CASE REPORT

Renal medullary carcinoma as an incidental finding in a horseshoe kidney: case report and literature review

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Renal medullary carcinoma is rare and extremely aggressive neoplasm that typically affects young patients of African decent who demonstrate sickle cell trait or disease. Since the original description in 1995, only few cases have been reported outside the United States. A 29 year-old Canadian male of Afro-Caribbean decent with sickle cell trait developed right-sided hemiparesis due to brain infarct. During the clinical work-up, a 3 cm renal tumor was detected in a horseshoe kidney. The patient died suddenly 2 weeks after the presentation of massive non-neoplastic pulmonary thromboembolism, confirmed at autopsy. The final diagnosis of renal medullary carcinoma was established after the autopsy. Due to the small size of the tumor and the limited metastatic spread only to the regional lymph nodes, the tumor was considered an incidental finding, and not the primary cause of patient's death.

Key Words: renal medullary carcinoma, horseshoe kidney, sickle cell trait

Case

A 29 year-old Canadian male of Afro-Caribbean decent (born in Guyana) presented with right-sided hemiparesis. The patient was known to have a sickle cell trait and experienced malaise, nausea and right-sided abdominal pain few weeks before the event. Computerized tomography (CT) of the head revealed left middle cerebral artery thromboembolism with extensive brain infarction. CT of the abdomen and pelvis showed a horseshoe kidney with a mass at the superior pole of the right kidney and a para-aortic lymphadenopathy. CT-guided fine needle aspiration of the tumor suggested a primary renal neoplasm, and collecting duct carcinoma was favored. The patient died suddenly 2 weeks after the presentation due to non-neoplastic pulmonary thromboembolism that was confirmed at autopsy. A 3 cm circumscribed mass was found at the superior pole of the right kidney,

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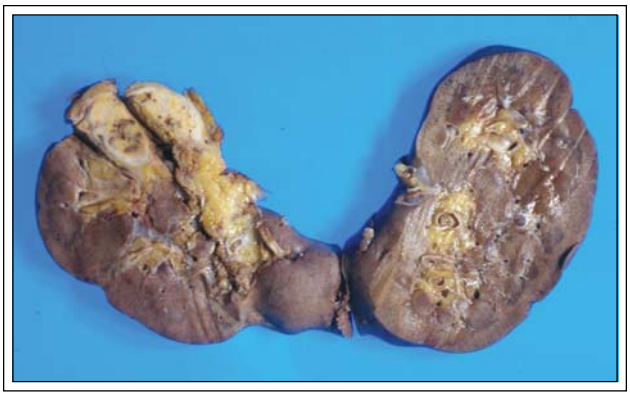

Figure 1. Gross photo of a renal medullary carcinoma: a circumscribed tumor involves the superior pole on the right side of a horseshoe kidney.

Figure 1. Metastatic disease was identified only in the regional para-aortic lymph nodes. As no distant metastases were found, the renal tumor was not considered a primary cause of patient's death.

The tumor showed a gray-tan cut surface with foci of hemorrhage. On microscopy, tumor cells demonstrated mainly reticular growth pattern. Collections of neutrophils and lymphocytes resembling microabscesses were admixed with the neoplastic cells that were cytologically malignant and exhibited abundant eosinophilic cytoplasm and irregular pleomorphic nuclei, Figure 2. Sickled red blood cells were focally admixed with the tumor cells, Figure 3. The tumor background consisted of desmoplastic connective tissue stroma.

Immunohistochemistry demonstrated reactivity of the malignant cells for the cytokeratin markers (AE1/

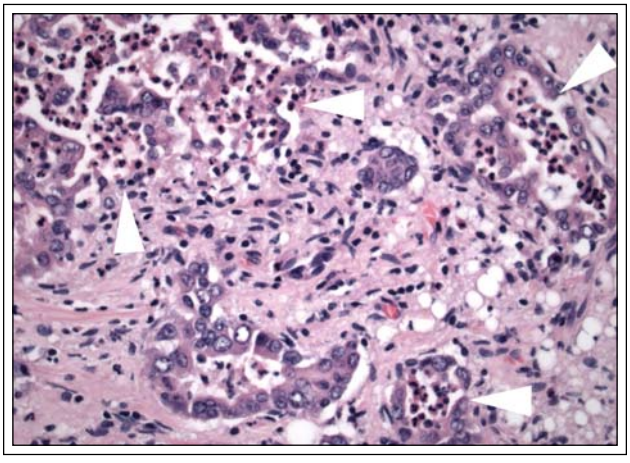

Figure 2. On microscopy, tumor cells are admixed with collections of neutrophils (arrowheads) and desmoplastic stroma (Hematoxylin and eosin x 400).

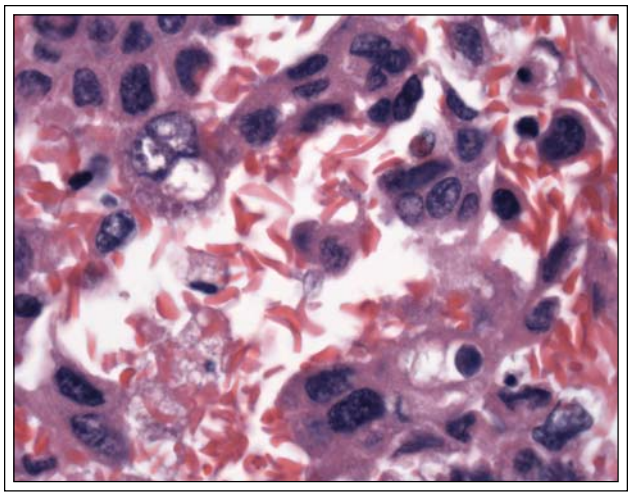

Figure 3. Cytologically malignant tumor cells admixed with sickled red blood cells (center) (Hematoxylin and eosin x 1000).

AE3, CAM 5.2, CK7, CK 20), epithelial membrane antigen and carcinoembrionic antigen; vimentin stained the stroma, but not the cells. Tumor cells were also non-reactive to antibodies for: high molecular weight cytokeratin (34βE12 and CK 5/6), desmin, S100, CD10, α-fetoprotein and p53.

Discussion

Approximately 4000 new renal cancers and 1450 cancer related deaths have been documented in Canada in 2002.[1] The most common type of adult renal cell carcinoma is conventional (clear) cell carcinoma, representing approximately 60%-70% of all cancers. Renal medullary carcinoma (RMC) is a rare and highly aggressive renal neoplasm, first described in a study of 33 patients documented over 22 years at the US Armed Forces Institute of Pathology (AFIP). The tumor was suggested to represent "the seventh sickle cell nephropathy", following the description by Berman of six nephropathies associated with sickle cell disease or trait that include: 1) gross hematuria, 2) papillary necrosis, 3) nephritic syndrome, 4) renal infection, 5) hyposthenuria (inability to concentrate urine) and 6) pyelonephritis.[3] Since the first report, less than 100 cases[4-29] have been documented and all patients have been encountered in the United States, except for three patients in France, UK and Mexico.[15,18,26] A recent study from the US National Wilms Tumor Registry included 40 cases documented over 25 years.[23] All remaining reports are either individual case studies or small series of two to three patients.[11,24,10,29] The neoplasm affects

predominantly, but not exclusively African-Americans; individuals of African, African-Caribbean, Brazilian, Hispanic and Caucasian descent have also been reported. Affected individuals are pediatric patients or young adults (median age 18, range 5-40 years) and males predominate 2 to 1. Patients present with gross hematuria, abdominal or flank pain, and weight loss. The majority of patients with known sickle cell status demonstrated sickle cell trait (HbAS) and only few patients demonstrated sickle cell disease (HbSS) or were heterozygous for hemoglobins S and C. Although the sickle cell status was unknown for many patients in the AFIP study, sickled red blood cells (drepanocytes) were identified in all patients microscopically. The tumors predominantly affect the right kidney and often involve the central portion of the kidney, ranging from 3 cm to 15 cm in size. Many tumors demonstrate early aggressive features including lymphatic and/or vascular invasion and metastatic spread to the regional lymph nodes. Other metastatic sites include adrenal, liver, lungs and retroperitoneum.

Grossly, RMC appears as a discrete mass or an ill-defined infiltrative mass in the renal medulla. Microscopic examination typically reveals three components: 1) cellular 2) stromal and 3) inflammatory. Tumor profile on immunohistochemistry has been inconsistent, but cytokeratin and epithelial membrane antigen have usually been positive. Differential diagnosis includes renal collecting duct carcinoma, high-grade urothelial carcinoma of renal pelvis, rhabdoid tumor, and metastases from other primary tumors. Consideration of patient's age, race, sickle cell status and the tumor pathology will exclude these possibilities. Pathogenesis of RMC is unknown. The tumor is thought to arise from the terminal collecting ducts of the kidney. It was hypothesized that the abnormalities of the β-globin gene, which is mutated in sickle cell disease and trait and which is located on the short arm of chromosome 11, may play a role in the development of the neoplasm.[4] Another possibility is that renal medullary hypoxia, secondary to hemoglobinopathy, may contribute to the pathogenesis of RMC through the increased expression of hypoxia-induced factor (HIF), vascular endothelial growth factor (VEGF) and TP53 protein.[23] Cytogenetics has been studied in a limited number of tumors and multiple structural and numerical abnormalities have been identified, including monosomy of chromosomes 3 and 11, t(3:8)(p21; q24)[4] and tetraploidy.[14,15] Bcr/abl translocation of chromosomes 9 and 22 has been identified in one patient,[14] but was negative in two patients tested with fluorescence in-situ hybridization.[29] A study that used comparative genomic hybridization did not reveal any abnormalities in eight of nine studied cases and found loss of chromosome 22 in only one tumor.[23] A recent study using gene expression profiling revealed a distinct molecular signature of renal medullary carcinoma, which clustered closely with urothelial (transitional cell) carcinoma of the renal pelvis.[28]

The prognosis of RMC is extremely poor and all patients in the AFIP study survived on average only 15 weeks after the surgery. All reported patients so far have succumbed within 15 months after the diagnosis, with the exception of four patients who have been alive at the time of the reporting.[18,20,21,24] However, two of these patients (also reported as disease free) had only a limited follow-up of 9 and 24 months.[18,20] One of these patients had a large infiltrative tumor (13 cm) that metastasized in the regional lymph nodes and lacked a detailed pathology description.[18] The other two patients who were reported alive had advanced disease at the time of the diagnosis; one patient presented with metastases,[21] while the other had recurrent disease in one year.[24] Although multiple chemotherapeutic regiments, radiotherapy and surgical modalities have been attempted in patients with RMC, a rapidly progressive and fatal course of the disease has not been altered. Chemotherapy with methotrexate, vinblastine, doxorubicin and cysplatin (MVAC) resulted in progression-free survival after nephrectomy for 4 months and complete response for 10 months in two patients who subsequently died of the disease.[14,16]

RMC should be included in the differential diagnosis of young black patients who present with gross hematuria and, in particular, abdominal or flank pain and weight loss. The initial diagnostic investigations should include hemoglobin electrophoresis to document the sickle cell status, imaging studies and urine cytology. Although radiological appearance is not specific, CT, magnetic resonance imaging (MRI) or intravenous pyelography (IVP) findings of a central renal mass that encases the renal pelvis in a young black patient with sickle cell trait and hematuria may strongly suggest medullary carcinoma and may lead to a biopsy and early diagnosis. In summary, we document the first Canadian patient with renal medullary carcinoma, a rare and extremely aggressive neoplasm of unknown pathogenesis that predominantly affects young patients of African descent with sickle cell trait or disease. The case presented herein is unusual because the neoplasm was small and it was detected incidentally during the clinical work-up for a right-

sided hemiparesis, it was located in a horseshoe kidney, and it was not the primary cause of patient's death. Familiarity with the clinical, radiological and pathological features of this uncommon tumor may lead to earlier diagnosis and improved patient survival. □

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