear cell