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CASE REPORT

Renal Medullary Carcinoma in a Six-Year-Old Boy with Sickle Cell Trait

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Renal medullary carcinoma (RMC), an aggressive malignant epithelial neoplasm, first emerged as a distinct clinicopathologic entity in 1995. It affects individuals 40 years of age or younger and is strongly associated with sickle cell disease or trait. The majority of patients with RMC have widely disseminated disease at the time of diagnosis and most fail to respond to both chemotherapy and radiotherapy. Mortality approaches 100%, and death usually occurs within a few months to a year of diagnosis. We report a 6-year-old African-American boy with a history of gross hematuria who died four weeks after diagnosis of disseminated metastatic disease. Autopsy showed a 4.4-cm renal mass with metastases to the contra lateral kidney, liver, lungs and multiregional lymph nodes. RMC should be included in the differential diagnosis of any patient 40 years old or younger with a history of hemoglobinopathy and gross hematuria and/or abdominal or flank pain. A brief discussion of the differential diagnosis, histogenesis and treatment is presented in this study. (Pathology Oncology Research Vol 9, No 3, 193–195)

Keywords: sickle cell disease, renal medullary carcinoma, collecting duct carcinoma

Introduction

Six nephropathies have been described in patients with sickle cell disease or sickle cell trait. These include hematuria, papillary necrosis, nephritic syndrome, renal infarction, inability to concentrate urine and pyelonephritis.[1] Renal medullary carcinoma (RMC) was recently described as the seventh nephropathy by Davis et al.[2] Clinically, RMC is characterized by high stage at the time of detection with widespread metastases and lack of response to both chemotherapy and radiotherapy.[3] Mortality approaches 100 percent, and death usually occurs within a few months of the diagnosis.

Case report

A 6-year-old African-American boy with a prior history of gross hematuria was admitted to Cardinal Glennon Children's hospital because of severe respiratory distress. The boy and his mother both had sickle cell trait. His older sibling died at the age of 3 months of sudden infant dead syndrome. An abdominal ultrasound revealed a markedly enlarged liver with inhomogeneous echotexture and multiple hipoechoic areas. A solid inhomogeneous mass was demonstrated in the upper pole of the left kidney. A CT scan confirmed the presence of a large left renal mass with extensive metastases to the liver and lungs as well as retroperitoneal, hilar and mediastinal lymph nodes. After discussing prognosis and treatment options, his mother declined chemotherapy. Twenty-seven days after admission, the patient developed bradycardia and cardiorrespiratory arrest. At autopsy widespread lung, liver and supraclavicular, peri-aortic, peri-tracheal, mediastinal and peripancreatic lymph nodes metastases were identified. The left kidney weighed 190 g and had a 4.4 cm poorly circumscribed yellow, solid tumor in the medulla extending into the cortex (*Figure 1*). The tumor did not extent into the renal vessels or ureter. A 1.0 cm nodular lesion in the right lower pole was identified.

The neoplasm was composed of glandular-like structures with reticular and microcystic patterns and poorly differentiated areas composed of solid sheets of large cells with vesicular nuclei, prominent nucleoli and eosinophilic

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cytoplasm (*Figures 2 and 3*). Numerous mitotic figures were present. Foci of myxoid change and inflammatory infiltrate were identified in the stroma. There were areas of necrosis and hemorrhage. Immunohistochemical studies were performed on paraffin sections employing the following antibodies: CAM 5.2, EMA, cytokeratin 34βE12, carcinoembrionic antigen and Ulex europeus. The tumor cells were positive for CAM 5.2 and EMA but negative for cytokeratin 34βE12, carcinoembryonic antigen and Ulex europeus.

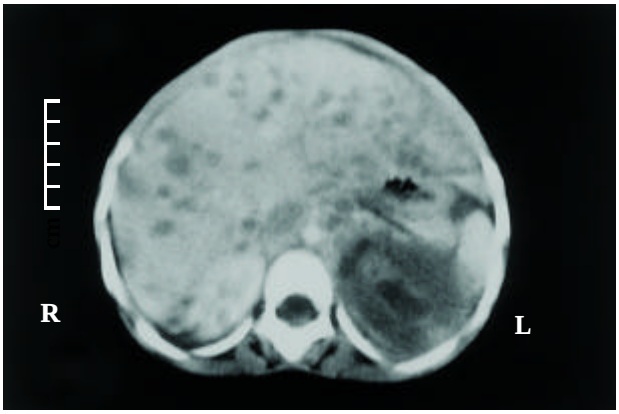

Figure 1. Poorly defined, tan yellow tumor in the left kidney.

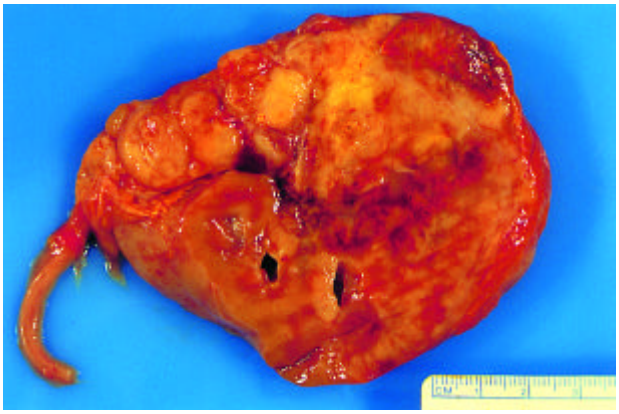

Figure 2. Microcystic pattern with desmoplastic areas.

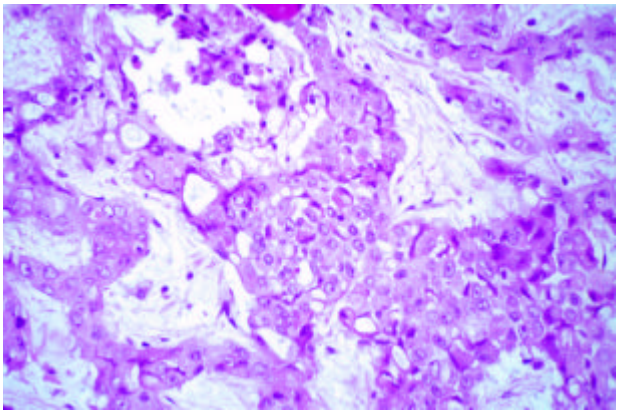

Figure 3. Polygonal cells with eosinophilic cytoplasm and prominent nucleoli.

Discussion

RMC is a highly malignant aggressive renal tumor that predominantly afflicts African-American young adults ranging in age from 5 to 40 years.[4-5] The first description of this neoplasm was made by Davis et al.[2] in 1995 who concluded that it represents another example of renal disease associated with sickle cell disorders. This condition has been described as "the seventh sickle cell nephropathy" in reference to the original six identified by Berman in 1974.[1]

The neoplasm is most commonly manifested by gross hematuria or abdominal or flank pain for an average of 8 weeks (range 1-20 weeks). At the time of diagnosis the RMC has usually metastasized to one or more lymph nodes, adrenal gland, peritoneum, retroperitoneum, liver, lungs or inferior vena cava. Death usually occurs a few months after diagnosis with a mean survival of 15 weeks.[2]

Grossly, the neoplasm is ill-defined, primarily occupying the renal medulla with extension into the calyces or renal pelvis.[2] Smaller satellite nodules are commonly found in the cortex and/or adjacent peripelvic soft tissue. The tumor is firm to rubbery, and tan to gray. Histologically, seven architectural patterns have been described: the most common and characteristic is the yolk sac-like or reticular pattern followed by the adenoid-cystic, microcystic, micropapillary, solid, tubular-trabecular and glandular. Hemorrhage, necrosis, prominent desmoplasia and inflammation are common.[2]

All 15 RMC studied immunohistochemically by Swartz et al[5] were positive for epithelial markers CAM 5.2 and epithelial membrane antigen; and negative for cytokeratin 34βE12. Cytokeratins 7 and 20 and carcinoembrionic antigen were variable expressed. Ulex europeus was focally positive in 7 cases.

Renal ultrasound and CT may reveal a centrally located, indistinct and infiltratrive mass, often associated with pelvic encasement.[6]

Collecting duct carcinoma (CDC) should be considered in the differential diagnosis. It accounts for approximately 1% of all renal neoplasms. Characteristically both tumors infiltrate the adjacent kidney and have a pronounced desmoplastic reaction. However, CDC more commonly displays a tubular or tubulopapillary patterns, whereas RMC has predominantly a reticular pattern. Moreover CDC is rare in children and immunohistochemically CDC typically is cytokeratin 34βE12 and ulex europeus agglutinin 1 lectin positive.[7]

RMC may have areas with a histological appearance similar to that of rhabdoid tumor. Both neoplasms are

characterized by aggressive behavior, cells with vesicular nuclei and prominent nucleoli. However rhabdoid tumors frequently show a monomorphous pattern and the classic cytoplasmic inclusions. Furthermore, rhabdoid tumors usually present in the first three years of life in contrast to RMC which have an older and wider age range.

It has been proposed that RMC arises from the calyceal epithelium.[2] This hypothesis is supported by Mostofi et al,[8] who examined 21 nephrectomy specimens obtained from patients with sickle cell trait and gross hematuria. They observed epithelial proliferation of the terminal collecting ducts in adjacent papillary mucosa rather than columnar ductal cells.

The environment of the renal medulla is characterized by acidosis, hypertonicity and hypoxia.[9] These factors tend to promote hemoglobin S polymerization and red blood cell sickling, thereby making this area of the kidney particularly susceptible to changes in oxygen delivery in patients with both sickle cell trait and disease.[9,10]

There is no effective treatment for this neoplasm. Surgery alone does not appear to alter the disease course. A wide variety of chemotherapies and immunotherapies have failed to alter the aggressive and fatal course of this tumor, including cyclophosphamide, doxorubicin, and cisplatin; interferon alone; vinblastine alone; or the combination of methotrexate, vinblastine, doxorubicin, and cisplatin.[3]

The differential diagnosis of a patient under 40 years of age with hemoglobinopathy and gross hematuria and/or flank pain should include RMC.

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