Soft tissue sarcomas of the kidney

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Abstract

Soft tissue sarcomas are rare mesenchymal tumors. Amongst others, primitive neuroectodermal tumors (PNET) of the kidney and synovial sarcoma of the kidney belong to the group of soft tissue sarcomas. Synovial sarcomas can occur almost anywhere in the body, most frequently, however, in the lower (62%) or upper extremities (21%). Metastases occur in 50-70% of cases, and thus the prognosis is poor. PNETs are rare, highly aggressive neoplastic lesions which mainly occur in the torso or axial skeleton in young adults. The prognosis is poor with a 5-year disease-free survival rate of 45-55%. The primary therapeutic approach is surgical resection. Most randomized studies assessing adjuvant chemotherapy for all types of localized soft tissue sarcomas did not show statistically significantly better overall survival times after chemotherapy, although they did show longer progression-free survival. We report on two cases of primary renal synovial sarcoma and one case of PNET of the kidney.

Introduction

Soft tissue sarcomas are rare mesenchymal tumors with an incidence of 50/1.000.000 population.[1] The newly issued WHO Classification includes more than 60 subtypes of soft tissue sarcomas.[2] About 60% of soft tissue sarcomas occur in the extremities and up to about 10% each in the retroperitoneum and torso. One third of patients with soft tissue sarcomas die from the tumor, usually after developing pulmonary metastasis.

Amongst others, primitive neuroectodermal tumors (PNET) of the kidney, or Ewing's sarcoma, and synovial sarcoma of the kidney belong to the group of soft tissue sarcomas.[3] Primary synovial sarcomas are extremely rare space-occupying lesions of the kidney. Synovial sarcomas are high-grade tumors and account for 5-10% of all soft-tissue sarcomas.[4-6] They can occur almost anywhere in the body, most frequently, however, in the lower (62%) or upper extremities (21%). Metastases occur in 50-70% of cases, and thus the prognosis is poor.[7,8] Characteristic for synovial sarcomas is the frequent occurrence of cysts in the tumor tissue,[9] although evidence of this tumor type is hardly never found in diagnostic radiological investigations of the kidney for suspected synovial sarcoma.

As with PNET, an exact diagnosis is based on molecular biological and histochemical investigations, and represents a challenge for the pathologist. PNET of the kidney and Ewing sarcoma are in the same spectrum of entity. PNETs are rare, highly aggressive neoplastic lesions which mainly occur in the torso or axial skeleton in young adults.[10,11] Differentiation between these and other primary tumors of the kidney is important for the right choice of therapy.[11] The prognosis is poor with a 5-year disease-free survival rate of 45-55%.[12] We report on 2 cases of primary renal synovial sarcoma and one case of PNET of the kidney.

Case Report #1

A male patient, 52 years old at the time of diagnosis, presented with a 5-month history of flank pain on the left side that had recently worsened. Ultrasound and CT showed a suspected malignant tumor of the left kidney with a maximum diameter of 10 cm (Figure 1) and suspected metastases in the region of the lungs and liver segment 7. Following tumor nephrectomy, retroperitoneal lymphadenectomy, removal of a tumor thrombus from the renal vein and inferior vena cava, and resection of liver segment 7, histological and molecular pathological workup showed primary poorly differentiated synovial sarcoma of the kidney with SYT translocation (18q 11.2). The Ki-67 (MIP-1)-index was 35-40%.

Immune histochemistry revealed focal expression of vimentin, strong, partially punctual positivity for MNF116 and a low positivity for EMA, CK 7, CK 19. In Hematoxylin & Eosin (H&E) staining, a high cell density with spindle shaped nuclei, arranged in short fascicles with prominent chromatin and hardly visible cytoplasma was observed (Figure 2).

Macroscopically, the kidney was lamellate and almost completely full of scattered beige-whitish, in some cases blotchy brown, different-sized tumor nodules, some running together.

Three months after surgery, spondylodesis had to be performed with implantation of a cage (L1-L4) because of new bony metastases. Following surgery, the patient underwent percutaneous radiotherapy to the lumbar spine and radiotherapy to the left side of the sacrum.

A course of palliative chemotherapy with doxorubicin and ifosfamide was started 5 months after diagnosis. Despite discontinuation of ifosfamide due to poor tolerance after the first cycle, the patient showed stable disease at the end of the course. One year after diagnosis, the patient had developed progressive pulmonary and hepatic metastases with peritoneal carcinosis and stenosing infiltration of the distal ileum.

The pulmonary, hepatic and peritoneal metastases continued to worsen despite subsequent chemotherapy with gemcitabine and docetaxel, after which treatment with the tyrosine kinase inhibitor pazopanib was started. Further progression of the metastases was seen under this therapy 18 months after diagnosis.

Case Report #2

A male patient, 50 years old at the time of diagnosis, underwent robot-assisted laparoscopic nephro-ureterectomy for suspected urothelial carcinoma of the right kidney. Before surgery, a chest CT showed an indeterminate round lesion in the middle lobe of the

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lung and a few granulomas, but there was no evidence for metastases on a CT of the abdomen or skeletal scinitgraphy.

The surface of the dissected kidney showed whitely, partly disintegrating tumor on the lower pole.

Histological investigation revealed poorly differentiated synovial sarcoma of the right kidney FNCLCC G3 with a t(X;18) translocation, an SYT/SSX2 break in real-time PCR. The Ki-67 (MIB-1)-index was 40%. Pan-CK and CD 99 were focally low positive, there was positivity for CD 56 and negativity for CD 34, S100, CD 45, Desmin, CK 20, RCC, CD 10, Myogenin, Myo D1, WT1, TTF1, Chromogranin, Synaptophysin, p63 and p53.

There was an extensive invasion of the blood vessels with formation of a tumor thrombus in the renal vein. The patient developed central and paracentral pulmonary emboli after surgery and was put on oral anticoagulants. Adjuvant chemotherapy with doxorubicin and ifosfamide was given. Thirteen months after the nephro-ureterectomy the patient underwent resection of the left lower lobe of the lung because of endoluminal metastases of the synovial carcinoma in an artery. Imaging one month later showed new pulmonary metastases.

Case Report #3

A male patient, 38 years old at the time of diagnosis, presented in our emergency department with bladder tamponade and macrohematuria. CT showed a tumor with a diameter of 10 cm in the region of the lower pole of the left kidney. Tumor nephrectomy was performed after an unremarkable cystoscopy.

The surface of the dissected kidney showed partly brown-beige nodular discoloration and partly necrotic, disintegrating cystic tissue.

Histological investigation showed a PNET of the kidney with extensive infiltration into the peripelvic adipose tissue and invasion by the tumor of numerous smaller and larger venous branches and individual lymph vessels.

FISH investigation of the tumor cells with an LSI EWSR 1 (22q12) dual color/break apart rearrangement probe showed split signals in 83% of the tumor cell nuclei. Immune histochemistry revealed diffuse expression of CD 99 (Figure 3) and NSE, and low positivity for S100 and CD 56, no expression of epithelial markers, no hormone expression, and negativity for GFAP and WT1. The Ki-67 (MIB-1)-index was 60-80%. H&E staining showed small round cells, separated by fibrous bands, forming Homer Wright rosettes.

One month after nephrectomy, the patient was started on adjuvant chemotherapy with the VIDE regimen (vincristine, ifosfamide, doxorubicin, etoposide) and developed febrile neutropenia as a complication. Chemotherapy was continued with the VAC regimen (vincristine, actinomycin C, cyclophosphamide). The patient was in complete remission 20 months after the nephrectomy.

Discussion

Primary sarcoma of the kidney is rare, and the subtype of synovial sarcoma is exceptionally rare. Since first being described in the literature by Argani *et al*.,[13] only 64 cases have been described up to 2012.[14] The differential diagnosis includes Wilms' tumor in adults, PNET, malignant tumors of the peripheral nerve sheaths, solitary fibrous tumors, sarcomatoid renal cell carcinoma, and metastases from other tumours.[14] Establishing a correct diagnosis can be extremely difficult and requires immune histochemical and molecular pathological methods. *SYT-SSX* gene fusion can be demonstrated using PCR. This is caused by a t(X;18) translocation and can be demonstrated in about 90% of all synovial sarcomas.[15]

At the time of diagnosis, 98% of patients had clinical symptoms, 67% had pain, and 38% hematuria. A median overall survival time of 48 months was calculated by Iacovelli *et al*. for the 64 cases. However, if metastases were present at diagnosis, the average was only six months.[16] The primary therapy for renal synovial sarcoma is radical surgical resection

No consensus has been reached on adjuvant treatment because only case reports have been published so far. The clinical course is, however, often aggressive with a poor clinical outcome. Anthracycline (adriamycin or epirubicin) combined with ifosfamide was the most frequently used regimen in the cases published.[14]

We found only 112 case reports on PNET or Ewing's sarcoma of the kidney up to 2013.[17] The tumours develop from cells of the primitive neuroectoderm. PNETs occur most frequently in the chest wall and the paraspinal region. 75% of patients are between 10 and 39 years old.

The differential diagnosis includes monophasic Wilms' tumor, neuroblastoma,

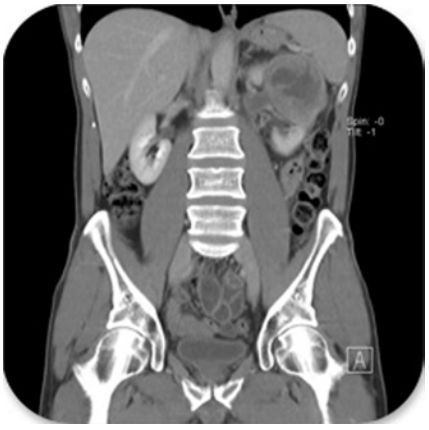

Figure 1. Computed tomography of abdomen and pelvic region with contrast medium: partially solid and partially necrotic tumor of the left kidney with infiltration of the left renal vein and slight involvement of the inferior vena cava.

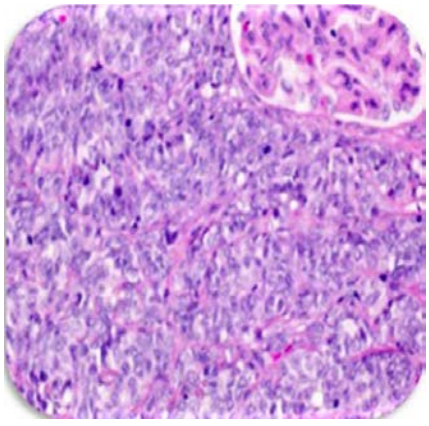

Figure 2. Hematoxylin & Eosin stained (20×) tumor cross section revealing tumor composed of spindle shaped nuclei, arranged in short fascicles with prominent chromatin and hardly visible cytoplasma.

Figure 3. Immune histochemistry of primitive neuroectodermal tumors: diffuse, marked expression of CD 99 (blue).

embryonal rhabdomyosarcoma, small-cell carcinoma, non-Hodgkin's lymphoma, and synovial sarcoma. Pseudorosettes are the characteristic growth pattern for these tumors.[18]

With regard to molecular pathology, PNETs are characterized by the translocation t(11;22)(q24;q12) with the fusion transcript of the EWS gene (22q12) and the ETS-associated oncogene FLI 1 (11q24).[9] This translocation is found in more than 90% of cases of PNET. With regard to immune histochemistry, renal PNET is positive for a range of biomarkers, such as S-100, Leu 7 (HNK-1) and NSE. The tumor cells are positive for CD99 in more than 90% of cases, but this marker is not specific to PNET.[19]

Renal PNETs are very aggressive tumors from the clinical point of view. In a study published in 1997, 20-50% of patients had metastases when diagnosed, mainly of the lymph nodes, lung and liver.[18,20] Median survival time after diagnosis was 10 months in a publication by Cuesta *et al*.[21]

The primary therapeutic approach is surgical resection with adjuvant (radio-) chemotherapy. The role of radiotherapy is unclear, but has been used to treat local tumor progression.[11]

The prognosis can be improved by adjuvant therapy; the most frequently used drugs are adriamycin, etoposide, dactinomycin, vincristine, cyclophosphamide and ifosfamide.[19]

Conclusions

Primary synovial sarcomas and PNETs are an extremely rare renal tumor and should be considered in the differential diagnosis of renal lesions, especially in young patients. The correct diagnosis can only be made using histological and molecular pathological investigations and is crucial in deciding on preoperative and post-surgical therapy. No studies have been conducted to establish the best approach to treatment in these rare entities. Most randomized studies assessing adjuvant chemotherapy for all types of localized soft tissue sarcomas did not show statistically significantly better overall survival times after chemotherapy, although they did show longer progression-free survival and better local and locoregional control in the patients treated with chemotherapy.[22]

The treatment of retroperitoneal and visceral sarcoma is complex and challenging for the attending physician.

The survival rate for retroperitoneal sarcomas is markedly lower than that for soft-tissue sarcomas of the extremities because of the size of the tumors, their tendency to invade other organs, and the difficulty of removing the entire tumor.

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