Response to immunotherapy in a patient with advanced epithelioid sarcoma of adrenal gland: A case report

JINGWEN WANG[1], CHEN LU[2] and XI TANG[1]

Departments of [1]Oncology and [2]Pathology, Huadong Hospital Affiliated to Fudan University, Shanghai 200040, P.R. China

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Abstract. Epithelioid sarcoma (ES) is a rare and highly invasive soft tissue malignant tumor with uncertain histogenesis. The localization of ES in the adrenal gland is rather unusual. The present study reported a case of stage IV ES in the adrenal gland of a 28-year-old male. The tissue biopsy of adrenal and lung lesions revealed epithelioid cells. Immunohistochemistry indicated that the tumor cells were strongly positive for cytokeratin (CK)8, CK, epithelial membrane antigen (EMA), CD34 and programmed cell death protein 1 ligand (PD-L1) but negative for nuclear integrase interactor 1 expression. The next-generation sequencing technology was applied using peripheral blood, indicating a low tumor mutation burden of 4.11 mutations (Muts)/Mb and somatic mutations in *SMARCB1*. After diagnosis, the patient underwent unsuccessful palliative chemotherapy and radiotherapy. However, application of immune checkpoint inhibitors (ICIs) achieved partial remission and the overall survival reached 25 months. ICI monotherapy may be a feasible treatment for patients with ES with a strong expression of PD-L1.

Introduction

Epithelioid sarcoma (ES), a rare soft tissue sarcoma, was first described by Enzinger (1) in 1970. It originates from primitive mesenchymal cells with multilineage differentiation potential; however, its epithelial differentiation is frequent. ES is prevalent in young males aged 20-40 years. Owing to its unique biological behavior, ES grows slowly but is prone to multifocal disease at presentation, local recurrence and regional lymph node spread (2). Radical tumor resection combined with regional lymphadenectomy is an effective treatment for patients with localized ES (3). For patients with unresectable or advanced ES, first-line conventional systemic therapies include anthracycline-based or gemcitabine-based regimens. Experience from clinical practice indicates that the effect of these regimens is limited, with an overall response rate (ORR) of 15-27% and median overall survival (OS) of 13-19 months (4,5). The tyrosine kinase inhibitor Pazopanib is mainly used after the failure of standard chemotherapy. However, its ORR varied between 0 to 11.1%, and the median OS was <20 months (4,6). Recently, a selective EZH2 inhibitor, tazemetostat, received Food and Drug Administration approval for the treatment of advanced ES with loss of INI1/SMARCB1. It was reported that the ORR of tazemetostat was 15%, with a median progression-free survival of 5.5 months and OS of 19 months (7). Consequently, the prognosis after regional recurrence or distant metastasis is alarming due to its poor response to systemic therapies, so new therapeutic strategies are warranted.

ES is divided into two subtypes according to the location, i.e., distal type (also known as the classical type, which is the most frequent and mainly located at the end of the limbs) and proximal type (occurring in proximal limbs, trunk or solid organs) (8). The present study reported a rare case of proximal adrenal ES in a Chinese male adult. To the best of our knowledge, only 3 adult cases of this disease have been reported (9-11) and this is the first report of effective treatment with immune checkpoint inhibitors (ICIs) in advanced adrenal ES.

Case report

A 28-year-old male complained of persistent bilateral lumbar backache, cough and frailty lasting for 8 months prior to admission to the Oncology Department of Huadong Hospital (Shanghai, China; October, 2018). The patient had a history of hypertension for 2 years. Ultrasonography demonstrated giant masses (>100 mm) in the bilateral adrenal regions, suggesting malignant disease. Positron emission tomography-CT revealed that in addition to the masses in the adrenal glands, multiple bilateral pulmonary lesions were present, and an enlarged lymph node was detected in the right neck with increased 2-deoxy-2-^{18}F-fluoro-D-glucose metabolism (Fig. 1). A comprehensive metabolic workup was performed, including plasma concentrations of angiotensin, aldosterone, cortisol, adrenocorticotropic hormones and plasma renin activity. All these adrenal hormone levels were in the normal ranges. Therefore, the laboratory test

Correspondence to: Dr Xi Tang, Department of Oncology, Huadong Hospital Affiliated to Fudan University, 221 West Yan'an Road, Shanghai 200040, P.R. China
E-mail: olivia9tang@126.com

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results were indicative of a non-functional adrenal tumor. The patient was referred for a nasopharyngeal biopsy in November 2018. Biopsy pathology revealed chronic nasopharyngeal inflammation. Sequentially, the patient underwent an adrenal biopsy and wedge resection of the lung. Microscopically, epithelioid cells with abundant eosinophilic cytoplasm were detected in both tissue samples. Typically, these cells had heteromorphic vesicular nuclei and prominent nucleoli. Immunohistochemistry (IHC) was performed using antibodies listed in Table I and indicated that the tumor cells were strongly positive for CD34, cytokeratin (CK), epithelial membrane antigen (EMA), (Fig. 2) and CK8 (data not shown). The cells exhibited negative staining for integrase interactor 1 (INI-1; Fig. 2), cytokeratin (CK)7, myoblast determination protein 1 (MYOD1), myogenin, desmin, anaplastic lymphoma kinase (ALK), cluster of differentiation (CD)31, Avian v-ets erythroblastosis virus E26 oncogene homolog (ERG), thyroid transcription factor 1(TTF-1), synaptophysin (SYN), chromogranin (CHG), protein 63 (P63), Melan-A (A103) and inhibin (data not shown). Therefore, the patient was diagnosed with proximal adrenal ES of stage IV.

After being diagnosed, the patient underwent two cycles of the VIDE regimen (vindesine 2 mg/m^2 d1, ifosfamide 1.5 g/m^2 d1-4, doxorubicin 25 mg/m^2 d1-2 and etoposide 80 mg/m^2 d1-4, Q3W) in January 2019. Subsequently, a CT scan revealed new lesions erupting in the bilateral lung while the adrenal lesions remained unchanged (longest diameter: Left, 137 mm; right, 102 mm). Next-generation sequencing technology (tested by AmoyDx Medical Institute; Table I) was performed with peripheral blood, revealing a low tumor mutation burden (TMB) of 4.11 Muts/Mb and somatic mutations in the *SMARCB1* (10.31%), *SDHC* (0.85%), *XPO1* (0.6%), *RANBP2* (0.98%), *FANCD2* (0.66%) and *SCN8A* (0.86%) genes. IHC of tumor samples suggested that the tumor proportion score of programmed cell death protein 1 ligand (PD-L1) was >50%. In February 2019, anti-programmed death receptor 1 (anti-PD-1) therapy was initiated with pembrolizumab (200 mg, Q3W) for seven cycles. The patient was closely followed up by CT at 2-3-month intervals. Follow-up CT scans indicated that masses began to reduce after two cycles of pembrolizumab and immune partial response [assessed by iRECIST (12)] was achieved at the 6th cycle (Fig. 3). Furthermore, the patient's blood pressure returned to normal; however, a decline in heart function was observed since the 5th cycle of pembrolizumab. The left ventricular ejective fraction (LVEF) was 66% at baseline but declined to 52% after anti-PD-1 therapy. The dynamic monitoring results of myocardium enzyme, brain natriuretic peptide and electrocardiogram were normal. Methylprednisolone did not improve cardiac function. Therefore, the treatment was terminated in November 2019. From December 2019 to March 2020, the patient was treated with anlotinib (12 mg po d1-14, Q3W). The follow-up CT scan revealed an increased left adrenal mass (longest diameter, 127 mm) and multiple bone metastases emerged. Palliative radiotherapy was given for bone metastases and adrenal lesions, but it failed to control the disease. When LVEF returned to the normal range, the patient was given anti-PD-L1 therapy (atezolizumab 1,200 mg Q3W) in May 2020 to avoid a cardiac adverse reaction. After three cycles, immune stable disease was observed during subsequent imaging that was performed in July. In October 2020, the patient developed cachexia and succumbed to community acquired respiratory infection.

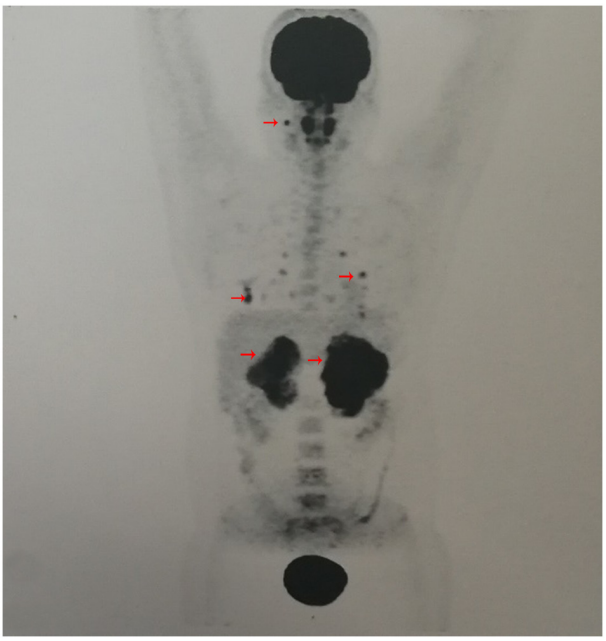

Figure 1. Positron emission tomography-CT at initial diagnosis indicated 2-deoxy-2-^{18}F-fluoro-D-glucose uptake in the bilateral adrenal regions (maximum SUV, 11.7), multiple bilateral pulmonary lesions (maximum SUV, 4.7) and enlarged lymph node in the right neck (maximum SUV, 4.6). Red arrows indicate lesions. SUV, standardized uptake value.

Discussion

Currently, most of the available studies on ES are case reports. Reports on the involvement of the adrenal gland in ES are rare. In 2017, Alikhan *et al* (9) first described a case of primary adrenal ES in an elderly patient. The disease relapsed 24 months after the patient underwent laparoscopic adrenalectomy, but a second open resection prolonged survival (9). The second adrenal ES case was reported by Huang *et al* (10) in 2019. A 31-year-old female was diagnosed with stage III by CT-guided core needle biopsy, after which the patient was given three cycles of neoadjuvant chemotherapy with ifosfamide and anthracycline. During cycle 3, the disease progressed, and in spite of the treatment with tazemetostat, an activating enhancer of zeste homolog 2 (EZH2) inhibitor for ES, the patient died 2 months later after the therapy. Recently, Martinez *et al* (11) reported the third adrenal ES case in an 82-year-old female. The patient underwent extensive surgical excision. However, the case report does not provide any information regarding prognosis due to the short follow-up period. In the current case, sufficient tissue was successfully obtained from both adrenal gland masses and lung lesions. A summary of the clinical characteristics and treatment outcomes of these four cases is provided in Table II. PubMed databases were searched from 1970 to 2022, combining terms describing epithelioid sarcoma and adrenal gland. The inclusion criterion was adult primary epithelioid sarcoma of adrenal gland confirmed by pathology. IHC staining suggested that the patient had an IHC pattern similar to those in the previous reports (9-11,13). Tumor cells were positive for epithelial markers (CK8, CK and EMA) and vascular marker (CD34) and negative for nuclear

Table I. Test kits and instruments used for immunohistochemistry and next-generation sequencing.

A, Kits

Procedure/step/test kit	Catalogue number	Supplier
Immunohistochemistry		
Hematoxylin	118604	Dako; Agilent Technologies, Inc.
INI-1	MAB-0696	MXB Biotechnologies
CD 34	kit-0004	MXB Biotechnologies
Cytokeratin	kit-0009	MXB Biotechnologies
EMA	kit-0011	MXB Biotechnologies
PD-L1	RMA-0732	MXB Biotechnologies
Preparation of DNA/RNA		
Construction		
NEBNext Ultra II DNA Library Prep Kit for Illumina	E7645L	New England Biolabs
KAPA HiFi HotStart Ready Mix	07958935001	Roche Diagnostics
Capture		
SeqCap EZ Capture Beads	06977952001	Roche Diagnostics
SeqCap EZ Accessory Kit v2	07145594001	Roche Diagnostics
KAPA HiFi HotStart PCR Kit	KK2502	Roche Diagnostics
SeqCap Hybridization and Wash Kit	05634253001	Roche Diagnostics
Sequencing		
NovaSeq 6000 S1 Reagent Kit (300 cycles)	20025960	Illumina, Inc.
Paired-end sequencing (151+8+8+151)		

B, Instruments for quantification of samples

Procedure/step/test kit	Catalogue number	Supplier
DNA		
Nanodrop	SMA4000	Amoydox
Quantus	E2670	Promega Corporation
Library		
Agilent 2100 Electrophoresis Bioanalyzer Instrument; Loading concentration: 271.7 nM; Concentration measured: 59 (ng/μl, fluorescence concentration) x1,000,000/329 (capture library fragment)/660		

INI1 expression. Characteristically, the somatic mutation of *SMARCB1* leads to INI1 expression loss (13). Therefore, the pathological diagnosis of ES was established, indicating huge masses in the bilateral adrenal glands as primary sites.

Due to the absence of large-scale prospective clinical studies, there is no standard systemic therapy regimen for advanced ES. Anthracycline-based therapy is one of the regimens with a wide application. In retrospective studies, palliative chemotherapy with anthracyclines was combined with ifosfamide, where median overall survival (OS) ranged from 9.8 to 16.8 months (6,14,15). Considering the performance status of the patient, the VIDE regimen was selected as the first-line chemotherapy. However, severe myelosuppression arose from the combined regimen without any improvement of prognosis. The effectiveness of tazemetostat monotherapy in patients with advanced ES characterized by loss of INI1/SMARCB1 has been confirmed in a basket study, reporting an ORR of 15% and median OS of 19.0 months. The safety and tolerability were excellent, as most toxicities were grade 1-2 (7). With the expectation of providing better survival data, a clinical trial of tazemetostat combined with doxorubicin is ongoing (NCT04204941). Unfortunately, tazemetostat is still unavailable in China.

Various studies reported that ICIs of PD-1 and its ligand PD-L1 have promising activity in multiple tumor types. However, PD1 or PD-L1 antagonist monotherapy has limited efficacy in unselected soft tissue sarcomas, with an ORR ranging from 5 to 18% (16-18). Most subtypes of soft tissue sarcoma (STS) are resistant to ICIs due to the insufficiency of CD8-positive T cells in the tumor microenvironment (19).

Table II. Clinical characteristics and treatment outcomes of adrenal epithelioid sarcoma cases.

Author (year)	Age, years	Sex	Symptoms	Relapse/metastatic sites	Treatment	Outcome	Overall survival	(Refs.)
Alikhan (2017)	72	Male	Abdominal pain, nausea	Local relapse	Adrenalectomy and radiotherapy	No evidence of disease after re-excision	>2.5 years	(9)
Huang (2019)	31	Female	Nausea, rectal bleeding	Retroperitoneal lymph node	Neoadjuvant chemotherapy, tazemetostat as first-line therapy after PD	PD after 3 cycles of neoadjuvant chemotherapy and 4 cycles of tazemetostat therapy	N/A	(10)
Martinez (2020)	82	Female	Flank pain	No	Nephrectomy, adrenalectomy and mass excision	No evidence of disease	N/A	(11)
Present case	28	Male	Lumbar backache, cough, frailty	Lung, bone	Palliative chemotherapy and radiotherapy, ICIs, anlotinib	PD occurred after chemotherapy, radiotherapy and anlotinib; the disease was controlled during ICI treatment	25 months	/

ICI, immune checkpoint inhibitor; PD, progressive disease.

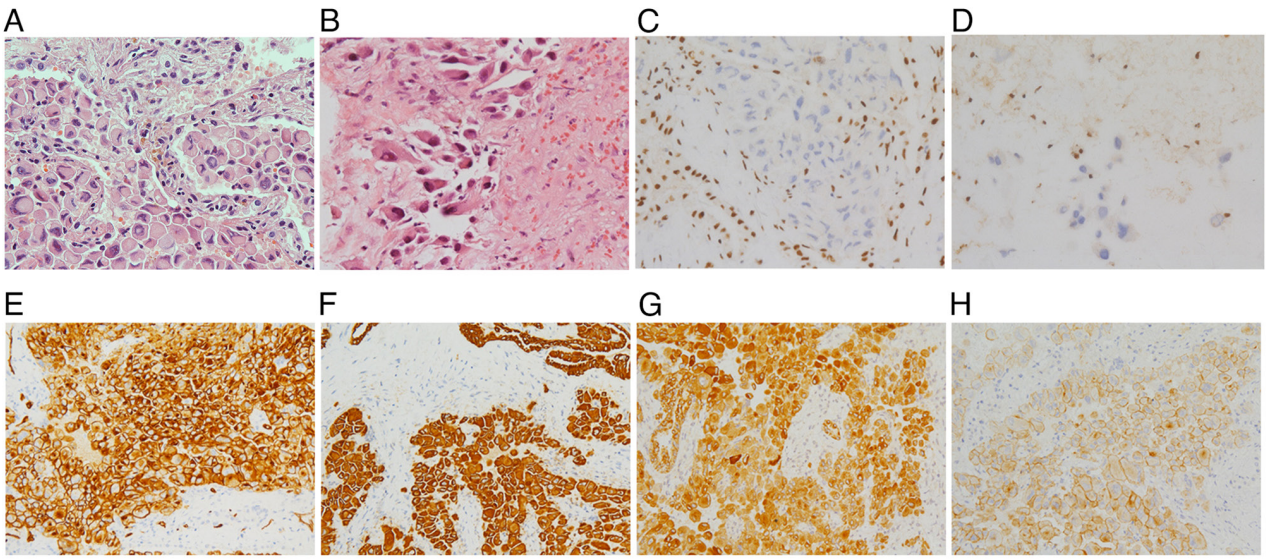

Figure 2. Histologic features of epithelioid sarcoma. The typical immunohistochemical results which were helpful for diagnosis and treatment planning are presented. (A) H&E staining of lung resection biopsy specimen. (B) H&E staining of adrenal needle biopsy specimen. (C) Tumor cells were immunonegative for INI-1 (lung). (D) Tumor cells were immunonegative for INI-1 (adrenal gland). (E) Tumor cells were immunopositive for CD34 (lung). (F) Tumor cells were immunopositive for cytokeratin (lung). (G) Tumor cells were immunopositive for EMA (lung). (H) Tumor cells were immunopositive for PD-L1, tumor proportion score >50% (lung) (magnification, x400 in A and B and x200 in C-H). Tumor proportion score: tumor cells with positive PD-L1 membrane staining at any intensity/total number of tumor cells x100%. EMA, epithelial membrane antigen.

The TMB is a controversial predictor of the treatment efficacy of ICIs. According to data from The Cancer Genome Atlas research network, STS is a category of diseases with a low somatic TMB (average, 1.06 Muts/Mb) (20). In addition, in certain STS, no correlation was established between TMB, the expression of PD-L1 by tumor cells and CD8+ tumor-infiltrating lymphocytes (21). Thus, TMB alone may not predict the likelihood of a response to ICIs. In the current case, the patient who had a low TMB but a high level of PD-L1 expression exhibited tumor shrinkage. Therefore, it may be presumed

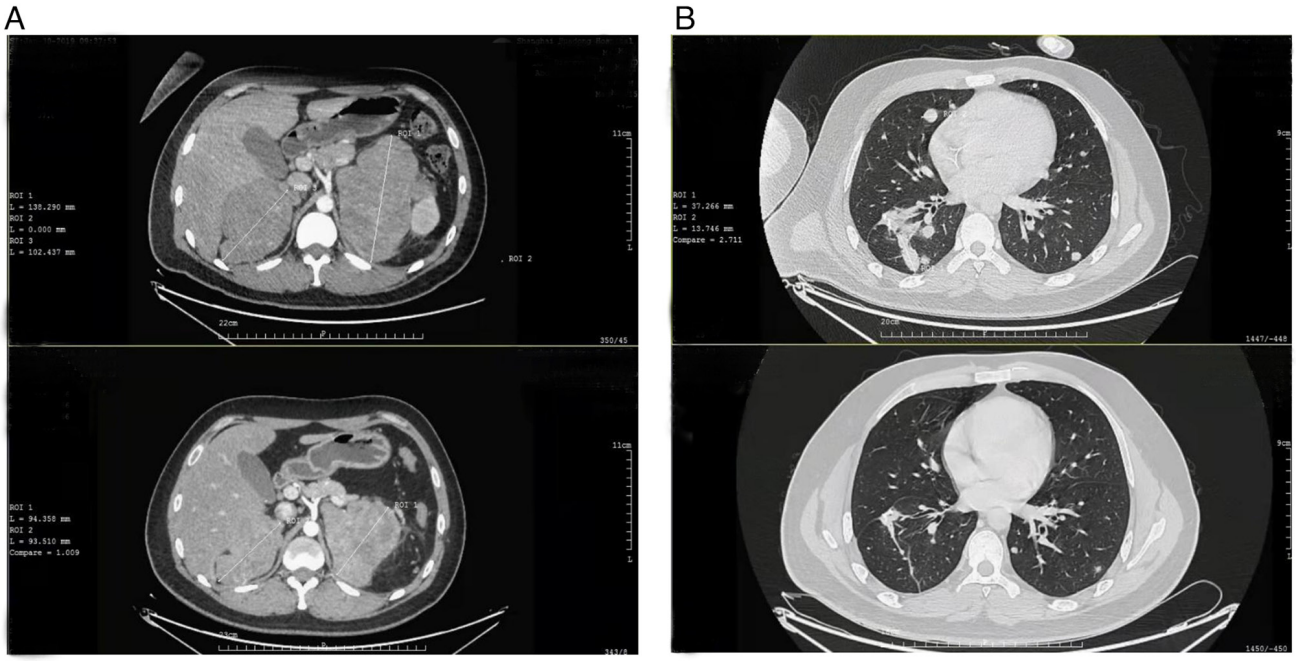

Figure 3. (A) CT-scan images indicated multiple metastatic lesions in adrenal glands at the baseline assessment (February 2019) and after treatment with anti-PD-1 therapy (June 2019; right, 102 mm reduced to 93.5 mm; left, 138 mm reduced to 94 mm). (B) Bilateral pulmonary lesions at the baseline assessment (February 2019) were reduced or even disappeared after treatment with anti-PD-1 therapy (June 2019). PD-1, programmed death receptor 1.

that PD-L1 expression is a stronger predictor of ICI treatment efficacy than TMB. Although patients with PD-L1-positive tumors gained survival benefits from ICI treatment, responses were also recorded in PD-L1-negative cases (16). The role of PD-L1 expression as a predictive biomarker remains unclear.

Due to the limited number of reports, it remains elusive whether ES is sensitive to ICI treatment. In a retrospective study of patients with relapsed metastatic/unresectable sarcomas, 3 patients with ES were enrolled. Among them, 1 patient had partial remission after four cycles of nivolumab combined with pazopanib, but progressive disease after four additional cycles. The other 2 patients suffered from progressive disease (22). In the case report by Pecora *et al* (23), the combination between anti-CTLA-4 and anti-PD-1 checkpoint inhibition therapy led to a durable complete response in a 19-year-old male with stage IV ES. The patient of the present study experienced partial remission after original anti-PD-1 therapy and stable disease (no change in volume) after sequential anti-PD-L1 therapy. The patient's OS reached 25 months. The main dose-limiting toxicity of pembrolizumab induced cardiotoxicity characterized by asymptomatic heart failure but was not observed in atezolizumab, which may be attributed to the differences in antibody-binding sites. ICI-associated cardiotoxicity is a rare occurrence that may be fatal. Although data from a large population-based epidemiology study indicated no difference between PD-1 and PD-L1 inhibitors in terms of risk of cardiotoxicity, patients initiated on pembrolizumab were vulnerable to developing cardiotoxicity (24).

In conclusion, the long survival of the present case demonstrated the effectiveness of ICI treatment in patients with ES. The IHC-based PD-L1 expression predicted the response to ICIs. Therefore, irrespective of the degree of TMB, ICI monotherapy may be a feasible treatment for patients with ES with a strong expression of PD-L1.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XT performed the therapeutic regimen. CL performed pathological diagnosis by immunohistochemistry. JW acquired the clinical data and drafted the manuscript. XT and JW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). This study was approved by the Ethics Committee at Huadong Hospital, Affiliated to Fudan University (Shanghai, China; approval no. 2021K111).

Patient consent for publication

Written informed consent was obtained from the patient's father for the publication of this case report including medical data and images.

Competing interests

The authors declare that they have no competing interests.

References

1. Enzinger FM: Epitheloid sarcoma. A sarcoma simulating a granuloma or a carcinoma. Cancer 26: 1029-1041, 1970.
2. Spillane AJ, Thomas JM and Fisher C: Epithelioid sarcoma: The clinicopathological complexities of this rare soft tissue sarcoma. Ann Surg Oncol 7: 218-225, 2000.
3. de Visscher SA, van Ginkel RJ, Wobbes T, Veth RP, Ten Heuvel SE, Suurmeijer AJ and Hoekstra HJ: Epithelioid sarcoma: Still an only surgically curable disease. Cancer 107: 606-612, 2006.
4. Frezza AM, Jones RL, Lo Vullo S, Asano N, Lucibello F, Ben-Ami E, Ratan R, Teterycz P, Boye K, Brahmi M, *et al*: Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: A multi-institutional case series. JAMA Oncol 4: e180219, 2018.
5. Gounder MM, Merriam P, Ratan R, Patel SR, Chugh R, Villalobos VM, Thornton M, Van Tine BA, Abdelhamid AH, Whalen J, *et al*: Real-world outcomes of patients with locally advanced or metastatic epithelioid sarcoma. Cancer 127: 1311-1317, 2021.
6. Touati N, Schöffski P, Litière S, Judson I, Sleijfer S, van der Graaf WT, Italiano A, Isambert N, Gil T, Blay JY, *et al*: European organisation for research and treatment of cancer soft tissue and bone sarcoma group experience with advanced/metastatic epithelioid sarcoma patients treated in prospective trials: Clinical profile and response to systemic therapy. Clin Oncol (R Coll Radiol) 30: 448-454, 2018.
7. Gounder M, Schöffski P, Jones RL, Agulnik M, Cote GM, Villalobos VM, Attia S, Chugh R, Chen TW, Jahan T, *et al*: Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: An international, open-label, phase 2 basket study. Lancet Oncol 21: 1423-1432, 2020.
8. Guillou L, Wadden C, Coindre JM, Krausz T and Fletcher CD: 'Proximal-type' epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features. Clinicopathologic, immunohistochemical, and ultrastructural study of a series. Am J Surg Pathol 21: 130-146, 1997.
9. Alikhan MB, Pease G, Watkin W, Grogan R, Krausz T and Antic T: Primary epithelioid sarcoma of the kidney and adrenal gland: Report of 2 cases with immunohistochemical and molecular cytogenetic studies. Hum Pathol 61: 158-163, 2017.
10. Huang X, Nayar R and Zhou H: Primary adrenal gland epithelioid sarcoma: A case report and literature review. Diagn Cytopathol 47: 918-921, 2019.
11. Martinez VP, Nicholson M and Patel T: Abnormal Adrenal mass presents as proximal epithelioid sarcoma. Case Rep Urol 2020: 8864218, 2020.
12. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, *et al*: iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18: e143-e152, 2017.
13. Hornick JL, Dal Cin P and Fletcher CD: Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am J Surg Pathol 33: 542-550, 2009.
14. Jones RL, Constantinidou A, Olmos D, Thway K, Fisher C, Al-Muderis O, Scurr M and Judson IR: Role of palliative chemotherapy in advanced epithelioid sarcoma. Am J Clin Oncol 35: 351-357, 2012.
15. Kim C, Yoo KH, Kim MH, Chon HJ, Lee SI, Lee HJ, Koh S, Lee HY, Lee HR, Kim KS, *et al*: Different subtypes of epithelioid sarcoma and their clinical implication: Long-term multi-institutional experience with a rare sarcoma. APMIS 125: 223-229, 2017.
16. Italiano A, Bellera C and D'Angelo S: PD1/PD-L1 targeting in advanced soft-tissue sarcomas: A pooled analysis of phase II trials. J Hematol Oncol 13: 55, 2020.
17. D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, Antonescu CR, Horvath E, Tap WD, Schwartz GK and Streicher H: Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): Two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol 19: 416-426, 2018.
18. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, D'Angelo S, Attia S, Riedel RF, Priebat DA, *et al*: Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): A multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 18: 1493-1501, 2017.
19. Toulmonde M, Penel N, Adam J, Chevreau C, Blay JY, Le Cesne A, Bompas E, Piperno-Neumann S, Cousin S, Grellety T, *et al*: Use of PD-1, targeting macrophage infiltration, and IDO pathway activation in sarcomas: A phase 2 clinical trial. JAMA Oncol 4: 93-97, 2018.
20. Cancer Genome Atlas Research Network. Electronic address: elizabeth.demicco@sinaihealthsystem.ca; Cancer Genome Atlas Research Network: Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. Cell 171: 950-965. e28, 2017.
21. He M, Abro B, Kaushal M, Chen L, Chen T, Gondim M, Yan W, Neidich J, Dehner LP and Pfeifer JD: Tumor mutation burden and checkpoint immunotherapy markers in primary and metastatic synovial sarcoma. Hum Pathol 100: 15-23, 2020.
22. Paoluzzi L, Cacavio A, Ghesani M, Karambelkar A, Rapkiewicz A, Weber J and Rosen G: Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res 6: 24, 2016.
23. Pecora A, Halpern S, Weber M, Paleoudis EG, Panush D, Patterson F and Toretsky J: Rapid and Complete response to combination anti-CTLA-4 and Anti-PD-1 checkpoint inhibitor therapy in a patient with stage IV refractory end-stage epithelioid sarcoma: A case report. J Immunother 43: 286-290, 2020.
24. Li C, Bhatti SA and Ying J: Immune checkpoint inhibitors-associated cardiotoxicity. Cancers (Basel) 14: 1145, 2022.