CASE REPORT

Round Cell Sarcoma of the Kidney on a Patient Treated for Acute Promyelocytic Leukemia: A Case Report and Literature Review

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This is a report of a patient who was diagnosed with acute promyelocytic leukemia (APL) last 2007 and was given a standard chemotherapeutic regimen of anthracycline, all-trans-retinoic acid and methotrexate. The patient completed treatment and recovered. Twelve years after chemotherapy, the patient was diagnosed to have renal tumor. The patient presented with intermittent episodes of non-bothersome flank pain. He was managed as a case of renal newgrowth, left, stage II (cT2bN0M0), which was eventually found to have intermediate grade, round cell sarcoma not further classified of the kidney. Immunohistochemical studies and literature review point to a newly classified subtype of sarcoma or a primitive neuroectodermal tumor, both of which are rarely found presenting in the kidneys.

Keywords: round cell sarcoma, secondary malignancy, acute promyelocytic leukemia, CIC DUX4, ES/PNET

Introduction

It has been postulated that APL survivors have an increased risk of developing secondary malignancies due to the mutations induced by cytotoxic chemotherapy.[1] Norsworthy and colleagues found a 1.4 per 1000 person-months incidence of secondary malignancies among acute promyelocytic leukemia patients previously treated with conventional chemotherapy.[2] To date, only myeloid neoplasms, therapy-related myelodysplastic syndrome (MDS), renal cell carcinoma and T-lymphoblastic lymphoma following successful treatment for APL have been reported. After an extensive search in PUBMED and ScienceDirect, this may be the first documented case of round cell sarcoma presenting in a patient previously treated for acute promyelocytic leukemia.

The Case

This is a case of a 48-year-old female patient who was previously treated for acute promyelocytic leukemia. She presented with a ten-year history of intermittent tolerable, non-bothersome flank pain associated with recurrent urinary tract infection for which she was treated with unrecalled antibiotics. Due to aggravation of flank pain, a KUB ultrasound was done revealing a calyceal mass at the left kidney. CT-urogram revealed a centrally located mass extending to the renal pelvis in the middle to lower aspect of the left kidney measuring 11.5cm x 9.5cm x 11.7cm (Figure 1). The patient is a non-smoker, a known diabetic and was previously treated for pulmonary tuberculosis. She underwent radical nephrectomy with intraoperative findings of a 20cm x 13cm mass almost completely occupying

the entire left kidney, and a normal left ureter (Figure 2). Histopathology revealed a malignant tumor composed of round to spindle cells in close solid to tubulocystic pattern occurring uniformly (Figure 3). The tumor cells exhibit mild pleomorphism with hyperchromatic enlarged nuclei, prominent nucleoli and eosinophilic cytoplasm with noted focal rosette formation (Figure 4). In addition, immunohistochemical studies revealed positive staining for CD99, Bcl-2, EMA, GATA3 and synaptophysin, negative staining for Cytokeratin, CK7, CAM5.2 and EMA and focal staining for S100, and negative LCA and Desmin, favoring an intermediate grade round cell sarcoma, not further classified. There was no involvement of the adrenal gland, vascular, ureteral margin and hilar lymph nodes. According to the American Joint Committee on Cancer and the French grading of soft tissue sarcomas, the patient can be considered as a case of round cell sarcoma of the kidney, not further classified, intermediate grade, stage IIIa (pT2N0M0). Patient tolerated procedure well and was discharged recovered. No obvious complications were observed post-operatively and patient was advised surveillance imaging and recurrent examinations. As of this writing, patient is alive with no subjective complaints. Informed consent for publication of this report was obtained from the patient.

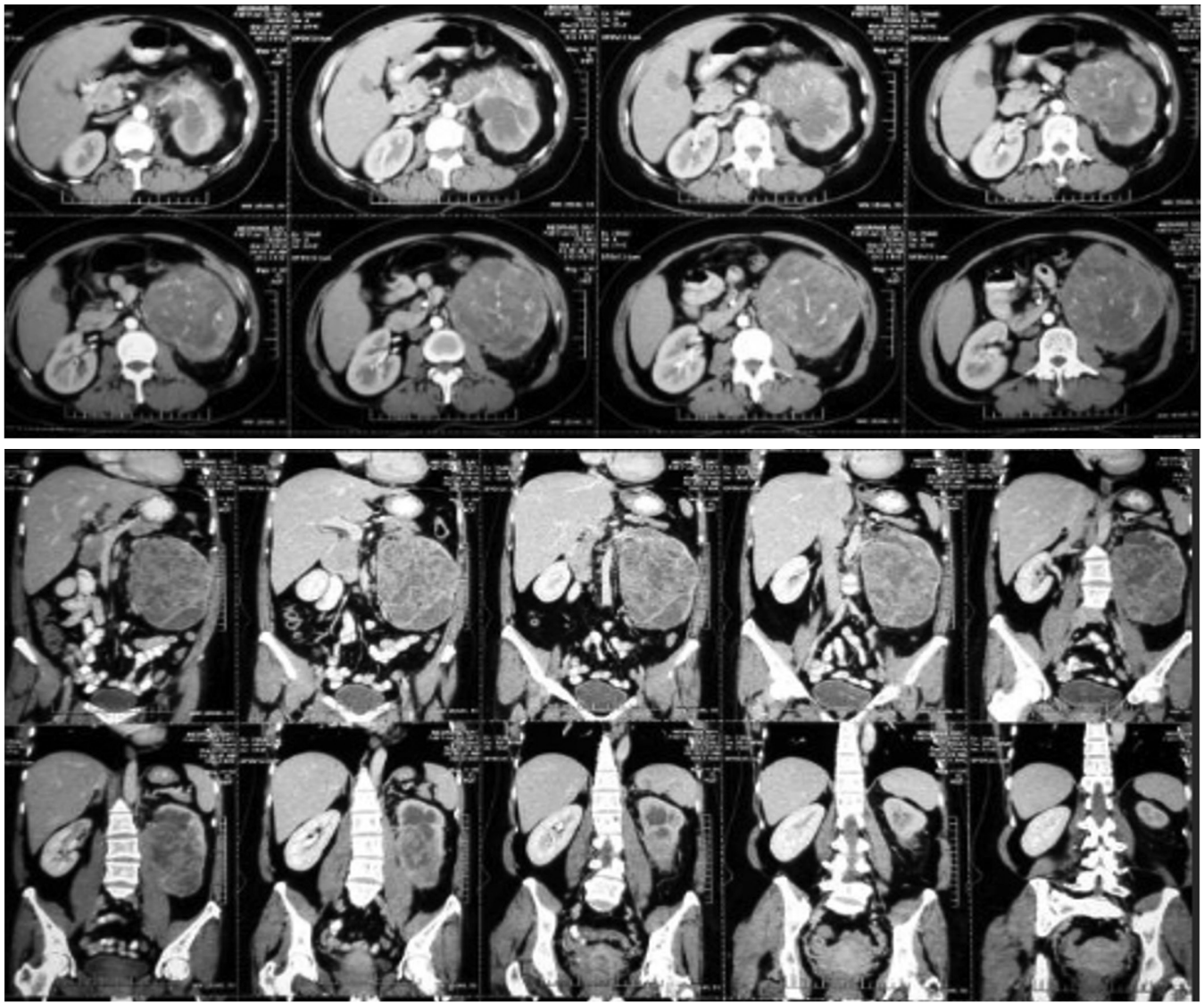

Figure 1. CT urogram showing a centrally located mass extending to the renal pelvis at the middle to lower aspect of the left kidney measuring 11.5cm x 9.5cm x 11.7cm.

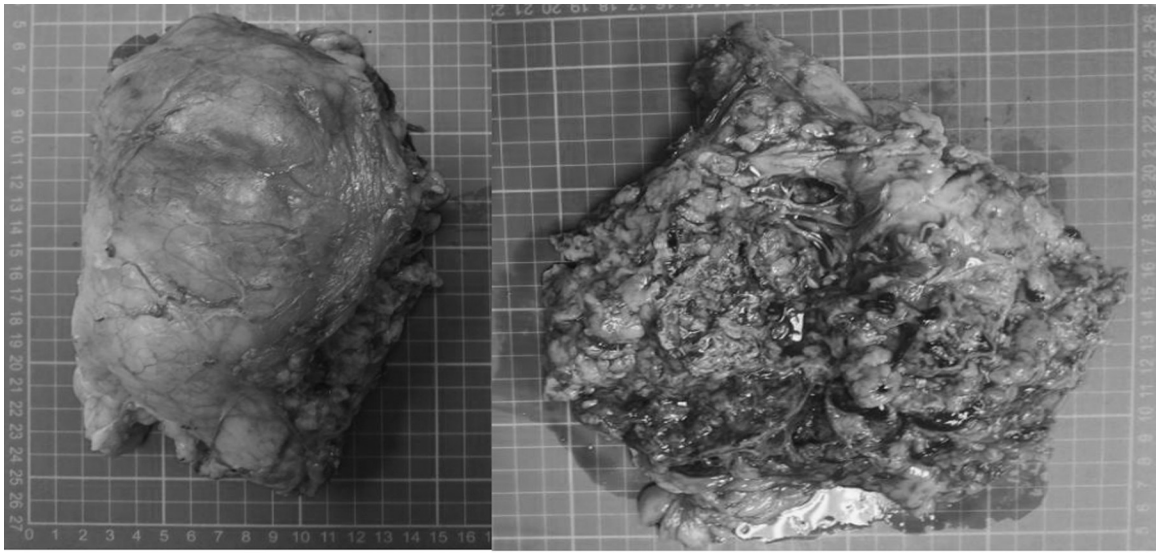

Figure 2. Cut section of the kidney shows a bulky light brown friable to solid mass partly with variegated to granular cut surface measuring 9cm x 6cm x 4.8cm. The mass obliterates/compresses the renal pelvis.

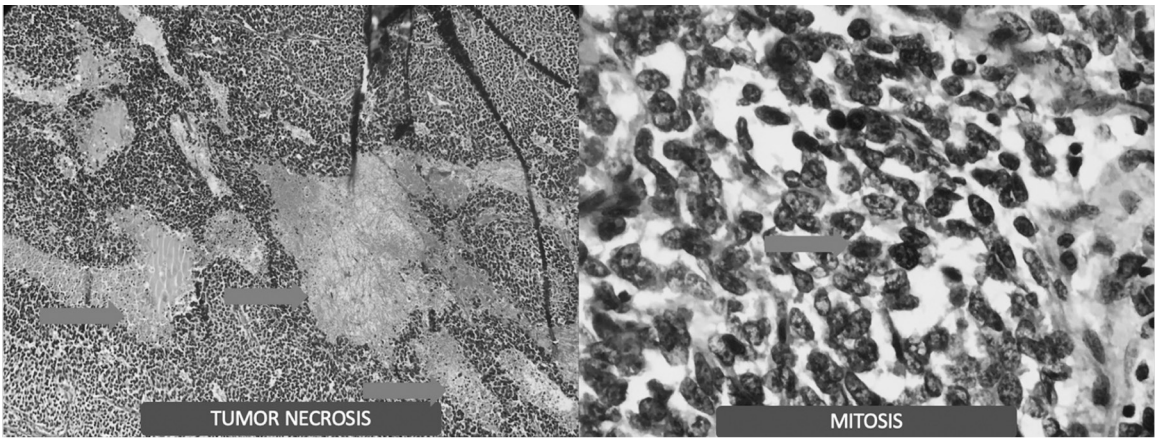

Figure 3. The morphology of this lesion is not classic for a specific tumor type. The overall findings favor a round cell sarcoma, not further classified, at least intermediate grade. This lesion demonstrates undifferentiated morphology, tumor necrosis comprising less than 50 % of sections submitted, mitotic count of 5-8/10 high power fields, consistent with intermediate grade in the French grading of soft tissue sarcomas

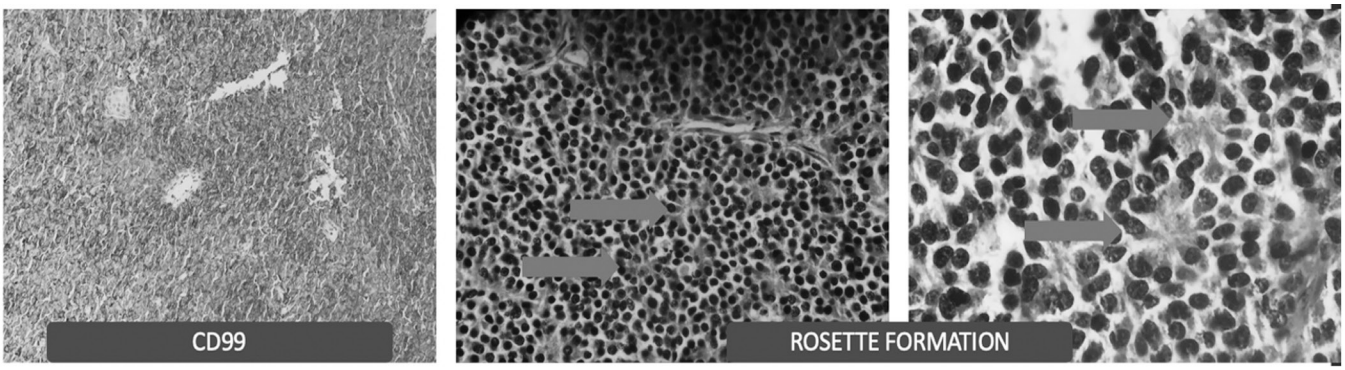

Figure 4. There is also a noted focal rosette formation along with diffuse membranous staining for CD99. This feature raises Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) as a possibility of soft tissue sarcomas

Discussion

Acute promyelocytic leukemia is a subtype of acute myeloid leukemia and accounts for 5 – 15% of all adult leukemias.[3] Current therapeutic guidelines warrant the use of anthracycline drugs (daunorubicin or idarubicin) plus all-trans-retinoic acid with an 80-90% remission rate.[4] Development of secondary tumors after treatment of hematological malignancies is a known risk factor. As such, a number of prior studies have documented myeloid neoplasms, and therapy-related myelodysplastic syndromes in patients who have been treated for APL.[5]

It has been postulated that APL survivors have an increased risk of developing secondary malignancies owing to the mutations induced by cytotoxic chemotherapy.[1] In 2001, Huang and colleagues reported a case of renal cell carcinoma in an 11-year-old boy previously treated for APL five years earlier.[6] In 2010, Parajuli and colleagues reported two cases of renal cell carcinoma diagnosed in patients undergoing treatment for APL.[1] In 2014, a cohort study by Eghtedar, et al., found that of the 160 patients followed up, secondary malignancies developed in 9 of the 54 (17%) APL patients who were treated with All-trans retinoic acid (ATRA) with idarubicin induction and 2 of the 106 (2%) patients who were treated with ATRA and arsenic trioxide. Secondary malignancies noted in their study included breast cancers, myelodysplastic syndromes, vulvar cancer, prostate cancer, colon cancer, pancreatic cancer, melanoma and soft tissue sarcoma.[7] Budhathoki, et al. noted an increased risk for salivary gland tumors and urinary bladder cancer among APL survivors after 5 years of latency period compared to the general population.[8]

Round cell tumors include entities such as peripheral neuroectodermal tumor (PNET), rhabdomyosarcoma, synovial sarcoma, non-Hodgkin's lymphoma, neuroblastoma, hepatoblastoma, Wilms' tumor, and desmoplastic small round cell tumor. Sarcomas often arise from bone or soft tissues more commonly in the pediatric and adolescent age group and rarely found in other parts of the body, such as the kidney, bladder, prostate, testis, ovary and uterus, etc.[9-13] Sarcomas represent 1% to 2% of all malignant renal tumors in adults, with a peak incidence in the fifth decade of life often with an aggressive course of disease.[14] Other reported mesenchymal renal sarcomas include leiomyosarcoma, liposarcoma, fibrosarcoma, rhabdomyosarcoma, angiosarcoma, osteosarcoma, synovial sarcoma, malignant fibrous histiocytoma and solitary fibrous tumor.

With the advances in molecular genetics, the 2013 WHO Classification of Tumors included a subset of undifferentiated round cell sarcomas harboring CIC-DUX4 or BCOR-CCNB3 fusion genes. CIC-DUX4 fusion sarcoma is a round cell tumor now considered an entity separate from Ewing sarcoma with a more aggressive clinical course, occurrence in older age, and predilection to soft tissues. BCOR-CCNB3 fusion sarcoma is cyclin B3-positive, usually occurs in bone or soft tissue of children, and may mimic a poorly differentiated synovial sarcoma.[15] Less than fifty cases of CIC-DUX4 round cell sarcomas have been reported since its initial description in 2006 by Miho Kawamura-Saito, et al. In 2017, Bergerat and colleagues reported a case of a highly aggressive CIC-DUX4 round cell sarcoma of the kidney with lung metastasis in a 29-year-old male.[16] The patient initially presented with lower abdominal pain with no accompanying hematuria and CT scan imaging revealed a 15.0cm × 9.0cm × 8.5cm heterogenous tumor in the superior pole of the right kidney invading almost two-thirds of the renal parenchyma. Similar to the present case, immunohistochemistry revealed diffuse staining for Bcl2 and CD99. RT-PCR analysis allowed for the detection of CIC-DUX4 gene fusion on frozen samples, certifying the definitive diagnosis of primary CIC-DUX4 round cell sarcoma of the kidney. Another related case was reported by Mangray and colleagues in 2016 of a 9-year-old boy with primary renal CIC-DUX4 sarcoma initially diagnosed as Wilm's tumor.[17]

Ewing sarcoma/Primary neuroectodermal tumor (ES/PNET) rarely occurs in the genitourinary system and in the patient's age group. First described in 1975, often affecting young adult males with a more aggressive clinical course as compared to PNET arising from other sites. It has a five-year disease-free survival rate of 45-55% in its well-confined stage and drops to 20-30% in its advanced stage. Factors that contribute to this poor prognosis include its non-specific disease presentation, tendency to metastasize and advanced stage at the time of diagnosis. So far, there has been less than 150 reported cases of

renal PNET.[16] In 2016, a case series by Sun, et al. reported 8 cases of PNET of the kidneys at the advanced stage.[18] The cohort of patients comprised five males and three females with a median age of 34 years (range, 17-45 years) at presentation of symptoms, namely, palpable abdominal mass and abdominal pain. On imaging, the tumors presented with heterogeneous contrast enhancement with the sizes ranging from 4-22 cm, some with noted calcifications. In contrast with the present case who presented with an organ confined pathology, the eight cases described were found to have nodal metastases or involvement of the pancreas, spleen or part of the inferior vena cava. Seven of these patients underwent radical surgery, five of whom proceeded with adjuvant chemotherapy and the rest did not. As with the present case, histology revealed small round cells with a high nuclear-to-cytoplasmic ratio with vaguely-defined cytoplasmic borders in the tumor. In addition, Homer-Wright rosette formation was identified in the tumors of three patients. In six of the cases, IHC revealed positivity for CD99, vimentin and neuron-specific enolase and showed negative staining for cytokeratin. The presence of focal rosettes and positivity for CD99 raise the possibility diagnosing ES/PNET in the present case; however, molecular testing for the translocation of ES/PNET is required to confirm this diagnosis. Fluorescent in situ hybridization (FISH) analysis using a locus-specific EWS/FLI-1 fusion gene dual color break apart rearrangement probe performed in one case a confirmed the diagnosis of ES/PNET. On follow-up of these patients, 5 had local recurrence only, 1 had both local recurrence and distant metastasis and two had distant metastasis only. Overall survival of those who underwent surgery with adjuvant chemotherapy was at 36 months, compared to those who had surgery alone at 10 months. Twelve months postoperatively, the patient has recovered and become asymptomatic. However, current restrictions due to the pandemic had made it difficult for the patient to undergo surveillance imaging.

In summary, reported is a case of a round cell sarcoma of the kidney in a 48-year-old patient previously treated for acute promyelocytic leukemia. The authors reviewed the literature on the possible association of this secondary malignancy with the previous chemotherapy of the patient. If it were available in local setting, the authors recommend further genetic testing for a definitive diagnosis of Ewing sarcoma/Primitive neuroectodermal tumor or a possible association with the newly emerging CIC-DUX4 subtype of sarcoma.

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