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Primary adrenal Ewing's sarcoma family of tumors with tumor thrombus of the inferior vena cava: a case report

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Abstract

Background Ewing's sarcoma is a malignant neoplasm that mainly occurs in skeletal tissue but can rarely arise in soft tissues. Recently, small round cell tumors (including Ewing's sarcoma) caused by chromosomal translocations have been collectively termed Ewing's sarcoma family of tumors. We report a rare case of primary adrenal Ewing's sarcoma family of tumors with tumor thrombus.

Case presentation A 22-year-old Asian woman was referred to our hospital with a left retroperitoneal tumor 19 cm in diameter. Tumor thrombus was identified from the left adrenal vein to the inferior vena cava, infiltrating the right atrium. Total tumor excision with left adrenalectomy, nephrectomy, and thrombectomy was performed under hypothermic circulatory arrest, followed by seven courses of adjuvant chemotherapy. The patient has shown no signs of recurrence as of 26 months postoperatively.

Conclusion Radical surgery combined with systemic chemotherapy may contribute to good prognosis in patients with primary adrenal Ewing's sarcoma family of tumors.

Keywords Ewing's sarcoma, Adrenal gland, Tumor thrombus, Vena cava

Introduction

Ewing's sarcoma (ES) is a malignant neoplasm that occurs primarily in the skeletal tissues of the long bones and pelvis in children and young adults, but on rare occasions arises in soft tissues [1]. Recently, small round cell tumors caused by chromosomal translocations have been collectively termed Ewing's sarcoma family of tumors (ESFT) [2]. We report herein a patient with ESFT arising in the left adrenal gland who achieved complete remission and long-term survival after surgery and adjuvant chemotherapy.

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Case presentation

A 22-year-old nulligravid Asian woman consulted a local clinic with a chief complaint of left thoraco-abdominal pain for 2 months. She was introduced to our hospital after diagnostic imaging revealed a large retroperitoneal tumor with tumor thrombus of the inferior vena cava. She did not have any complications or relevant past or family history. Results from blood testing, including tumor markers and hormonal examinations, and urine testing were all within normal ranges. Contrast-enhanced computed tomography (CT) revealed irregular contrast enhancement of a left retroperitoneal tumor measuring 19 cm in diameter, along with tumor thrombus in the left adrenal and renal veins and inferior vena cava (Fig. 1a). Magnetic resonance imaging (MRI) revealed an encapsulated multilocular tumor with a partially solid component, showing hypointensity on T1-weighted imaging, irregular hyperintensity with septa on T2-weighted imaging, and strong signals on diffusion-weighted imaging (DWI) (Fig. 1b–d). Strong accumulation was seen on ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), with a maximum standardized uptake value of 12.2 and no distant metastases (Fig. 1e). Preoperative transthoraco-abdominal and intraoperative transesophageal ultrasonography revealed tumor thrombus in the vena cava extending into the right atrium (data not shown). The patient underwent en bloc tumorectomy with left adrenalectomy and nephrectomy, and thrombectomy by open-heart and open-abdominal surgery. The right atrial tumor thrombus was excised from the distal side via both vena caval and right atrial approaches under complete circulatory arrest as a deep hypothermic procedure without distal clamping of the vena cava. On day 4 after surgery, a tumor embolism that might have migrated intraoperatively was found in the left pulmonary artery. The tumor was urgently resected by left thoracotomy (Fig. 1f).

Macroscopic examination revealed a tumor measuring $19 \times 14 \times 8$ cm. The cross-sectional surface was grayish white in color with internal necrosis (Fig. 2a). Microscopic findings for the tumor using hematoxylin and eosin (HE) staining included uniform small, round cells with round nuclei, intense chromatin staining, and a high nucleus/cytoplasm ratio proliferating solidly and showing a partially rosette-like structure. Frequent mitosis was evident, with a count of 32 per 10 high-power fields. Small cells resembling the existing adrenal cortex were occasionally observed in the region just below the capsule, so the tumor was considered to have been primarily derived from the adrenal gland (Fig. 2b). Immunohistochemical examination of the tumor with anti-cluster of differentiation (CD)99 and Friend leukemia integration 1 transcription factor (FLI-1) antibodies yielded strongly positive results (Fig. 2c, d), but results for CD34,

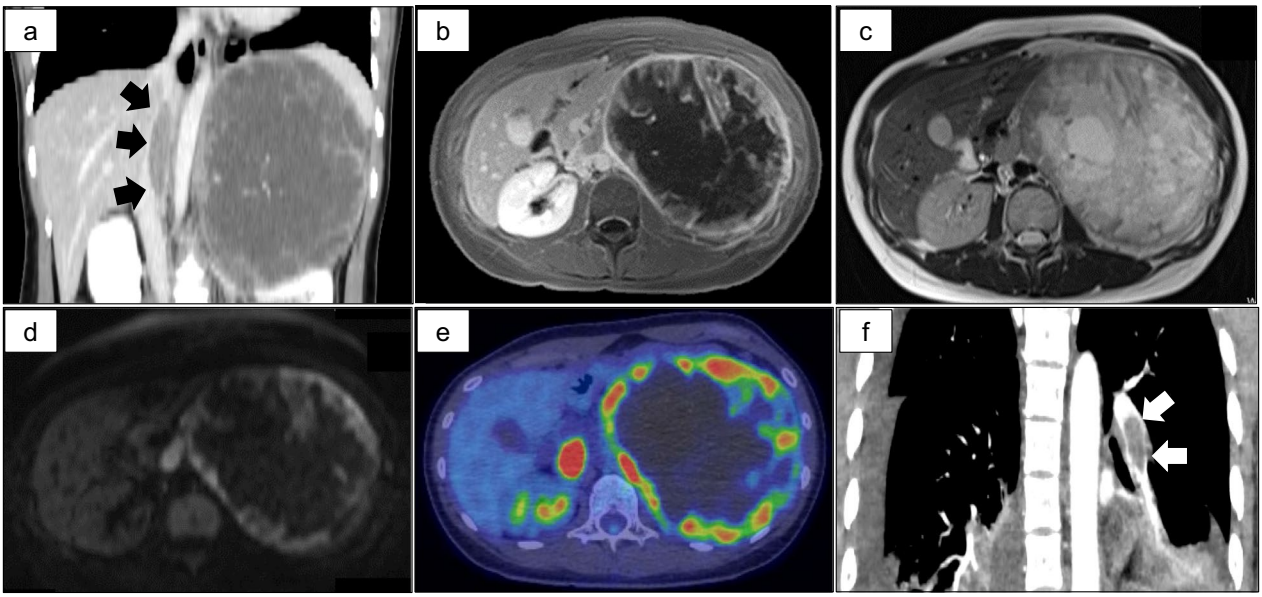

Fig. 1 Preoperative CT, MRI, and FDG-PET. **a** Contrast-enhanced CT reveals irregular contrast in a left retroperitoneal tumor 19 cm in diameter, showing tumor thrombus in the left renal vein, adrenal vein, and vena cava. Black arrows indicate tumor thrombus within the inferior vena cava. **b**–**d** MRI reveals an encapsulated multilocular tumor with partially solid component, showing hypointensity on T1-weighted imaging, irregular hyperintensity with a septum on T2-weighted imaging, and strong signals on DWI. **e** On ^{18}F-FDG-PET–CT, maximum standardized uptake value is 12.2 and no distant metastases are evident. **f** Contrast-enhanced thoracic CT on day 4 after surgery reveals tumor embolization in the left pulmonary artery (white arrow)

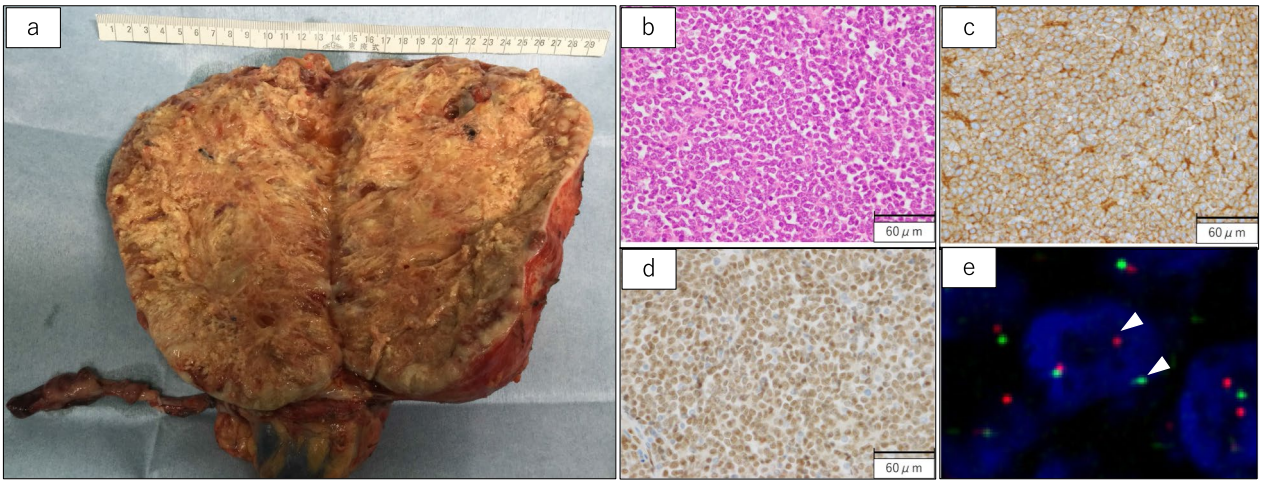

Fig. 2 Macro- and microscopic findings of the tumor, and FISH assay of tumor cells. **a** The tumor cross-section is grayish-white in color with internal necrosis. **b** Microscopic examination with hematoxylin and eosin staining reveals uniform small round cells with round nuclei, intense chromatin staining, and a high nucleus-to-cytoplasm ratio proliferating solidly and partially showing a rosette-like structure. Immunohistochemical examination with anti-CD99 (**c**) and FLI-1 (**d**) antibodies shows strongly positive results. **e** A typical result of FISH assay to identify the chromosomal break point of EWSR1 in paraffin-embedded tissue reveals break-apart signals, shown as separate red and green signals (white arrowheads)

leukocyte common antigen, terminal deoxynucleotidyl transferase, chromogranin A, and desmin were negative (data not shown). We performed a dual-color, break-apart fluorescence *in situ* hybridization (FISH) assay to identify the chromosomal break point of Ewing's sarcoma breakpoint region 1 (EWSR1) in paraffin-embedded tissue (Abbott Molecular Inc., Des Plaines, IL, USA). EWSR1 in this case showed gene splitting in 87% of cells. Typical EWSR1 break-apart signals are shown in Fig. 2e. These findings led to a final diagnosis of ESFT.

Seven cycles of traditional alternating adjuvant chemotherapy with vincristine (1.5 mg/m^2 on day 1), doxorubicin (37.5 mg/m^2 on days 1 and 2), cyclophosphamide (1200 mg/m^2 on day 1), ifosfamide (1800 mg/m^2 on days 1–5), and etoposide (100 mg/m^2 on days 1–5) (VDC-IE) were administered for 7 months from 73 days after surgery. Before commencing chemotherapy, oocytes were conserved. Grade 4 neutropenia resolved with administration of granulocyte colony-stimulating factor and chemotherapy was tolerated. The patient has shown no signs of recurrence or organ dysfunction, including the kidneys as of 26 months postoperatively. At present, childbearing is not desired by the patient, and they have no plan to use conserved oocytes.

Discussion

Previously reported cases of adrenal ESFT with tumor thrombus in the inferior vena cava are summarized in Table 1 [3–8]. Primary adrenal ESFT most commonly occurs in young adults, with a median age of 26 years (range 20–34 years). No sex difference has been noted. The most typical presenting complaint for patients with ESFT of the adrenal gland is abdominal pain. Median tumor diameter is 14.9 cm (range 11.3–22 cm), including the present case. Recently, ESFT including ES, extraskeletal ES, primitive neuroectodermal tumor, and Askin tumor has been recognized as originating from the primitive neural tube, with a common translocation of the *EWSR1* gene at chromosome 22q12. Approximately 85% of ESFT show translocation with *FLI-1*, and the *EWSR1*/*FLI-1* chimeric fusion gene resulting from t(11:22)(q24:q12) may lead to tumorigenesis. Ten percent of cases involve translocations with ETS-related gene (*ERG*) by t(16;21)(p11;q22), and translocations with ETS variant transcription factor 1 (*ETV1*), *ETV4* and fifth Ewing's variant (*FEV*) have been reported rarely, each with frequencies less than 0.1% [9]. Immunostaining with anti-CD99 and FLI-1 antibody, and FISH assay to confirm fusion genes, are useful investigations to reach the final diagnosis of ESFT.

Radiological imaging, including CT, MRI, and FDG-PET, contributes to the initial detection and determination of the extent of tumors and distant metastases [7]. In our case, CT and MRI also contributed to diagnosis of the origin, detailed surgical planning, and detection of tumor emboli in the pulmonary artery after the initial surgery.

The standard therapy for adrenal ESFT is complete resection and combination chemotherapy, as in this case using VDC-IE [10]. The 5- and 10-year survival rates of patients with ESFT are 69% and 62%, respectively, in patients with completely resected tumors for localized

Table 1 Nine cases of Ewing's sarcoma originating from the adrenal gland with inferior vena cava thrombosis

No	Report year	References	Age (years)	Sex	Laterality	Tumor diameter (cm)	Initial infiltration/metastasis	Surgical therapy	Chemotherapy	Prognosis
1	2006	Kim *et al.*	25	Female	Left	15.2	IVC + RA/lung	NR	NR	NR
2	2010	Zhang *et al.*	30	Male	Right	12	IVC	Adr + Neph (incomplete)	NR	Dead (POM 8)
3	2010	Zhang *et al.*	22	Male	Left	17	IVC	Adr + Neph + Spl + IVCt	+	Alive with local rec. (POM 1)
4	2012	Saboo *et al.*	26	Female	Left	NR	Kidney + spleen + IVC	Adr + Neph + Spl + IVCt	+	Alive
5	2013	Abi-Raad *et al.*	26	Female	Left	11.3	IVC	Adr + Neph + Spl + IVCt	+[a]	Alive (POM 8)
6	2019	Christopher *et al.*	34	Male	Right	14.5	IVC	Adr + IVCt	+	Alive (POM 3)
7	2022	Ji-Lian *et al.*	20	Female	Right	22	IVC + RA/liver	Adr + IVCt + RAt	+[b]	Alive (POM 20)
8	2022	Present case	22	Female	Left	20	IVC + RA	Adr + IVCt + RAt + Pt	+[c]	Alive (POM 25)

IVC inferior vena cava *RA* right atrium, *IVCt* inferior vena cava thrombectomy, *Adr* adrenalectomy, *Neph* nephrectomy, *Spl* splenectomy, *RAt* right atrium thrombectomy, *Pt* pulmonary thrombectomy, *NR* not recorded, *POM* postoperative month, *rec* recurrence

[a] Vincristine/doxorubicin/cyclophosphamide + ifosfamide/etoposide 10 cycles

[b] Ifosfamide/etoposide 3 cycles + gemcitabine/paclitaxel 6 cycles

[c] Vincristine/doxorubicin/cyclophosphamide + ifosfamide/etoposide 7 cycles

ESFT [11]. In our review of the literature, complete resection resulted in good prognosis for patients with adrenal ESFT, even with direct infiltration to the kidney, spleen, inferior vena cava, and right atrium, or even pulmonary tumor emboli from surgical maneuvers, as in the present case. Incomplete resection might be a factor associated with poor prognosis (Table 1). The standard chemotherapy for patients with adrenal ESFT is according to the traditional therapy for ES. No consensus has been reached regarding the priority of surgery or chemotherapy for primary localized adrenal ESFT. In our case, surgery was prioritized because of the symptomatic disease and tumor thrombus reaching the right atrium. Complete wide excision is necessary for patients with localized ESFT. Subsequent external irradiation therapy is recommended if complete tumor excision is not achieved, or if the patient did not show good response to prior chemotherapy [12].

Conclusion

We encountered a rare case of primary adrenal EES with tumor thrombus in the inferior vena cava. The combination of complete tumor excision and combination chemotherapy may provide good prognosis for patients with localized ESFT.

Abbreviations

ES	Ewing's sarcoma
EES	Extraskeletal Ewing's sarcoma
ESFT	Ewing's sarcoma family of tumors
CT	Computed tomography
MRI	Magnetic resonance imaging
DWI	Diffusion-weighted imaging
FDG-PET	Fluorodeoxyglucose-positron emission tomography
SUV	Standardized uptake value
HE	Hematoxylin and eosin
CD	Cluster of differentiation
FLI-1	Friend leukemia integration 1 transcription factor
LCA	Leukocyte common antigen
FISH	Fluorescence *in situ* hybridization
EWSR1	Ewing's sarcoma breakpoint region 1
VDC-IE	Vincristine, doxorubicin, cyclophosphamide-ifosfamide, etoposide
ERG	ETS-related gene
ETV1	ETS variant transcription factor 1
FEV	Fifth Ewing's variant

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Author contributions

KA and TK drafted the report and contributed to the concept and design. TK, KM, HF, SF, YM, AM, KH, SU, RM, and TA contributed to the surgical work. MY and MS contributed to systemic chemotherapy. MI contributed to histopathological analyses. KI contributed to supervision, and approved the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

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