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Oncology

Unclassified Renal Cell Carcinoma With Medullary Phenotype Versus Renal Medullary Carcinoma: Lessons From Diagnosis in an Italian Man Found to Harbor Sickle Cell Trait

Piergiuseppe Colombo [a,*], Steven C. Smith [b], Simona Massa [a], Salvatore L. Renne [a], Simona Brambilla [c], Roberto Peschechera [d], Pierpaolo Graziotti [d], Massimo Roncalli [a], Mahul B. Amin [e]

[a] Department of Pathology, Humanitas Research Center, IRCCS, Humanitas University, Rozzano, Milan, Italy
[b] Department of Pathology, VCU Health System, Richmond, VA, USA
[c] Clinical Laboratory, Humanitas Research Center, IRCCS, Rozzano, Milan, Italy
[d] Department of Urology, Humanitas Research Center, IRCCS, Rozzano, Milan, Italy
[e] Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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ABSTRACT

Medullary carcinoma is a rare malignant tumor of the kidney. It affects individuals of African descent and all cases reported show evidence of sickle cell trait. We reviewed an unusual carcinoma arising in a white man, the ninth in the literature. The tumor demonstrated features associated with renal medullary carcinoma, or unclassified renal cell carcinoma, medullary phenotype as recently described; the presence of sickle cell trait confirmed the diagnosis of medullary carcinoma. This case is helpful in the differential diagnosis with non-sickle cell associated "renal cell carcinoma, unclassified with medullary phenotype," and study of this spectrum of tumors is ongoing.

Introduction

Renal medullary carcinoma (RMC) is a rare aggressive subtype of renal tumor, with 182 cases reported in the English literature,[1–5] originating from the medulla of the kidney and associated with sickle cell trait and disease.[1] The great majority of patients reported have been African-Americans. Herein we describe the clinicopathologic features of an RMC arising in a white man with sickle cell trait. RMC has never been reported in Italy, highlighting the degree of clinical suspicion necessary to identify such a case.

Case presentation

A 23-year old white male presented with left-sided loin pain, without hematuria. Ultrasound examination showed a renal mass. Abdominal computed tomography (CT) scan confirmed the sonographic findings demonstrating a 42 mm mass in the upper pole of the left kidney, with enlargement of regional lymph-nodes. The histology of CT-guided needle biopsy revealed necrotic tissue and only a focus of viable neoplastic proliferation of atypical epithelial cells, primarily compatible to renal cell carcinoma, not otherwise specified. Subsequently patient underwent to a staging full body CT, which revealed multiple bilateral lung metastases. Radical nephrectomy with regional lymphadenectomy was performed. At gross examination, the specimen revealed a yellowish-white mass in the upper renal pole, 5.5 cm in diameter, with invasion of both perirenal and renal sinus fat (Fig. 1A).

Histologically, the tumor showed proliferation of epithelioid cells, arranged in tubular and cribriform structures, in desmoplastic and myxoid stroma (Fig. 1B). There were multiple foci of necrosis (~40% of the tumor), and a rich acute inflammatory infiltrate (Fig. 1C). There was also a massive metastasis in one hilar lymph node. Drepanocytes (sickle forms) were histologically noted, and taken with the tumor morphologic characteristics, tests were ordered to screen for hemoglobinopathies (Fig. 1D). A peripheral blood hemoglobin electrophoresis, performed in the Clinical

* Corresponding author. Department of Pathology, Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Tel.: +39 02 82244712; fax: +39 02 82244791.
E-mail address: piergiuseppe.colombo@humanitas.ii (P. Colombo).

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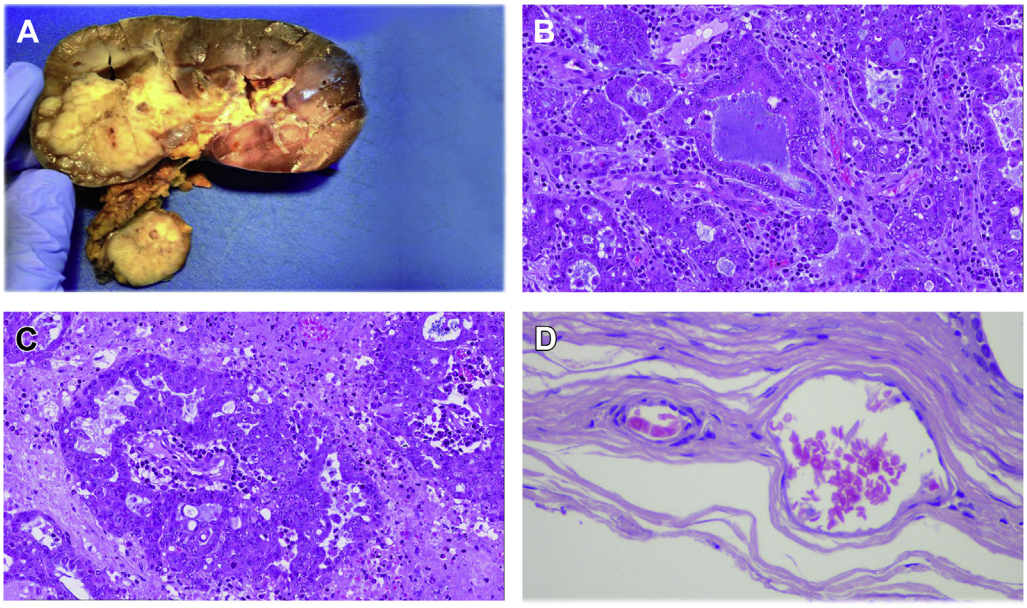

E

Peak Name	NGSP %	Area %	Retention Time (min)	Peak Area
A1b	---	0.6	0.257	13827
F	0.6	---	0.406	10484
LA1c	---	0.6	0.725	15697
A1c	5.5	---	0.924	44452
P3	---	2.7	1.546	68435
Ao	---	51.4	1.736	1290548
A2	2.5	---	2.925	59683
Unknown	---	1.2	3.263	29278
S	---	39.0	3.452	979729

Total Area: 2,512,132

HbF = 0.6 %
HbA1c (NGSP) = 5.5 %
HbA2 = 2.5 %

HbA1c (IFCC) = 37 mmol/mol

Analysis comments:

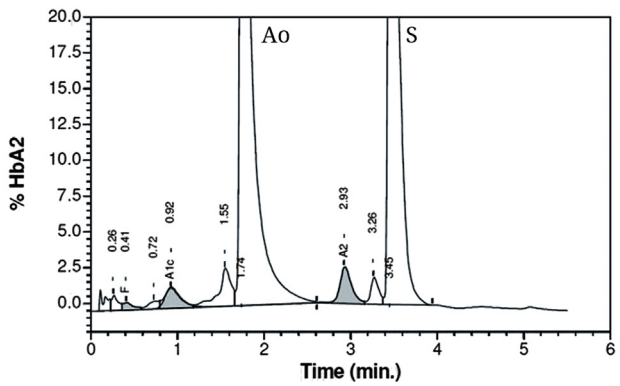

Figure 1. Gross and microscopic characteristics of the tumor and sickle cell status (A–E). A, Note that the tumor is located in the cortico-medullary region, with lymph node hilar metastasis. B and C, Glandular differentiation and desmoplastic stroma with inflammatory cells in the medullary carcinoma. D, Drepanocytes identified between and at the periphery of the carcinoma. E, Electrophoretic analysis documented high level of mutated Hemoglobin (S).

Analysis Laboratory, uncovered a sickle cell trait, confirming the histological suspicion (Fig. 1E).

Given the rarity of this tumor in Caucasians, extensive immunohistochemical studies were performed, showing reactivity for cytokeratins, polyclonal CEA, PAX8, PAX2, AMACR, S100A1, and OCT3/4. An immunostain for the chromatin-modifying protein SMARCB1 (also known as INI-1) was negative (Fig. 2). In the light of these findings taken together, a diagnosis of RMC was made.

Disease progressed, under treatment with Sunitinib and Sorafenib, and the patient died at 10 months of follow-up with multiple pulmonary metastases.

Discussion

Since the original studies by Davis et al, 182 cases of renal RMC have been reported, and the great majority in African-American