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Review article

Sarcomatoid renal cell carcinoma: Biology and treatment advances

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Abstract

Sarcomatoid transformation in renal cell carcinoma, so called sacromatoid RCC (sRCC), is associated with an aggressive behavior and a poor prognosis. Current therapeutic approaches are largely ineffective. Recent studies looking into the genomic and molecular characterization of sRCCs have provided insights into the biology and pathogenesis of this entity. These advances in molecular signatures may help development of effective treatment strategies. We herein present a review of recent developments in the pathology, biology, and treatment modalities in sRCC.

Keywords: Sarcomatoid renal cell carcinoma; Renal cell carcinoma; Nephrectomy; Chemotherapy; Targeted therapy; Immunotherapy

1. Introduction

In the United States, cancers of the kidney and renal pelvis are the sixth most common type of cancer and an estimated 63,990 new patients will be diagnosed in 2017 [1]. Renal cell carcinoma (RCC) is the most common cancer of the kidney and it consists of multiple histologic subtypes [2]. Sarcomatoid transformation in RCC is characterized by a transformative growth pattern of the epithelial neoplasm into malignant spindle-shaped cells, and confers an aggressive phenotype [3]. Sarcomatoid RCC (sRCC) is no longer considered a distinct histological subtype, rather sarcomatoid components are found in variable proportions in association with other histologic subtypes of RCC [4–6]. About 5% of RCCs contain sarcomatoid elements, although this number can go up to 20% in patients who present with advanced disease [7,8]. sRCC tumors are usually large, invasive (Fig. A) and metastatic in the majority of cases [9,10]. sRCC carries a poor prognosis with a median survival of around 6 months, and a higher percentage of sarcomatoid components confers a worse outcome [9,11]. The biology of sRCC has been poorly understood and its response to conventional therapies is disappointing. The need for better treatment strategies has led to the unraveling of its molecular and genomic characterization in a number of recent studies.

2. Pathology

Historically, sRCC was defined by Farrow et al. [12] as a "renal cell carcinoma, intimately associated with a more pleomorphic spindle cell or giant cell malignancy resembling sarcoma." Modern classifications of RCCs have taken into consideration the variable but pervasive association of sarcomatoid components with conventional histological subtypes of RCC [13,14]. Sarcomatoid transformation is now recognized as a pattern of "dedifferentiation" with loss of characteristic epithelial features of RCC [3]. The incidence of sarcomatoid transformation varies among RCC subtypes but it is higher in clear cell (~5%–8%) and chromophobe RCCs (~8%–10%) [11,15]. Because of the overall higher prevalence of clear cell RCC (ccRCC), the majority of sRCCs are found to be in association with ccRCC [9,16]. Sarcomatoid areas are also seen with high-grade RCCs associated with the renal cell collecting system, including collecting duct carcinoma and renal medullary carcinoma [15,17]. Recently, sarcomatoid patterns have also been noted in the emerging types of RCCs associated with hereditary cancer syndromes, including fumarate hydratase (FH)-deficient RCC and succinate dehydrogenase

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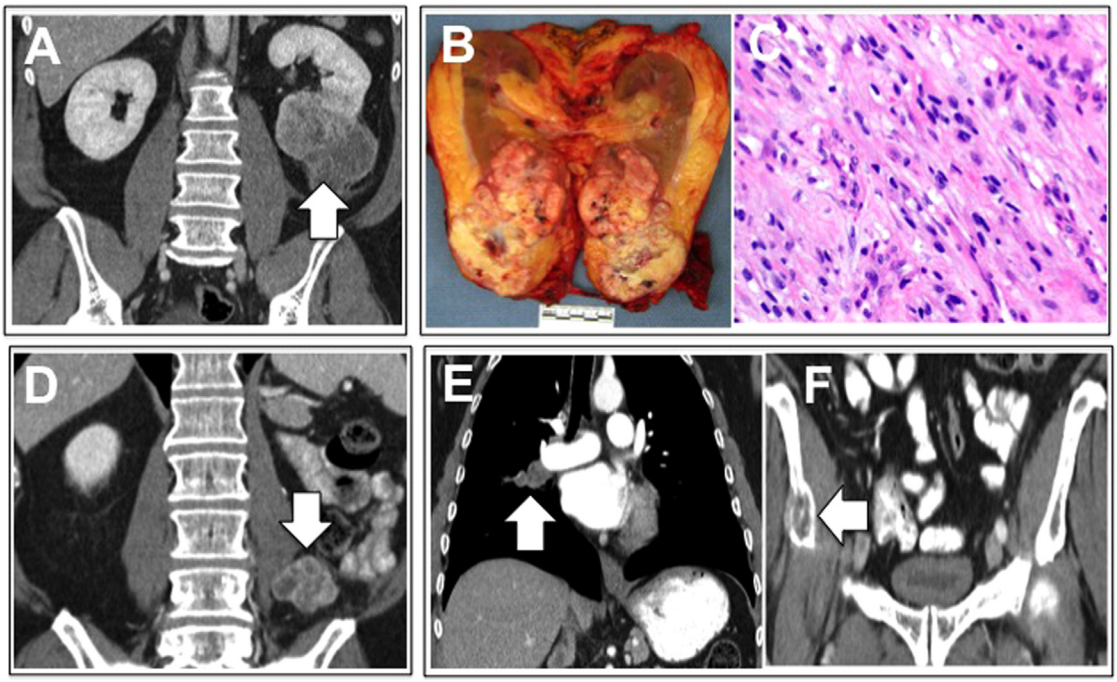

Fig. Representative images of a 67-year old male with an aggressive sarcomatoid RCC. An incidentally detected 8 cm mass arising from the lower pole of the left kidney (A). The patient underwent a left-sided nephrectomy. The macroscopic photograph (B) of the bisected left kidney shows a hemorrhagic and variably necrotic fleshy mass with invasion of perinephric adipose tissue. Pathology revealed a clear cell carcinoma with 50% sarcomatoid component. Microscopic features of an extensive sarcomatoid component showing spindle cell morphology, nuclear pleomorphism and hyperchromasia (ISUP grade 4), and a coarse chromatin pattern (C). A restaging CT scan 3 months following nephrectomy showing recurrence of disease with a new soft tissue mass in the LLQ of the abdomen encroaching on the left psoas muscle (D). Furthermore, 3 months after initiation of combination therapy with sunitinib and gemcitabine, the LLQ mass decreased in size, but there were multiple new lesions, including right-sided hilar lymphadenopathy (E) and a new osteolytic lesion in the right hip (F). CT images were displayed in coronal planes and white arrows in CT images indicate a target lesion. CT = computed tomography; LLQ = left lower quadrant. (Color version of figure is available online).

(SDH)-deficient RCC [18–20]. The histology of the sarcomatoid component has been found to be very variable, with particular note of fibrosarcoma-like or pleomorphic undifferentiated sarcoma-like patterns, although other heterologous sarcomatoid patterns such as osteosarcoma, chondrosarcoma, or rhabdomyosarcoma have been reported [14,15]. Necrosis is present in the vast majority of cases (90%) [11,15]. sRCC is described grossly as showing dense, gray, and fleshy cut surfaces (Fig. B). Careful sectioning is recommended, as the sarcomatoid component may be extensive rendering the differential diagnosis with a primary renal sarcoma quite challenging. To this end, immunohistochemistry (IHC) may be performed to help establish a renal epithelial origin or a subclassification of RCC. Common markers that may be performed include broad-spectrum epithelial markers (keratins, epithelial membrane antigen, EMA), renal histogenesis markers (PAX8, PAX2), or the ccRCC-associated marker, carbonic anhydrase IX (CA IX), as ancillary findings supportive of sRCC classification.

Recent consensus meetings in genitourinary surgical pathology have attempted to address several key issues regarding criteria for and reporting of key parameters for sRCC. These include issues of definition and minimal criteria for an sRCC designation, the conundrum of classifying apparently pure sRCC and clarification of the relation of sarcomatoid cytomorphology to tumor grading. Although the original description of the Fuhrman grading system [21] noted that grade 4 tumors very often had spindle cell areas resembling sarcoma, the issue of overlap had remained somewhat nebulous. Although a universal definition of sarcomatoid morphology has not been accepted, it was noted in the 2012 International Society of Urological Pathology (ISUP) Vancouver consensus [22] that the most consensus respondents would designate an RCC as sarcomatoid “if it consists of atypical spindle cells and resembles any form of sarcoma” [14]. The consensus also deemed that there is no explicit minimum amount or percentage of sarcomatoid differentiation required to make the diagnosis.

The question of grade was addressed formally by the consensus proposing and accepting a new grading system, the ISUP grading system [14]. The ISUP grading system, now endorsed by the World Health Organization, defined grade 4 to include sarcomatoid differentiation [13]. Additionally, the Vancouver consensus recommended reporting the histologic type of conventional RCC associated with sRCC, reflective of some data supporting greater efficacy of targeted therapies in ccRCC-associated sRCC [23]. Finally, it was decided that pure sRCC without a conventional RCC