CASE REPORT

Primary Ewing sarcoma of the kidney: a case report and treatment review

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Abstract Ewing sarcomas/primitive neuroectodermal tumors (ES/PNET) of the kidney are rarely found high-grade malignant tumors, offering poor prognosis. Although established treatment guidelines for ES of kidney are scarce, a multi-modality treatment approached is typically implemented. Herein, we report a 14-year-old female patient with ES of right kidney. Post-nephrectomy disease recurrence was treated with chemotherapy (i.e., vincristine, doxorubicin and cyclophosphamide); marked reduction in tumor size (i.e., from $18.5 \times 11.3 \text{ cm}^2$ to $3.7 \times 2.2 \text{ cm}^2$; ~96% reduction in size) as per computed tomography images was observed. We present our treatment experience and review from the available literature.

Keywords Chemotherapy · Disease recurrence · Ewing sarcoma kidney · Radiotherapy · Nephrectomy

Introduction

Ewing's sarcoma of kidney (ESK) or primitive neuroectodermal tumor (PNET) is a rare neoplasm, typically presented with irradiating flank pain that mimics the pain associated with kidney stones. Total surgical resection is considered as the treatment of choice for these tumors. However, chemotherapy in adjuvant setting has also shown promising results.

Herein, we report a case of 14-year-old female diagnosed with ESK. After nephrectomy, significant response

to multi-agent chemotherapy (i.e., vincristine, doxorubicin, and cyclophosphamide) was observed.

Case report

A 14-year-old female with complain of pain in the right flank underwent sonography followed by computed tomography (CT) scan, which revealed large ($8.8 \times 7.7 \text{ cm}^2$) heterogeneous mass involving the mid and lower pole of the right kidney with large necrotic component and invading the perinephric fat and ipsilateral vein (Fig. 1a). The patient underwent right nephrectomy. It is noteworthy that radical nephrectomy (i.e., adequate resection margins plus lymph node dissection) was not possible, primarily because of the extensive nature of the disease at the presentation, as demonstrated by preoperative CT (Fig. 1a).

Histopathology revealed a neoplastic lesion composed of small-to-medium-sized cells arranged in sheets, nests, and trabeculae separated by fine fibrous septae. The tumor cells having rounded to oval nuclei, finely granular chromatin, small nucleoli, and pale-to-clear scanty cytoplasm (Fig. 2). Glycogen was highlighted in tumor cells on PAS staining. Moreover, the tumor infiltrated the renal capsule and renal sinus fat. Ureteric resection margins and hilar vessels were free of tumor. Immunohistochemical staining pattern in tumor cells was as follows: strongly positive CD99 and FLI1, patchy positive synaptophysin, and CKAE1/AE3 and negative TLE and WT-1. All these findings were consistent with ESK/PNET.

The patient remained at home without any treatment for 4 months; during this period, the disease progressed with marked increase in the tumor size ($18.5 \times 11.3 \text{ cm}^2$) as illustrated by post-nephrectomy CT scan (Fig. 1b). There

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Fig. 1 Illustrative CT scan images of whole abdomen showing the ESK tumor (*solid arrows*) and metastasis in the right abdominal wall laterally (*open arrows*); **a** images before surgery showing large heterogeneously enhancing mass ($8.8 \times 7.7 \text{ cm}^2$) involving the right kidney, **b** post-right-nephrectomy images with recurrent large soft tissue density mass ($18.5 \times 11.3 \text{ cm}^2$) in the right renal area and metastasis in the right abdominal wall laterally, and **c** images after chemotherapy (i.e., vincristine, doxorubicin, and cyclophosphamide, alternated by etoposide and ifosfamide) showing markedly reduced ($3.7 \times 2.2 \text{ cm}^2$; $\sim 96\%$ reduction in size) necrotic non-enhancing hypo-dense tumor. In addition, there was no evidence of right abdominal wall metastasis. In all cases, CT images with largest tumor size are shown only

was evidence of two soft tissue opacities in the right abdominal wall laterally, apparently due to abdominal wall metastasis.

The patient was treated with multi-agent chemotherapy: vincristine (2 mg/m^2), doxorubicin (75 mg/m^2), and cyclophosphamide (1200 mg/m^2) every three weeks, alternated by etoposide (100 mg/m^2) and ifosfamide (1800 mg/m^2). The toxicity of chemotherapy was evaluated after every cycle and found well-tolerated. The tumor size markedly reduced (from 18.5×11.3 to $3.7 \times 2.2 \text{ cm}^2$; $\sim 96\%$ reduction in size; Fig. 1c) after four cycles of the aforementioned chemotherapy.

Discussion

ESK/PNET is a rare but relatively aggressive renal neoplasm that typically manifest in old children and young adults, as observed in this study. The clinical presentation of ESK/PNET includes flank pain, palpable mass, and hematuria. Histopathology in tandem with immunochemistry has been used to provide the definite diagnosis.

Guidelines for effective treatment of ESK/PNET seem scarce, presumably due to the rarity of the disease. Nevertheless, surgery is accentuated as the first line of intervention. Importantly, nephrectomy remained the sole treatment in 14.3% cases [1] and offered considerable

Fig. 2 Illustrative histopathology and immunohistochemistry (IHC) images of the resected tumor. **a, b** H&E staining ($\times 40$) showing the lesion composed of small-to-medium-sized cells arranged in sheets, nests, and trabeculae separated by fine fibrous septa. The tumor cells have rounded to oval nuclei with finely granular chromatin, small nucleoli, and pale-to-clear scanty cytoplasm. **c** IHC, synaptophysin, illustrating patchy positive staining in the tumor cells. **d** CKAE1/AE3 showing patchy dim positive staining in scattered tumor cells

survival advantage [2, 3]. For instance, an ESK/PNET patient underwent radical nephroureterectomy; the patient was disease-free (i.e., no recurrence or metastasis) at 18 months postoperatively [4]. Nevertheless, ESK/PNET tumors are typically aggressive and thereby involve the lymph nodes and metastasize to lung, bone, and liver [5], demanding for multi-modality treatment. Typically, surgery followed by adjuvant chemotherapy is considered as the principal management for ESK/PNET.

ESK/PNET has been speculated as relatively sensitive to chemotherapy. In particular, initially, vincristine, actinomycin, and cyclophosphamide were found effective in treating ESK/PNET [6]. Later, doxorubicin, ifosfamide, and etoposide also demonstrated activity towards these tumors [7]. Currently, the chemotherapeutic treatment of ESK/PNET makes use of these agents in various combinations; the efficacy differs among clinics. In particular, the EUROpean Ewing tumor working initiative of national groups 1999 (EURO-EWING 99) protocol prescribes six courses of chemotherapy (i.e., vincristine, ifosfamide, doxorubicin, and etoposide) for Ewing tumors. Clinically, an ESK patient treated with seven cycles of chemotherapy (vincristine, cyclophosphamide, actinomycin, and doxorubicin) after radical nephrectomy remained disease-free

for 7.5 years [7]. Further, post-operative residual renal mass involving liver and lymph nodes was treated with chemotherapy (i.e., six cycles of vincristine, doxorubicin, and cyclophosphamide); the response was estimated at 90% based on the Recist guidelines [8]. Not surprisingly, the patients may not benefit from the multi-modal therapy owing to the more aggressive nature of the disease (i.e., late diagnosis, advanced stage at presentation, early metastasis, etc.). That said, six cycles of multi-agent chemotherapy (i.e., cyclophosphamide, doxorubicin, vincristine, ifosfamide, and etoposide) resulted in apparent disease-free period of 5 months only; however, subsequent assessment showed disease progression with bilateral pulmonary metastasis [9]. Moreover, disease relapse has been seen after seven courses of same chemotherapy [10]. In addition, chemotherapy (i.e., etoposide, cisplatin, ifosfamide, and doxorubicin) showed substantial results in metastatic ESK/PNET of the kidney with 8 years durable clinical remission [11]. In this study, we observed significant response of ESK/PNET (i.e., tumor size reduction $\sim 96\%$) to only four cycles of chemotherapy (i.e., vincristine, doxorubicin, and cyclophosphamide), as illustrated by the comparison of CT scan images before and after chemotherapy; importantly, no involvement of abdominal wall was observed after chemotherapy (Fig. 1b vs. c).

Radiotherapy has also been employed for management of ESK/PNET in adjuvant settings. In particular, radiation to the tumor bed to eradicate local residual disease has demonstrated promising results. Specifically, adjuvant radiotherapy (dose 50–60 Gy) to renal bed and positive regional lymph nodes was implemented in nine patients of ESK/PNET; complete response in terms of reducing residual local disease was achieved [6]. Moreover, Miser et al. claimed that radiotherapy (recommended dose of 50.4–60 Gy) can produce good local control in ESK/PNET patients, particularly when total tumor resection is not possible [12]. Based on the aforementioned studies, we suggest radiotherapy in the presence of residual disease after surgical dissection, positive surgical margins, and loco-regional lymphadenopathy. Although it is speculated that radiotherapy should be avoided as the first-line treatment; it may prove beneficial in salvage setting [13].

Combination of post-operative chemo and radiotherapy has demonstrated limited evidence for effective management of ESK/PNET. Specifically, post-nephrectomy chemotherapy (i.e., ifosfamide, carboplatin, and etoposide), followed by concurrent radiotherapy (i.e., 36 Gy to the hemiabdomen and 16.5 Gy both lungs) and chemotherapy (i.e., weekly vincristine and biweekly actinomycin D) illustrated no response; the patient developed new bilateral pleuropulmonary metastases [5].

Compliance with ethical standards

Conflict of interest It is declared that the results presented in this paper have not been published previously in whole or part. Furthermore, the authors have no conflict of interest.

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