Case Report doi: 10.5146/tjpath.2014.01259

A Translocation Renal Cell Carcinoma with Skeletal Muscle Metastasis in a Child

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ABSTRACT

Renal cell carcinoma is a tumor that is well known for a high rate of metastasis to several locations like the lung, liver and bones. Skeletal muscle is a rare location for dissemination of the disease. Herein, we describe a 7-year-old boy who presented with flank pain. On physical examination, an abdominal mass located on the left kidney as well as a solid palpable lesion on the left upper arm were detected. Total nephrectomy with subsequent excision of the arm mass was performed. Pathology examination revealed presence of translocation renal cell carcinoma. The patient received α-interferon followed by multikinase inhibitor (Sorafenib) treatment but was lost due to progressive disease. This is the first description of a pediatric patient with skeletal muscle metastases of translocation renal cell carcinoma in the literature.

Key Words: Translocation renal cell carcinoma, Pediatric, Skeletal muscle, Metastases

INTRODUCTION

Renal cell carcinoma (RCC) is a rare cancer of children. It represents 5% of the malignant renal neoplasms of children and adolescents. The unique subtype of RCC that preferentially presents in adolescence and young adults is translocation RCC, which bears gene fusions in the TFE-3 transcription factor gene (1,2). The presence of translocation significantly increases the risk of advanced stage at presentation (1,3). Metastasis in RCC predominantly occurs to the regional lymph nodes, lung parenchyma, bones and liver. Skeletal muscle is a very rare site for metastasis despite a rich blood supply. Approximately 1% of adult patients develop muscle metastasis (4,5). The majority occur between 6 months to 18 years after the diagnosis (6). There are only a few case reports of adult patients expressing muscle metastasis at presentation (4). The optimal treatment modality for TFE-RCC has not been determined yet. Radical surgery is the recommended treatment for organ-confined stages of the disease and new medical targeting treatments are currently used for advanced disease. There is no recommended treatment for metastatic disease. Herein, we present a 7-year-old boy with TFE-3 positive RCC with metastasis to the deltoid muscle at the time of initial diagnosis. This is the first published pediatric RCC case with metastasis to the skeletal muscle.

CASE REPORT

A 7-year-old boy presented with flank pain for the last month. Physical examination revealed an abdominal mass and a solitary mass on the lateral side of the left upper arm. Complete blood count, urine and biochemistry tests were unremarkable. Computed tomography showed a solid nonhomogeneous mass containing focal calcification with a diameter of 15x12x11 cm originating from the upper pole of the left kidney. Left arm magnetic resonance imagining (MRI) with contrast demonstrated a hyperintense (T1-T2 weighted scan), 3x2x2 cm soft tissue mass, deeply located in the deltoid muscle on the proximal humerus (Figure 1). Total nephrectomy including retroperitoneal lymph node dissection and subsequent total excision of the lesions on the left upper arm were performed. Pathology examination showed RCC of the kidney and a metastatic lesion in the left arm (Figure 2). The 1100 gr, 15x13x10 cm, fragile, pink-cream, nodular tumor was surrounded with a capsule and located over 11x7x4 cm healthy kidney tissue. The perinephric fat tissue and capsule were invaded by the tumor but the pelvis was free of tumor involvement. Regional and para-aortic lymph nodes (three from the renal hilum, three splenic vein, one splenic hilum, two adrenal, four para-aortic area) were all negative for tumor involvement. Histologically, the tumor was solid with the alveolar subtype. Tumor necrosis and microvascular invasion were identified. The tumor was evaluated as nuclear grade IV according to the Fuhrman grading system. The surgical margins of the kidney and arm were negative. Immunohistochemical staining of the tumor showed diffuse nuclear TFE-3 positivity (Figure 3). Other immunohistochemical staining revealed AMACR cytoplasmic positivity in 10%, pan-cytokeratin positivity in 10%, vimentin positivity in 30%, and synaptophysin

(Turk Patoloji Derg 2017, 33:248-250)

Received : 15.02.2014 **Accepted :** 26.03.2014

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positivity in 70% of cells. CD10 was focally positive, and chromogranin and cytokeratin 7 were negative in tumor cells. Bone scintigraphy, thorax CT, cranial MRI and bone marrow biopsy were free of metastases. The patient was evaluated as Stage 4 RCC according to the Robson staging classification system and treatment with interferon-alfa-2b (IF) was initiated (3 million units 3 times per week). Radiological tests performed at the 6th month of therapy showed widespread metastases to the liver and lungs. Sorafenib (400 mg p.o. bid) was added to the IF treatment because of poor response. The disease progressed despite the combined use of the drugs for 2 months. The patient deteriorated and died 9 months after the initial diagnosis due to disease progression and respiratory failure.

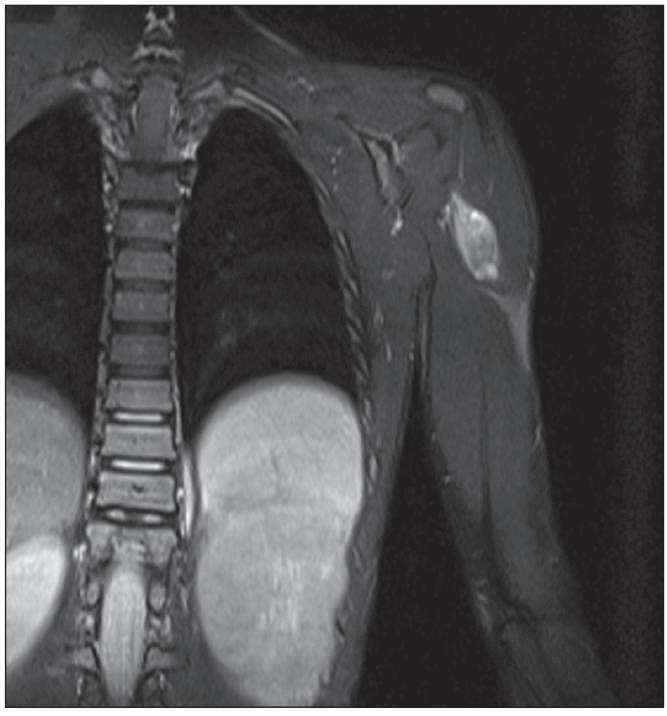

Figure 1: Coronal STIR image of left arm MRI.

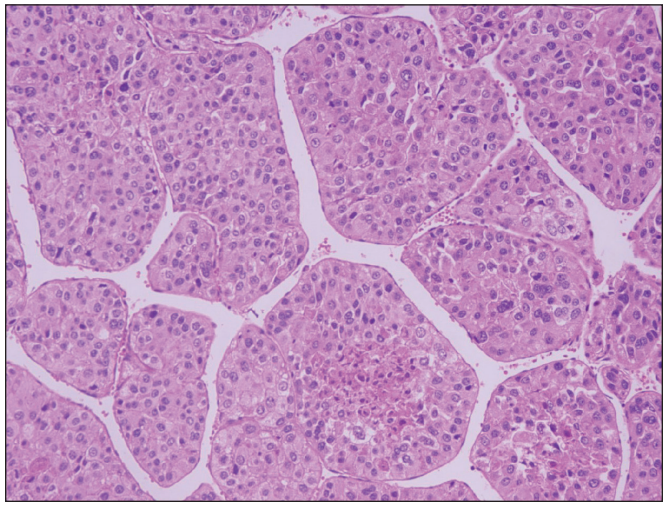

Figure 2: Nested pattern of tumor cells (H&E; x200).

DISCUSSION

Renal cell carcinoma is assumed to arise from the epithelial cells of the renal tubules. The disease is rare in children, accounting for only 0.1 - 0.3% of all neoplasms and 5% of malignant renal tumors (7). Most cases of pediatric RCC are sporadic but some may present in patients with risk factors such as the von Hippel-Lindau syndrome or tuberous sclerosis, and as secondary tumors in cancer survivors (8). The disease in children differs from adult forms with its distinct clinical presentation, genetics and features. However, survival rates for pediatric RCC decrease with advancing stage (I 90%, II 80%, III 70% and IV 15%), similar to adult patients (9). The difference between pediatric and adult patients may be explained by the presence of the translocation subtype. Translocation RCC is a relatively newly identified distinct subset of RCC with chromosomal translocations including TFE-3 (Xp11.2) or rarely TFEB (6p21) (10). The TFE-3 subtype predominantly develops in children and young adults in the 2nd and 3rd decade and has a female predominance (1, 2). This subtype is common in pediatric cases (20-40%) (11). The presence of the translocation significantly increases the risk of advanced stage at presentation (1,3). In a 30-year retrospective analysis of metastatic pediatric RCC, 5 of 9 patients were reported to have TFE-3 positivity in the tumor specimen (12). While a third of patients show metastasis at the time of initial diagnosis or later on in adults (13), the reported metastasis rate in pediatric cases

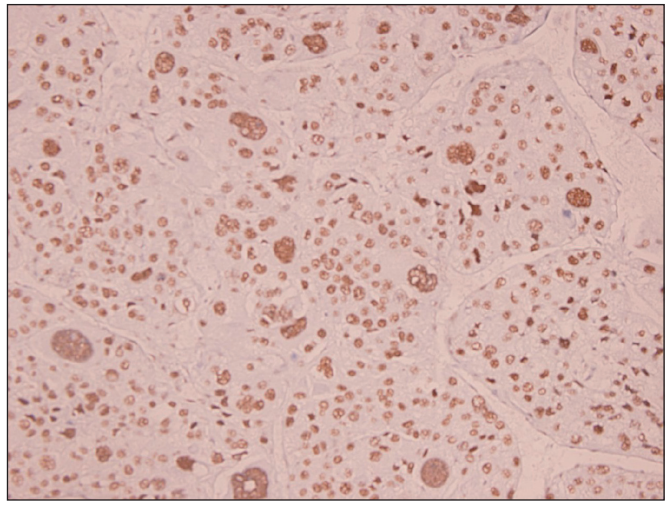

Figure 3: Nuclear TFE-3 positivity of tumor cells by immunohistochemistry (TFE-3; x200).

is around 20-25% (14,15). Metastases occur commonly to the lungs, liver, bone and brain. Atypical presentations and distant metastases are features of RCC and related to its early hematogenous spread (16). Metastasis to skeletal muscles is very rare despite the rich blood supply and the reported incidence in adults is 0.4 - 1% (4,5). Metastasis to soft tissues is nearly always as a solitary soft tissue deposit developing from a few months to several years after the initial diagnosis of RCC (6).

Surgical resection is the cornerstone of the treatment of RCC. Prognosis is poor in metastatic disease even with radical surgery. A randomized trial of adults with RCC showed that 5 of 29 patients (17.2 %) had complete response to alfa-interferon-2b treatment combined with surgery and only 1 of 40 (2.5 %) patients had complete response with alfa-interferon-2b treatment alone (17). The reported survival rate for metastatic RCC is poor in pediatric series. In the study from California Cancer Registry, the 5 year survival rate for metastatic RCC was reported to be less than 10% (15). In a 30-year retrospective analysis of metastatic pediatric RCC among 14 patients, all were lost due to disease progression (12). RCC is resistant to chemotherapy and radiotherapy and the efficacy of immunotherapy are not well defined. Molecular targeted therapies such as multikinase inhibitors (sorafenib and sunitinib) and the mammalian target of rapamycin pathways (temsirolimus and everolimus) have lately been developed and might have an effect on patient survival in adults (18). Despite the common use of these drugs in adult RCC patients, there are only a few case reports concerning these therapies in the pediatric population and further studies are warranted (19,20). We used immunotherapy with alfa interferon 2b as first line treatment and Sorafenib as a second line option in our case. A new treatment with receptor protein tyrosine kinase inhibitor; sunitinib and thalidomide was considered but they are not approved for children. Our patient was lost due to disease progression despite the combined therapy. In this study we wanted to emphasize a rare dissemination of translocation RCC to the skeletal muscle.

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