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Significant Response to Sunitinib in an Adult with Advanced clear cell Sarcoma of the Kidney: Report of a Rare Case and Literature Review

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Abstract

Clear Cell Sarcomas of the Kidney (CCSK) is an exceedingly rare neoplasm that predominantly affects the pediatric age group. Primary localized disease is treated with radical nephrectomy and adjuvant chemotherapy and/ or radiotherapy. Optimal therapy at relapse is controversial. We report a 22-year-old male who presented with abdominal pain following a prior radical right nephrectomy for a kidney tumor. Imaging studies showed local recurrence and peritoneal metastasis. Pathology review confirmed a diagnosis of CCSK. Three months after starting sunitinib, Computed Axial Tomography (CT) scan of the chest, abdomen, and pelvis showed significant regression of his diseased consistent with partial response. Clear cell sarcoma of the kidney is extremely rare in adults. To our knowledge, this is the first report of advanced CCSK in an adult responding to sunitinib. Clinical trials are needed to better define the role of systemic treatments in patients with relapsed CCSK.

Keywords: Sarcoma; Kidney; Response; Therapy

Introduction

Clear Cell Sarcoma of the Kidney (CCSK) is a rare malignant neoplasm of childhood. It ranks the second most common kidney malignancy after Wilms' tumor in the pediatric population. Patients with CCSK commonly present with flank pain and hematuria. Some patients may also present with weight loss, anorexia, or fever [1,2]. The disease has propensity for late relapses after nephrectomy. Bone and soft tissue is the common metastatic sites. Diagnosis of CCSK in adults is extremely rare, with only few cases reported in literature [3-6].

The diagnosis of CCSK is often made following careful evaluation of the pathology specimen. Histopathological examination usually reveals a well-circumscribed large tumor replacing the Kidney. The cut surfaces area variable most of the tumors are soft tan-grey, mucoid, cystic or sometimes more firm in consistency. Microscopically; the classic pattern of clear cell sarcoma of the kidney is characterized by small plump and oval tumor cells with indistinct cell borders, arranged in nests and cords and separated by thin arborizing chicken-wire capillaries. Some of the cells may exhibit spindle cell morphology. The nuclei are uniform in shape with fine chromatin and inconspicuous nucleoli. Frequently the nuclei show clearing resembling "Orphan Annie" nuclei typically seen also in papillary thyroid carcinoma. The cytoplasm is usually sparse and clear. Most of the tumors shows the classic pattern described above. Other variants exist in combination with the classic pattern, including myxoid pattern, sclerosing pattern, cellular pattern, epithelioid pattern, Palisading Pattern, spindle cell pattern, storiform pattern and anaplastic pattern [7].Immunohistochemistry is used to diagnose CCSK and to exclude the possibility of renal cell carcinoma and other primary renal tumors and sarcomas including rhabdomyosarcoma, Nephroblastoma (WILMS' tumor), synovial sarcoma, EWING sarcoma, rhabdoid tumor, and desmoplastic small round blue cell tumor. Previously, there was no specific immunohistochemical marker to diagnose clear cell sarcoma of the Kidney. Recently BCL6 Corepressor (BCOR) antibody has been utilized to diagnose CCSK. Strong and diffuse nuclear staining is highly specific for CCSK while it is usually negative in other pediatric tumors including WILMS' tumor and congenital mesoblastic nephroma [8]. Cyclin-D1 is usually strongly and diffusely positive in CCSK and helps to distinguish it from WILMs' tumor, congenital mesoblastic nephroma and rhabdoid tumor [9].Treatment of localized disease commonly includes radical nephrectomy with adjuvant chemotherapy and/ or radiotherapy. With this approach, 5 years Overall Survival (OS) rates approximate 90% [10]. Owing to its' rarity in the adult population, data addressing the clinical manifestations, treatment options, and outcomes in adults are scarce. In the current paper, we present an adult patient who presented with relapsed CCSK following nephrectomy that was performed at another institution.

Details of clinical presentation, pathologic diagnosis, findings on imaging studies, and outcome following sunitinib therapy are presented.

Case Report

A 21-year-old male patient presented to us in October, 2021 with a 2 months history of dull abdominal pain that was progressive in intensity. The pain was located mainly at the right lumbar region, and has become recently refractory to pain medications. He has previous history of right radical nephrectomy for a kidney tumor performed outside our center in Nov, 2020. Following nephrectomy, no adjuvant therapy was given. He was kept on routine follow up, Computed Tomography (CT) chest, abdomen, and pelvis was carried out at another institution (seven months post- surgery), and he was informed that he has a recurrence. He did not observe any change in his baseline weight or appetite, and has remained fully active with Eastern cooperative oncology group performance status of 0. Physical examination showed a well looking young man, with stable vital signs and an old healed incision at his right flank corresponding to prior nephrectomy surgery. No other abnormal findings were identified on examination. Laboratory investigations including blood counts, liver, and kidney function tests were within normal ranges. A review of CT chest, abdomen, and pelvis that was performed in June, 2021 showed multifocal intra-abdominal masses representing local recurrence and peritoneal metastasis (Figure 1). Pathology review of the nephrectomy specimen revealed the diagnosis of CCSK (Figures 2 and 3). The patient management plan was discussed at the sarcoma multidisciplinary tumor board, where panel recommended to proceed with sunitinib which has been started in July, 2021, at a dose of 50 mg PO once daily, 4 weeks on- 2 weeks off schedule. He reported significant improvement in his abdominal pain a few weeks after starting sunitinib. In Oct, 2021, CT chest, abdomen, and pelvis showed significant regression of the multi-focal abdominal masses compared with the baseline CT in June, 2021. A subsequent CT was done in Dec, 2021 and showed continued disease response, consistent with partial response according to response evaluation criteria in solid tumors (RECIST v.1.1). He tolerated sunitinib very well without any toxicities. Currently, he is still alive at 11 months following diagnosis of his relapsed disease. Sunitinib treatment is still ongoing and is well tolerated.

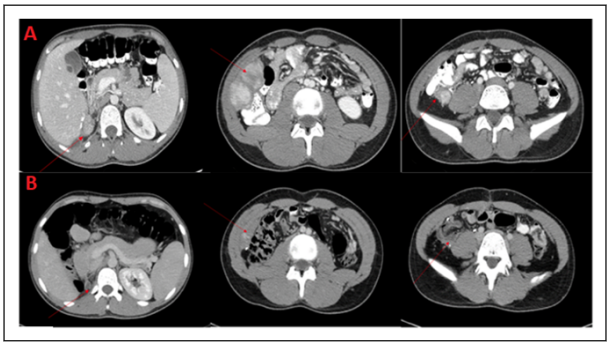

Figure 1: A)Initial abdomen and pelvis CT scan with IV contrast showing multiple soft issue masses seen at the surgical bed (site of nephrectomy) and within the peritoneum, suggestive of disease recurrence. B) Follow up abdomen and pelvis CT scan with IV contrast (6 months later) showing signi icant regression in the size of the so t tissue masses seen in the surgical bed and peritoneum.

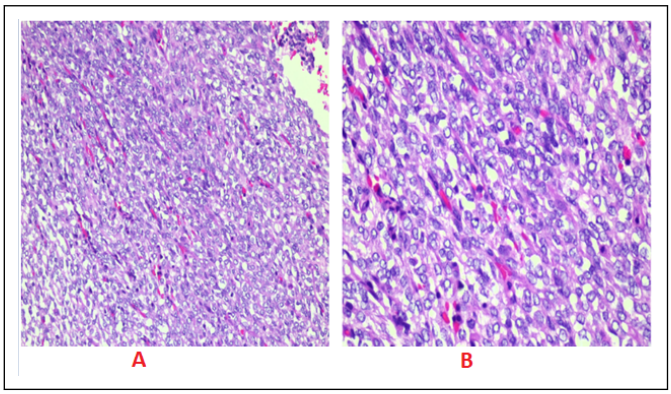

Figure 2: A) Classic pattern of clear cell sarcoma: Nests of round and spindle cells with clear cytoplasm, seperated by delicate vascular septa. (H&E 20x). B) Tumor cells exhibit washed-out nuclei and clear cytoplasm (H&E 40x).

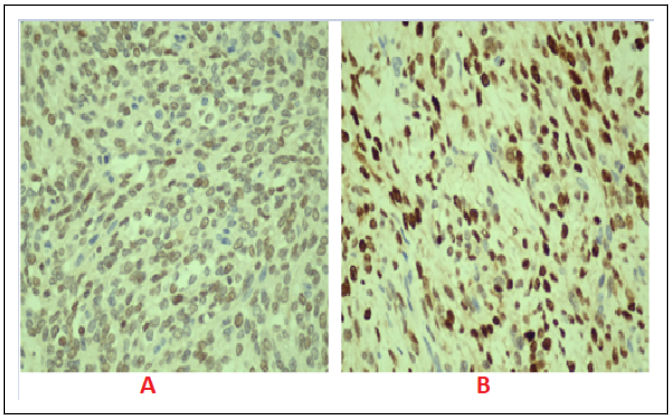

Figure 3: A) Immunostaining for BCOR shows positive nuclear staining in tumor cells compared to negative staining in endothelial cells. This reflects BCOR gene duplication (40x). B) Cyclin D1 immunostain is strongly positive in tumor cells compared to negative staining in endothelial cells (40x).

Discussion

Clear Cell Sarcoma of the Kidney (CCSK) is a rare malignant neoplasm that typically affects the pediatric age group [1,2]. The peak age at diagnosis is between 3 and 5 years [3]. Whilst Wilm's tumor is the most common malignant kidney neoplasm in childhood, CCSK ranks the second; accounting for less than 5%of all kidney tumors in children. However, the most common kidney tumor in adults is clear cell Renal Cell Carcinomas (RCC), followed by variety of non-clear cell histologies such as papillary, chromophobe and sarcomatoid RCC [11].

The clinical characteristics and behavior of CCSK is well described in literature based on data from pediatric cohorts. CCSK has the propensity for later relapses when compared to Wilms' tumors. Another recognized difference between the two tumors relates to sites of distant metastasis. Contrary to Wilm's tumors that have tendency to metastasize to lungs, liver, and LN, CCSK has predilection to metastasize to bone, soft tissue, and brain [1,2].

In addition, there are no recognized congenital anomalies in CCSK, as opposed to Wilms' tumors, which might be associated with congenital anomalies such as hypospadias, cryptorchidism, isolated aniridia, and trisomy 18 [12].

The mainstay of treatment of primary localized CCSK is radical nephrectomy that can be accompanied by LN dissection. Surgery is often followed by adjuvant chemotherapy and / or radiotherapy according to the National Wilms Tumor Studies (NWTS) protocols [13,14]. Chemotherapy is typically given in combination regimens. According to data from the third National Wilms Tumor Study (NWTS-3), addition of doxorubicin to vincristion, actinomycin-D, and radiotherapy after surgery improves disease free survival [7,15]. Longer courses of chemotherapy seem to minimize the risk of recurrence or delay the relapse. According to data from the NWTS-4 trial, a longer coarse of chemotherapy (15 months as opposed to 6 months) was associated with a longer relapse free survival [14].

Optimal therapy for relapsed CCSK is controversial due to limited data. Systemic chemotherapy is commonly utilized. Data on the use of targeted therapies is scarce. In a prospectively analyzed data of CCSK for pediatric patients treated utilizing European trial protocols, 37 out of 237 patients (16%) developed a relapse. The treatment at relapse of those 37 patients consisted of chemotherapy (n=30), surgery (n=19) and/or radiotherapy (n=18), followed by high-dose chemotherapy and autologous bone marrow transplantation in 14 patients [2,16]. In that study, the reported 5-year event free survival and overall survival after relapse were 18% and 26% respectively.

For adult patients with CCSK, data pertaining to treatment of primary and relapsed disease is very limited. In addition, there is limited data on clinical presentation, disease characteristics, relapse rate, and patterns of recurrence in adult patients owing to the rarity of CCSK in this age group. There are only few adult patients with CCSK reported in the English literature [3-6,17-23]. The presentation, clinical characteristics, treatments, and outcomes of these patients are summarized (Table 1). To the best of our knowledge, this is the first report of relapsed CCSK treated with and responded to sunitinib. Furthermore, in contrast to the recognized propensity for late relapse, our patient had early relapse after surgery. Absence of adjuvant therapy following nephrectomy might be a reason why our patient had a short interval to recurrence after nephrectomy.

Ref.	Age/ gender	Presentation	Treatment	Outcomes
Cao M, et al. [3]	24 M	Right kidney mass	Nephrectomy and regional lymphadenectomy. LN were free. No	Alive with NED at 2 years
Rosso D, et al. [4]	53 M	Hematuria, right kidney mass.	Right radical nephrectomy with lymphadenectomy. LN were free.	Alive with NED at 12 months
Raman S, et al. [5]	49 M	Hematuria, left kidney mass, ascites, bilateral leg edema.	left radical nephrectomy with renal hilar and retrodudodenal lymph node dissection and IVC thrombus dissection. Locally advanced, LN not involved.	Not reported.
Goudarzi A.K. H, et al. [6]	31 M	Right flank pain and hematuria. Rt. Kidney mass, tumor thrombus extending to IVC.	Radical right nephrectomy and resection of intra IVC mass, followed by adjuvant chemotherapy with doxorubicin, ifosfamide, and MESNA	Alive with NED at 5 months
Kural AR, et al. [17]	22 M	Left flank pain, left kidney mass infiltrating left psoas muscle.	Left radical nephrectomy with hilar lymphadenectomy. No LN metastasis. Adjuvant radiotherapy, adjuvant chemotherapywith	Alive with NED at 24 months.

			actinomycin D, vincristin, and doxorubicin.	
Zhang Y, et al. [18]	62 M	Pruritus and right kidney mass.	Radical right nephrectomy. Adjuvant chemotherapy with doxorubicin, vincristine, cyclophosphamide, and etoposide	Alive with NED at 20 months
Lanka K, et al. [19]	38 F	Left loin pain, hematuria, left kidney mass	Left radical nephrectomy	Not reported
Caballero Vázquez A, et al. [20]	70 F	Two months history of cough, weight loss, and one month history of right loin pain and hematuria. Lung metastasis, left kidney mass, and vertebral lytic lesion.	Not reported	Not reported
Chikkannaiah P, et al. [21]	25 M	Abdominal pain of 2 months and left kidney mass.	left radical nephrectomy with hilar lymphadenectomy. LN were free.	Not reported
Kattub H, et al. [22]	34 F	Hematuria, dysuria, right flank pain and fever. Right kidney mass.	Right radical nephrectomy followed by radiotherapy.	Not reported
El-Hawary AK, et al. [23]	27 M	Right loin pain, haematuria, right kidney mass.	Right nephroureterectomy with bladder cuff excision.	Not reported
Current case	21 M	Right loin pain after prior right radical nephrectomy. Local recurrence and peritoneal metastasis	Prior nephrectomy. Sunitinib for relapsed disease.	Partial response to sunitinib. Ongoing response/ Alive and free of progression at 11 months of starting sunitinib

Table 1: Clinical characteristics, treatments, and outcomes of adult patients with clear cell sarcoma of the kidney reported in literature. NED: No Evidence of Disease

Conclusion

CCSK is extremely rare in the adult population. Patients with CCSK are often treated with radical nephrectomy followed by adjuvant chemotherapy and/ or radiotherapy. However, data addressing treatment of advanced/ relapsed disease particularly in adults is limited.

The observed objective response to sunitinib in our patient might suggest anti-tumor activity in this disease. Clinical trials are needed to identify effective therapeutic options in relapsed CCSK.

Conflict of Interest

No conflict of interest to declare.

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