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Primary Renal Sclerosing Epithelioid Fibrosarcoma: Report of Two Cases with *EWSR1-CREB3L1* Gene Fusion

Pedram Argani, MD^{1,2}, Jack R. Lewin, MBBCh, M Med (Path) F F Path³, Pamela Edmonds, MD⁴, George J. Netto, MD^{1,2}, Carlos Prieto-Granada, MD⁵, Lei Zhang⁵, Achim A. Jungbluth, MD⁵, and Cristina R. Antonescu, MD⁵

¹Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA

²Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA

³Department of Pathology, Abbingdon Medical Center, Abbingdon, PA, USA

⁴Department of Pathology, University of Mississippi Medical Center, Jackson, MS, USA

⁵Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

We report the first two genetically confirmed cases of primary renal sclerosing epithelioid fibrosarcoma (SEF), occurring in a 17 year-old male and a 61 year-old female. In both cases, the tumors demonstrated the typical epithelioid clear cell morphology associated with extensive hyalinizing fibrosis, raising the differential diagnosis of solitary fibrous tumor, metanephric stromal tumor, and the sclerosing variant of clear cell sarcoma of the kidney. Both neoplasms demonstrated diffuse immunoreactivity for MUC4, a highly specific marker for SEF, and both demonstrated evidence of rearrangement of both the *EWSR1* and *CREB3L1* genes which have recently shown to be fused in this entity. Both neoplasms presented with metastatic disease. Primary renal SEF represents yet another translocation-associated sarcoma now shown to arise primarily in the kidney.

Keywords

Renal Neoplasm; Fibrosarcoma; Translocation

Introduction

Given the vast potential of Wilms tumor (nephroblastoma) to demonstrate mesenchymal differentiation, the existence of primary renal sarcomas in children was historically difficult to accept. Due in large part to the meticulous, classic clinicopathologic studies of Dr. J. Bruce Beckwith, three major primary renal sarcomas were recognized: rhabdoid tumor of the kidney (RTK)^{1,2}, clear sarcoma of the kidney (CCSK)^{3,4,5,6}, and congenital mesoblastic nephroma (CMN)^{7,8}. The distinctive nature of these lesions was later corroborated by the

demonstration of distinctive, characteristic genetic alterations in each of them; specifically, deletion of the *SMARCB1* gene and SMARCB1 protein loss in RTK^{9,10}, the *ETV6-NTRK3* gene fusion in cellular CMN^{11,12,13}, and the *YWHAE-FAM22*¹⁴ gene fusion in a subset of CCSK.

Over the past 20 years, a variety of translocation-associated soft tissue sarcomas have been documented to arise primarily within the kidney. In each case, the existence of these distinctive entities has been proven by molecular assays documenting the presence of a characteristic specific gene fusion product. Examples of these sarcomas arising in the kidney include primitive neuroectodermal tumor (PNET)^{15,16}, synovial sarcoma,¹⁷ intra-abdominal desmoplastic small round cell tumor¹⁸, and a rare case of clear cell sarcoma of tendon sheath (melanoma of soft parts)¹⁹. Some of these entities were likely previously confused with other established lesions, contributing to misinformation regarding the behavior of the latter. For example, primary renal PNET^{15, 16} was historically often confused with blastemal Wilms tumor in young adults, contributing to the perception that adult Wilms tumors had a particularly poor prognosis. Primary renal synovial sarcomas were often confused with sarcomas arising in cystic nephroma, some of which are now thought to belong to the family of *DICER1*-related sarcomas²⁰. Hence, delineation of novel specific morphologic and molecular entities in the kidney has also helped clarify the clinicopathologic features of existing ones.

We report in the first two genetically confirmed cases of primary renal sclerosing epithelioid fibrosarcoma. In both cases, the diagnosis was confirmed by fluorescence in situ hybridization (FISH) showing the characteristic *EWSR1-CREB3L1* gene fusion, which has recently been found to be highly prevalent in this entity. Both patients presented with large renal masses and evidence of metastatic disease. Both cases raised the morphologic differential diagnosis of a variety of mesenchymal lesions including the sclerosing variant of clear cell sarcoma of the kidney.

Materials and Methods

Cases

Both cases were sent in consultation to one of the authors (PA), with the differential diagnosis of clear cell sarcoma of the kidney (CCSK). In each case, H&E stained slides and paraffin tissue blocks were available for immunohistochemistry and fluorescence in situ hybridization (FISH) as described below.

Immunohistochemistry

At Johns Hopkins University, immunohistochemical labeling was performed on the Benchmark XT autostainer (Ventana Medical Systems Inc, Tucson, AZ) using the I-View detection kit. The standard antibodies used, vendors, pretreatments, and dilutions were as follows: desmin (Dako M0760, clone D33, steam, 1:100), cytokeratin AE1/3 (Chemicon, steam, 1:4000) vimentin (Ventana, 790-2917, prediluted), EMA (Ventana, 760-4259, steam, prediluted), CD99 (Leica, Clone 12E7, steam, prediluted), Bcl2 (Leica, ORG-8714, steam, prediluted), S100 protein (Ventana, 760-2914, steam, prediluted), and CD34 (Immunotech/

Coulter, catalog 0786, steam, prediluted). MUC4 immunohistochemical staining was performed at Memorial Sloan Kettering Cancer Center using anti-human mouse monoclonal antibody clone 8G7 at a dilution of 0.1 ug/ml (Santa Cruz Biotechnology, Santa Cruz, CA).

Fluorescence in situ hybridization (FISH)

FISH was performed in the laboratory of one of the authors (CRA) at Memorial Sloan Kettering Cancer Center as previously described²¹. Briefly, FISH on interphase nuclei from paraffin embedded 4-micron sections was performed applying custom probes using bacterial artificial chromosomes (BAC), covering and flanking the *EWSR1* and *CREB3L1* genes. BAC clones were chosen according to USCS genome browser (<http://genome.uscs.edu>) (see Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/PAS/A238>). The BAC clones were obtained from BACPAC sources of Children's Hospital of Oakland Research Institute (CHORI) (Oakland, CA) (<http://bacpac.chori.org>). DNA from individual BACs was isolated according to the manufacturer's instructions, labeled with different fluorochromes in a nick translation reaction, denatured, and hybridized to pretreated slides. Slides were then incubated, washed, and mounted with DAPI in an antifade solution. The genomic location of each BAC set was verified by hybridizing them to normal metaphase chromosomes. Two hundred successive nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems). A positive score was interpreted when at least 20% of the nuclei showed a break apart signal. Nuclei with incomplete set of signals were omitted from the score.

Results

Case Histories

Case 1—Patient one was a 17 year-old white male who presented with left flank, back and abdominal pain, 40 pound weight loss over six months, dysuria and decreased appetite. He was found on imaging to have a 25 × 15 × 20 cm tumor arising in the lower pole of the left kidney, along with evidence of metastases involving the right fifth rib, vertebrae, epidural spinal cord, and liver (Figure 1). Following tumor embolization, the patient underwent left radical nephrectomy, with excision of a liver lesion and epidural spinal cord tumor. Beginning one month following resection, the patient received 10 fractions of radiotherapy with a total dose of 30Gy over a period of 3 weeks. However, he then developed volvulus and closed small bowel obstruction secondary to adhesions, which were treated surgically. Soon after he developed abdominal pain and was found to have free air in the abdomen. On surgical exploration, he was found to have extensive ischemic necrosis involving his abdominal organs, not thought to be compatible with continuation of life. The patient expired without further intervention.

Case 2—The patient was a 61 year-old female who presented with rib pain. She was found to have a 5cm left renal mass with metastatic lesions involving the ribs, lung, bone, and lymph nodes. A nephrectomy was performed. The patient's disease progressed and she was placed in hospice 6 months after diagnosis.

Pathology

On gross examination, both lesions were described as firm, white tumors centered on the kidney. In case one, the tumor grossly penetrated the renal capsule to involve perirenal soft tissue (Figure 2A). In case 2, the tumor abutted the renal capsule (Figure 2B) and protruded into the renal pelvis.

The morphologic features of the two cases were similar and therefore they are described together (Figure 3, 4). Both neoplasms were predominantly composed of cords of epithelioid cells with angulated nuclei and clear cytoplasm, in a background of hyaline sclerosis (Figure 3A-3E, 4A-4C). Cellularity was variable within the neoplasms, with frequent abrupt transitions from areas of high cellularity to highly sclerotic areas of low cellularity (Figure 3C). In areas of high cellularity, vague nodules of collagen reminiscent of those seen in hyalinizing spindle cell tumor with giant rosettes (HSCTGR) were identified (Figure 3F, 4E)²². Focally, metaplastic bone was present in each case (Figure 4D). Each neoplasm encircled native renal tubules and glomeruli (Figure 3D, 4B). In case one, a focal myxoid nodule contained bland spindle cells in a swirling pattern adjacent to a hypocellular fibrous zone, closely resembling low grade fibromyxoid sarcoma (Figure 3G). Also in case one, native renal tubules entrapped by the neoplasm demonstrate tubulopapillary hyperplasia, simulating a biphasic neoplasm (Figure 3B). The liver and epidural lesions sampled in case 1 showed metastatic disease morphologically similar to that of the primary renal tumor.

By immunohistochemistry, both neoplasms were immunoreactive for vimentin and Bcl2, but negative for cytokeratin AE1/AE3, desmin, S100 protein, and CD34. Case one was focally positive for CD99 and negative for EMA, while case two was focally positive for EMA and negative for CD99. Both neoplasms demonstrated diffuse cytoplasmic immunoreactivity for mucin 4 (MUC4) (Figure 3H, 4F).

By fluorescence in situ hybridization, both neoplasms demonstrated evidence of rearrangement of the *EWSR1* gene and the *CREB3L1* gene (Figure 5). No evidence of *FUS* gene rearrangement was found (not shown).

Discussion

We report the first two genetically confirmed cases of sclerosing epithelioid fibrosarcoma of the kidney. Sclerosing epithelioid fibrosarcoma (SEF) and low grade fibromyxoid sarcoma (LGFMS) are related members of the so-called “fibrosing fibrosarcoma family”²³, with SEF considered the higher grade end of this spectrum. As seen in our cases, SEF affects patients in a wide age range. SEF typically arises as a deep seated mass in the extremities, and is characterized by infiltrative, carcinoma-like cords or nests of epithelioid cells with angulated nuclei and clear cytoplasm in densely hyalinized stroma²⁴. Many cases, including case one of this study, have small spindle cell foci which overlap with LGFMS. LGFMS typically affects young adults and similarly arises in the deep soft tissue. LGFMS typically features hypocellular fibrous zones with abrupt transitions to myxoid nodules showing increased cellularity of spindle cells with a whorling pattern, supported by curvilinear vessels^{25, 26}. A subset of LGFMS demonstrate giant collagen rosettes, leading to the prior description of these cases as hyalinizing spindle cell tumor with giant rosettes (HSCTGR)^{27,28}. Other cases

have areas that resemble SEF. More recently, genetic studies have demonstrated the relatedness of HSCTGR, LGFMS, and SEF. First, a *FUS-CREB3L2* gene fusion resulting from a t(7;16)(q33;p11) chromosome translocation was found to be present in over 90% of LGFMS, HSCTGR and hybrid forms of LGFMS/SEF²⁹⁻³². An alternative *FUS-CREB3L1* resulting from a t(11;16)(p11;q11) chromosome translocation was subsequently found in a minority of LGFMS³³. Finally, an *EWSR1-CREBL1* gene fusion resulting from a t(11;22)(p11;q12) chromosome translocation was found in the majority of SEF^{34, 35} and in a minority of LGFMS³⁶. The ability of the *FUS* and *EWSR1* genes to substitute in gene fusions is logical since they are highly related RNA binding proteins. These genes function as alternating fusion partners in three other soft tissue sarcomas: Ewing sarcoma, myxoid liposarcoma, and angiomatoid fibrous histiocytoma³⁷. Our cases both demonstrated the *EWSR1-CRB3L1* gene fusion which predominates in SEF. Further corroborating the diagnosis, both neoplasms overexpressed the mucin 4 (MUC4) protein, which has been identified as overexpressed in LGFMS by gene expression profiling, and found to be overexpressed by immunohistochemistry in LGFMS and SEF^{38, 39}.

SEF represents the latest soft tissue sarcoma to have been documented genetically to arise primarily within the kidney, joining PNET, synovial sarcoma, intra-abdominal desmoplastic small round cell tumor, and clear cell sarcoma of the kidney. Given that the cellular variant of congenital mesoblastic nephroma shares clinical, morphologic and immunohistochemical features with infantile fibrosarcoma, and harbors the same *ETV6-NTRK3* gene fusion, many would add infantile fibrosarcoma to this list.

Two other primary renal neoplasms which may be related to renal SEF have been reported. First, Rubenstein et al recently reported a case of LGFMS arising in the kidney of a 16 year old male⁴⁰. This 16cm neoplasm harbored the *EWSR1-CREB3L1* gene fusion that is more commonly seen in SEF (including our two cases of renal SEF) than in LGFMS of soft tissue. We note that there is a precedent for differing frequencies of usage of alternative gene fusions in a sarcoma when it arises in the kidney compared to soft tissue. In synovial sarcoma of soft tissue, the *SYT-SSX1* gene fusion predominates, whereas in renal synovial sarcoma *SYT-SSX2* gene fusion predominates¹⁷. Hence, it will be interesting to see if the prevalence of the *EWSR1-CREB3L1* gene fusion, now identified in all three cases of fibrosing fibrosarcoma family neoplasms arising in the kidney, is greater in the kidney than it is in these same tumors in soft tissue. Second, Arbajian et al included a case of a primary renal neoplasm in a recent series of sclerosing epithelioid fibrosarcomas³⁴. This 41 year-old female presented with a 9 cm renal mass and bone and lung metastases at diagnosis, and died of disease at 22 months. The case was not illustrated, and while FISH studies demonstrated loss of signal corresponding to the 3' portion of the EWS gene (suggesting a rearrangement), a fusion partner was not identified.

The differential diagnosis for renal SEF is broad and includes several mesenchymal lesions previously documented to occur in the kidney; specifically, metanephric stromal tumor (MST), renal synovial sarcoma, renal solitary fibrous tumor, renal osteosarcoma, and the sclerosing variant of clear cell sarcoma of the kidney. Metanephric stromal tumor typically affects the pediatric age group, and can also be associated with extensive fibrosis/sclerosis⁴¹. Cases resembling MST with overtly malignant areas have been suggested to represent

malignant counterparts to this typically benign neoplasm. However, unlike SEF, MST typically encircles entrapped native renal tubules in an onion-skinning, concentric pattern, is associated with angiodysplasia and juxtaglomerular cell hyperplasia, and often labels for CD34. Like SEF, renal synovial sarcoma may have hemangiopericytomatous vasculature and be associated with extensive collagen deposition, and typically labels for Bcl2 but not CD34¹⁷. In addition, the glandular component of synovial sarcoma can label for MUC4³⁸. However, unlike SEF, primary renal synovial sarcomas are typically monophasic spindle cell lesions lacking an epithelial component, and feature only thin, ropey, non-sclerotic strands of collagen. The neoplastic cells of monophasic synovial sarcoma are typically ovoid and have more primitive chromatin than those of SEF. Both benign and malignant SFT have been documented to occur in the kidney^{42, 43}, and like SEF these lesions feature extensive fibrosis/sclerosis, and hemangiopericytomatous vasculature. In contrast to SEF, SFT label for CD34 and are comprised of spindled not epithelioid cells. The presence of osteoid/bone matrix in both examples of renal SEF presented herein raises the differential diagnosis of renal osteosarcoma. Renal osteosarcoma is rare^{44, 45}, and it is possible that some of the cases reported could represent incompletely-sampled sarcomatoid carcinomas. Of note, like the cases of renal SEF reported herein, cases of primary renal osteosarcoma have tended to present at advanced stage. Given that most cases reported as primary renal osteosarcoma were published before SEF was first described in 1995, it seems possible that some of these could in fact represent SEF. It should be noted, however, that a single case reported as a small cell osteosarcoma of bone has been found to harbor the *EWSR1-CREB3L1* gene fusion of SEF, suggesting that this distinction may not always be clear-cut⁴⁶.

Clear cell sarcoma of the kidney (CCSK) represents the most difficult differential diagnosis for renal SEF, specifically the sclerosing variant of CCSK⁶. In addition to its classic pattern featuring cords of epithelioid cells in a branching capillary vasculature, CCSK demonstrates a wide range of variant patterns including ribbons or rosettes, spindle cells, myxoid pools, sclerosis, palisading and anaplasia. The sclerosing variant of CCSK is characterized by extensive hyaline sclerosis surrounding cords and nests of epithelioid cells with clear cytoplasm, similar to the morphologic appearance of renal SEF. Like SEF, CCSK is negative for most standard immunohistochemical markers such as desmin, S100, CD34, and cytokeratin. Variable labeling for CD99 has been reported in CCSK, but most cases have proven to be negative, similar to SEF⁶. Like SEF, CCSK is a relatively slow growing tumor which encircles native renal tubules and characteristically incites hyperplasia of entrapped renal tubular epithelium, very similar to the hyperplasia of entrapped tubules seen in case one of this study. Finally, both CCSK and LGFMS/SEF may recur late, mandating long-term follow-up. Given this overlap, it seems possible some cases reported as sclerosing CCSK in the literature might in fact represent SEF, given that the latter was not described before the former were reported. Along these lines, most cases of CCSK present as localized disease, but a minority present with disseminated disease similar to the presentation of renal SEF seen in this study. One wonders if such “stage 4” CCKs might in fact be renal SEF. Morphologic features that would favor CCSK over SEF include the admixture of other variant patterns with sclerosing areas, along with the characteristic fine, evenly dispersed chromatin of CCSK. MUC4 immunoreactivity could potentially help distinguish these

entities, though we are unaware of MUC4 labeling being examined in CCSK. Detection of the characteristic gene fusions of SEF should distinguish this entity from CCSK, which in minority of cases harbors a distinct *YWHAЕ-FAM22* gene fusion.

In summary, we report the first two genetically confirmed cases of renal sclerosing epithelioid fibrosarcoma. Both cases had an aggressive clinical course, presenting with advanced stage disease at diagnosis. Given the relatively recent recognition of SEF as a distinctive entity, one wonders if renal SEF in prior years were misclassified as CCSK, renal osteosarcoma, or other entities. Sclerosing epithelioid fibrosarcoma represents yet another soft tissue sarcoma documented to occur primarily within the kidney.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
(Case 1) Computerized Tomography scan of the abdomen demonstrates a large tumor effacing the left kidney.

Figure 2.

A. Gross photograph of the sectioned specimen from case 1 reveals a pale solid tumor emanating from the lower pole of the left kidney, and extending through the capsule into the perirenal fat. A satellite nodule of tumor deeper within the kidney is also evident. B. Gross photograph of the sectioned specimen from case 2 reveals a pale solid tumor emanating from the lower pole of the left kidney, abutting the capsule and protruding into the renal sinus

Figure 3.

(Case 1) A. Low power view shows the spindle cell neoplasm centered within the kidney and entrapping renal tubules at its periphery. B. The neoplasm consists of epithelioid cells with clear cytoplasm, associated with stromal hyalinization. The neoplasm entraps native renal tubules, which show micropapillary epithelial hyperplasia. C. In other areas the neoplasm is remarkably hypocellular and fibrous, surrounding obstructed native renal tubules. D. The neoplasm encircles a native glomerulus. E. At high power, one can appreciate the angulated nuclei, clear cytoplasm, and thin strands of collagen separating the neoplastic cells. These are typical features of SEF. F. More cellular areas of the tumor are associated with hypocellular collagenized nodules, similar to those of HSCTGR. G. Focally within the neoplasm there was a nodule of myxoid stroma with spindle cells having a whorled appearance, reminiscent of LGFMS. H. The neoplastic cells label diffusely for MUC4, while the entrapped native renal tubules are appropriately negative.

Figure 4.

(Case 2). A. This variably cellular fibroblastic neoplasm is centered in the kidney and entraps native glomeruli and renal tubules. B. The neoplasm encircles a native renal glomerulus. C. The neoplasm is composed of epithelioid clear cells in a background of dense strands of sclerotic collagen which separate individual neoplastic cells. D. Areas of metaplastic bone formation are evident. E. More cellular areas of the tumor are associated with hypocellular collagenized nodules, reminiscent of those of HSCTGR. F. Neoplastic cells are diffusely immunoreactive for MUC4.

Figure 5.

FISH showing rearrangement of *EWSR1* and *CREB3L1* genes in Cases 1 and 2. A. Case 1, *CREB3L1* break apart (arrows) (red centromeric, green telomeric). B. Case 1, *EWSR1* unbalanced rearrangement with loss of telomeric part (green). C. Case 2, *CREB3L1* break apart (arrows) (red centromeric, green telomeric). D. Case 2, *EWSR1* unbalanced rearrangement with loss of telomeric part (green).