Urology Case Reports 2 (2014) 39–42

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Oncology

Lymphangitic Retroperitoneal Carcinomatosis Occurring From Metastatic Sarcomatoid Chromophobe Renal Cell Carcinoma

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ARTICLE INFO

Article history:
Received 17 December 2013
Accepted 18 December 2013

Keywords:
Renal cell carcinoma
Chromophobe
Sarcomatoid
Lymphangitic carcinomatosis
Lymph node metastasis

ABSTRACT

A 45-year-old man with left renal mass underwent nephrectomy to reveal a 20-cm tumor diagnosed as sarcomatoid chromophobe renal cell carcinoma. Lymph node metastasis of chromophobe and sarcomatoid components, disseminated tumor in retroperitoneal fat, lymphatic vessels, and perirenal adipose tissue in lymphangitic carcinomatosis pattern were identified. Chromophobe epithelial cells were positive for epithelial membrane antigen, c-Kit, and cytokeratin 7; sarcomatoid cells were positive for CD10 and smooth muscle antigen with high proliferation index. Chromophobe epithelial cells had loss of heterozygosity in chromosomes 1p and 1q, whereas sarcomatoid cells had loss of heterozygosity in 3p, 1p, and 1q. In conclusion, sarcomatoid chromophobe renal cell carcinoma has aggressive biologic behavior and potential to metastasize in unusual patterns.

Introduction

Malignant kidney tumors account for 2% of cancer incidence and mortality in the United States, and studies show increased incidence worldwide.[1] The chromophobe subtype is rare, constituting 5% of renal cell carcinoma (RCC). Overall, chromophobe renal cell carcinoma (CRCC) has favorable prognosis when compared with conventional clear cell type.[2] Sarcomatoid transformation in RCC portends poor prognosis, with median survival of 4-9 months after diagnosis.[3] We report a unique case of sarcomatoid transformation in CRCC to further characterize this rare entity.

Case presentation

A 45-year-old man presented to the National Institutes of Health with a 6-year history of a left renal mass. The mass was discovered incidentally in 2006, at which time it was reported as a 12-cm hyperdense cystic lesion that was interpreted as being benign. In the interim, he was followed up by imaging only, with interval growth. In May 2012, he was referred to the National Institutes of Health for consideration in a protocol, and magnetic resonance imaging showed a 16-cm solid left renal mass. Biopsy of the renal mass confirmed the diagnosis of RCC. Subsequently, the patient underwent a radical left nephrectomy.

Gross examination showed a 20-cm, 1600-g spherical encapsulated tumor mass with a variegated hemorrhagic and firm white cut surface with irregular borders. Microscopic evaluation of the tumor revealed 2 distinct morphologies (Fig. 1A). Specifically, areas characteristic of CRCC were intermixed with a spindle cell proliferation consistent with sarcomatoid dedifferentiation. The CRCC had morphology typical of this tumor, with large cells exhibiting abundant clear cytoplasm with distinct cell borders and irregular nuclei with occasional prominent small nucleoli. The spindle cell component was diffusely admixed with nests of chromophobe neoplastic cells and comprised approximately 50% of the tumor mass. The spindle cells were arranged in loose fascicles of pleomorphic spindle-shaped cells with high cellularity and atypia (Fig. 1B). In addition, there were areas of hemorrhage, necrosis, sclerotic stroma, vascular invasion, and the tumor permeated the capsule. Three of 50 lymph nodes were positive for metastatic tumor—2 of 40 periaortic lymph nodes were positive for *both* spindle and chromophobe cell components, and 1 of 10 hilar lymph nodes was positive for only the chromophobe cell component (Fig. 1C). There were multiple foci of disseminated

Funding disclosure: This research was supported by the Intramural Research Program of the NCI, NIH.

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http://dx.doi.org/10.1016/j.eucr.2013.12.008

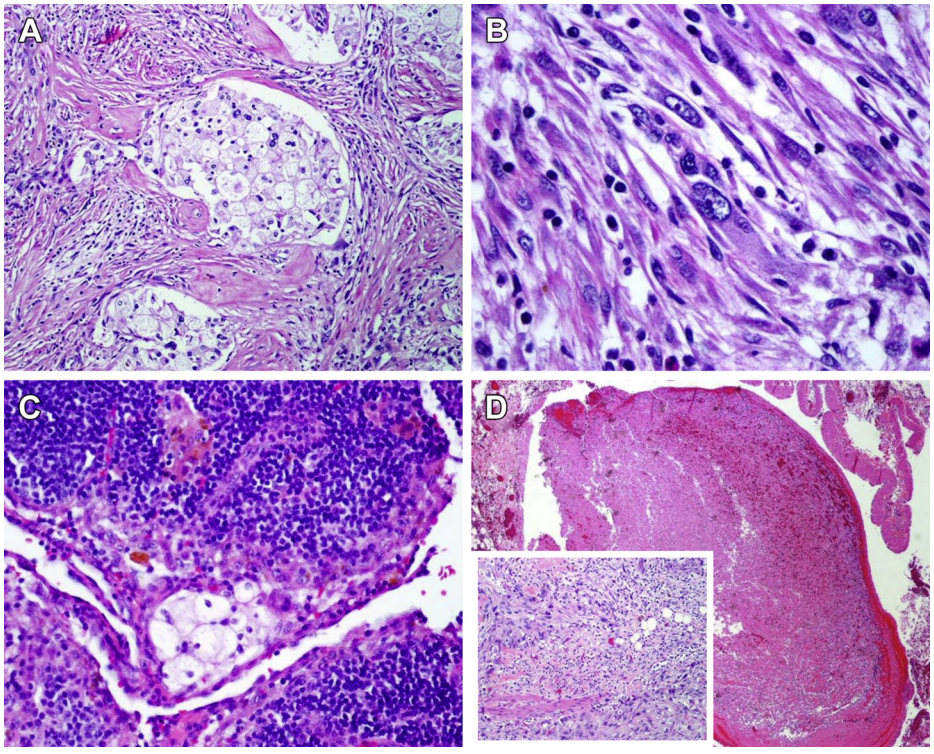

Figure 1. (A-D): Chromophobe renal cell carcinoma—2 distinct morphologies. Epithelial tumor cells are admixed with sarcomatoid tumor cells (**A**, ×100), spindle cell/sarcomatoid tumor cells (**B**, ×400). Metastatic chromophobe renal cell carcinoma to lymph node (**C**, ×200). Tumor involvement of a lymphatic vessel in the perirenal adipose tissue (**D**: H&E, ×40), inset shows spindle cell tumor infiltration of muscle and adipose tissue in perirenal soft tissue (H&E, ×100).

tumor, specifically the sarcomatoid component, in lymphatic vessels and infiltrating adipose tissue (Fig. 1D). The residual left kidney showed chronic interstitial nephritis. The ureter and vascular margins were free of tumor. The final TNM classification was rendered as pT3pN2pMX.

The tumor displayed 2 distinct immuhistochemical profiles of its 2 components (Fig. 2A-F). The chromophobe neoplastic cells were positive for c-Kit (CD117), cytokeratin 7, and epithelial membrane antigen, whereas the sarcomatoid neoplastic cells were positive for CD10 and smooth muscle antigen. MIB-1 (Ki-67) immunostain demonstrated a higher proliferation index in sarcomatoid regions (Fig. 2F).

Both chromophobe and spindle cell components were evaluated by electron microscopy. Ultrastructural features typical of CRCC, such as cytoplasmic vesicles and abundant mitochondria with disrupted, tubulovesicular, or absent cristae were seen in

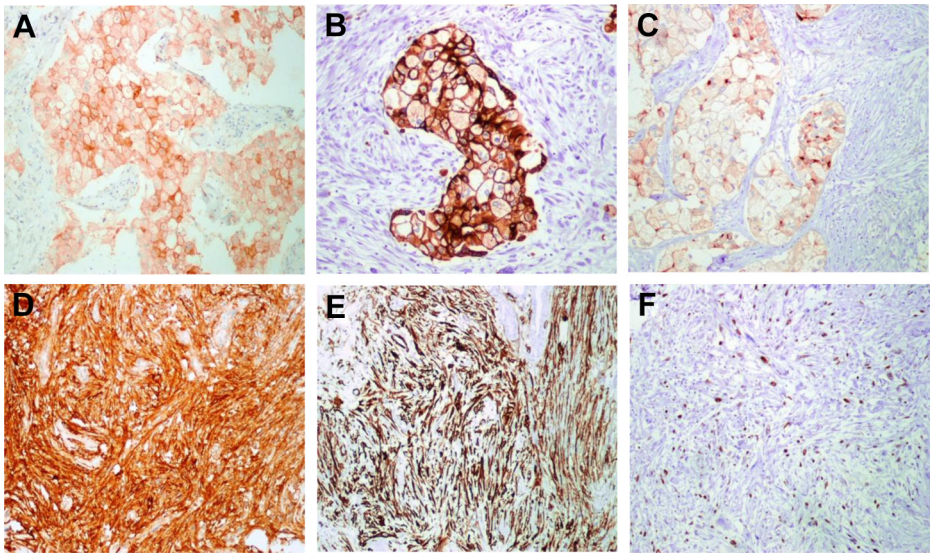

Figure 2. (A-F): Distinct immunophenotype of the 2 components of this tumor. The chromophobe component is positive for c-Kit (**A**, ×100), cytokeratin 7 (**B**, ×100), and epithelial membrane antigen (**C**, ×100), which are negative in the spindle cell component. The spindle cell component is positive for CD10 (**D**, ×100) and smooth muscle antigen (**E**, ×100), which are negative in the chromophobe component. MIB-1 (Ki-67) immunostain demonstrates a high proliferation index in the spindle cell component (**F**, ×100).

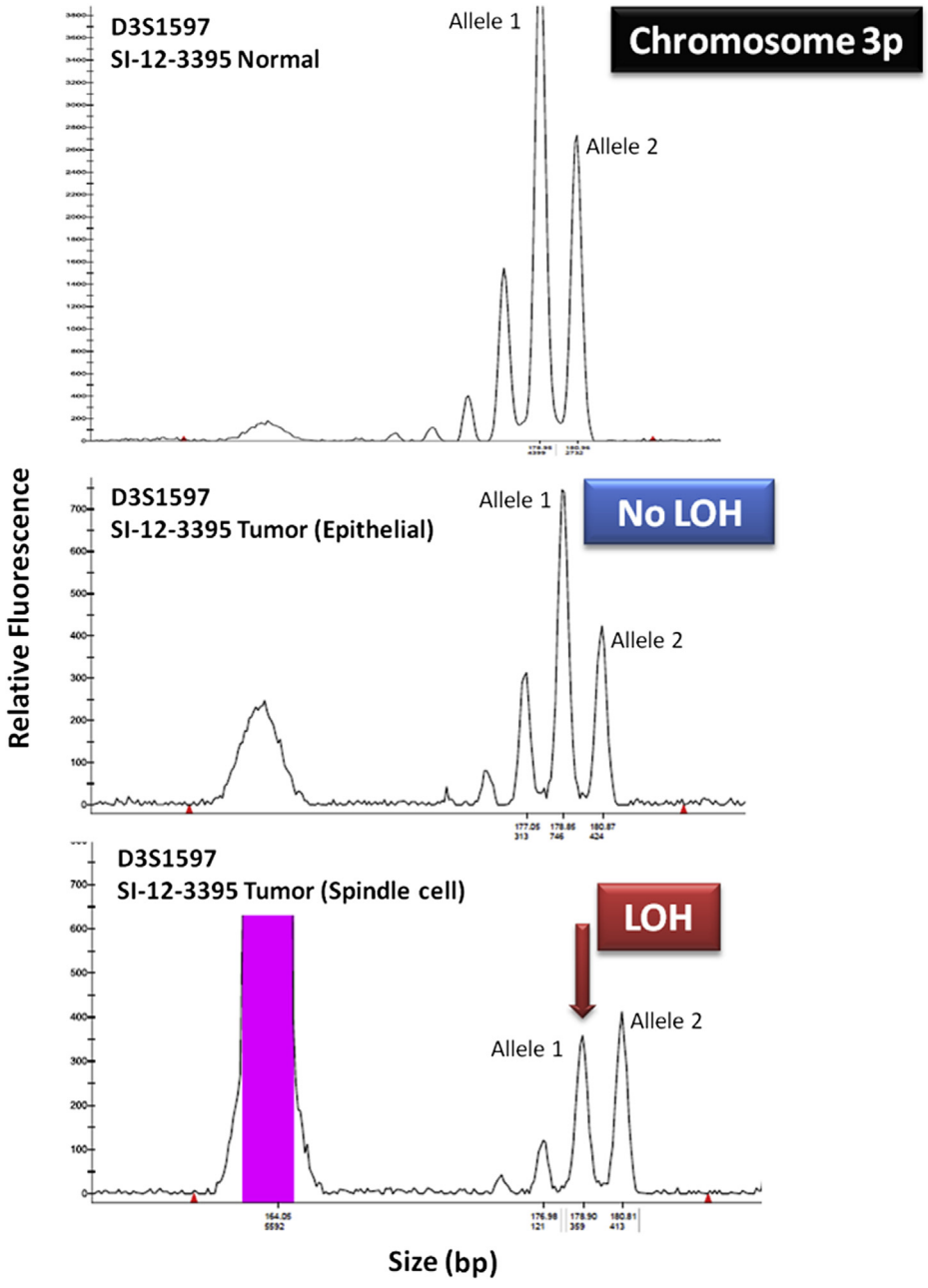

Figure 3. Tumor cells of spindle cell morphology displayed loss of heterozygosity (LOH) in chromosome 3p, whereas the epithelial tumor component did not.

the chromophobe component, in addition to multiple contiguous intercellular attachments consistent with epithelial differentiation. The spindle cell component exhibited ultrastructural features consistent with 2 distinct cell populations, one being myofibroblastic with subplasmalemal filaments and abundant rough endoplasmic reticulum and the other being consistent with a chromophobe cell phenotype, as shown by the presence of abundant abnormal mitochondria.

Normal, epithelial, and sarcomatoid components of tumor were microdissected and deoxyribonucleic acid extracted for loss of heterozygosity (LOH) analysis using polymorphic markers for chromosomes 3p25, 1p35-36, and 1q42-43. There was LOH in chromosomes 1p and 1q in tumor cells of typical chromophobe morphology. In contrast, tumor cells of spindle cell morphology displayed LOH in chromosomes 3p (Fig. 3) in addition to 1p and 1q.

Discussion

Chromophobe subtype of RCC is uncommon, and its sarcomatoid dedifferentiation is rare. Few cases of sarcomatoid CRCC have been reported.[4,5] The mean age of presentation of sarcomatoid CRCC is higher than sarcomatoid clear cell RCC, suggesting that sarcomatoid change occurs in long-standing CRCCs, such as in our current case. Sarcomatoid component represents poorly differentiated transformation that occurs in any histologic subtype.[6,7] Clinicopathologic studies confirm that sarcomatoid transformation is associated with dismal prognosis. It is

important to emphasize that most studies refer to sarcomatoid differentiation in the most common subtype of RCC, that is, clear cell type, and there is limited information about sarcomatoid change in the chromophobe subtype.

Metastasis of CRCC is deemed rare. Contrary to the belief that it is usually the sarcomatoid component that metastasizes to lymph nodes,[5,8] we find lymph node metastasis of both chromophobe and spindle cell components.

An unexpected finding in the current case is the unusual pattern of lymphangitic spread. Multiple foci of the sarcomatoid tumor were in lymphatic vessels and permeating retroperitoneal and perirenal adipose tissue. We considered lymphangiosarcoma in our differential diagnosis. However, morphologic comparison with the primary renal tumor and immunophenotype (cytokeratin AE1/AE3 positivity) was in favor of lymphangitic carcinomatosis by sarcomatoid CRCC. There are only few instances of lymphangitic carcinomatosis of clear cell RCC.[9,10]

The chromophobe and spindle cells demonstrate distinctive immunohistochemical profiles. The sarcomatoid cells are positive with smooth muscle antigen, suggesting myofibroblastic differentiation, and with CD10 and cytokeratin AE1/AE3, indicative of an epithelial/chromophobe cell nature.

The electron microscopic features support the immunohistologic profile of the tumor cells. They confirmed the chromophobe nature of the epithelial cells, characterized by intracytoplasmic vesicles and increased numbers of mitochondria with tubulovesicular cristae,[11] and the dual phenotype of the spindle cells, as myofibroblastic[12] and chromophobe. Although studies have used electron microscopy as an important ancillary technique to characterize RCC subtypes,[11,13] ultrastructural characterization of the sarcomatoid component has been limited,[14] and we are not aware of any other case of sarcomatoid CRCC in which the sarcomatoid cells retain features typical of chromophobe cells.

Our genetic studies revealed LOH in 3p in addition to 1p and 1q in regions of sarcomatoid morphology. Loss of 3p is frequently seen in clear cell type RCC. Our findings suggest that loss of 3p in CRCC correlates with biologic aggressiveness.

Although CRCC is associated with a better prognosis than clear cell RCC, it is important for the pathologist to recognize a subset of CRCC that has aggressive biologic behavior. Our case report adds information critical to better characterization of sarcomatoid CRCC—with widespread metastasis in lymph nodes and lymphatic vessels in a lymphangitic carcinomatosis pattern of tumor involvement.

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