Confirmatory diagnosis and successive chemotherapeutic treatments of metastatic skeletal *EWSR1::NFATC2* sarcoma: A case report

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Abstract. *EWSR1::NFATC2* sarcoma is rare and its clinical features remain unclear. Given the similarity in presentation, it is possible that previously reported cases of Ewing-like adamantinoma may have been *EWSR1::NFATC2* sarcoma. The present case report describes a tumor in a 55-year-old man that was originally thought to be a Ewing-like adamantinoma, but was recently found to be an *EWSR1::NFATC2* sarcoma following direct sequencing. The patient experienced pain in their left lower leg at 38 years of age. The initial pathological diagnosis was 'epithelioid malignant tumor of the left tibia suggesting Ewing-like adamantinoma'. The patient underwent wide excision of the tumor in their left tibia with left total knee arthroplasty and a medial gastrocnemius muscle flap. Thereafter, the patient continued with no evidence of recurrent or metastatic disease; however, 14 years later, they developed multiple lesions in the left lung, left pleural dissemination, and enlargement of the mediastinal, left hilar and juxtaesophageal lymph nodes. Pathological diagnosis of transbronchial lung biopsy was consistent with 'Ewing-like adamantinoma'. The patient received doxorubicin-based systemic chemotherapy as first-line therapy, which resulted in stable disease. After disease progression, the patient received eribulin monotherapy, which resulted in stable disease for 15 months. Reverse transcription-polymerase chain reaction followed by direct sequencing revealed an in-frame *EWSR1::NFATC2* fusion where exon 8 of *EWSR1* (ENST00000397938.7) was fused to exon 3 of *NFATC2* (ENST00000371564.8), and their diagnosis was changed to *EWSR1::NFATC2* sarcoma. The disease progressed, left pleural dissemination progressed, left pleural effusion increased and peritoneal dissemination in the left paracolic gutter was suspected. Therefore, the patient was started on trabectedin monotherapy during 16 months of stable disease, and thereafter received pazopanib after they presented with progressive disease on prior trabectedin monotherapy. It is likely that there are more patients with undiagnosed *EWSR1::NFATC2* sarcoma. To make a definitive diagnosis, a thorough investigation should be performed.

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Abbreviations: BCOR, B cell lymphoma 6 corepressor; CIC, capicua transcriptional repressor; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IE, ifosfamide and etoposide; MSI, microsatellite instability; mTOR, mammalian target of rapamycin; PD, progressive disease; RT-PCR, reverse transcription-polymerase chain reaction; SD, stable disease; TBLB, transbronchial lung biopsy; VAC, vincristine, actinomycin D, and cyclophosphamide; VDC, vincristine, cyclophosphamide, and doxorubicin

Key words: Ewing-like adamantinoma, *EWSR1::NFATC2* sarcoma, trabectedin, fluorescence *in situ* hybridization, direct sequencing

Introduction

Ewing sarcoma is a round cell sarcoma commonly found in younger patients (children and young adults), and standard therapy includes vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) chemotherapy in combination with surgical resection and/or radiation therapy (1). Meanwhile, round cell sarcomas which resemble Ewing sarcoma are referred to as 'Ewing-like sarcomas'. According to the latest edition of the World Health Organization classification, in undifferentiated round cell sarcomas of the bones and soft tissues, Ewing-like sarcoma

has been classified into three categories: round cell sarcoma with *EWSR1::non-ETS* fusions, capicua transcriptional repressor (CIC)-rearranged sarcoma, and sarcoma with B cell lymphoma 6 corepressor (BCOR) genetic alterations (2). CIC-rearranged sarcomas and sarcomas with BCOR genetic alterations are well-established clinicopathologically, whereas round cell sarcomas with *EWSR1::non-ETS* fusions are a heterogeneous and premature group.

Since the discovery of *EWSR1::NFATC2* sarcoma as an *EWSR1::non-ETS* sarcoma by Szuhai *et al* (3), new clinical and pathological information on this sarcoma has accumulated. Yoshida *et al* (4) reported that, in addition to the co-expression of CD99, NKX2-2, and PAX7, NKX3-1 is a useful immunohistochemical marker of *EWSR1::NFATC2* sarcomas, similar to Ewing sarcoma (5-7). In addition, Perret *et al* (8) demonstrated the utility of aggrecan immunohistochemistry for the identification of *NFATC2*-rearranged sarcomas, including *EWSR1::NFATC2* and *FUS::NFATC2* fusions. Furthermore, unlike Ewing sarcoma, these sarcomas often form focal nests, cords, or trabeculae within a fibrotic, hyalinized, or myxoid stromal background, mimicking myoepithelial tumors (4,9).

EWSR1::NFATC2 sarcoma is very rare but is considered to be the most common subtype of *ESWR1::non-ETS* sarcoma. Regarding pathological diagnosis, the histological features of *EWSR1::NFATC2* sarcoma are similar to those of other sarcomas such as Ewing-like adamantinoma, which was first reported by Lipper *et al* (10) as a variant of adamantinoma of the long bones. Notably, Makise *et al* (11) reported the case of a patient previously diagnosed with Ewing-like adamantinoma who was finally diagnosed with *EWSR1::NFATC2* sarcoma using fluorescence *in situ* hybridization (FISH)-amplified fusion signals of *EWSR1* and *NFATC2*.

EWSR1::NFATC2 sarcoma is thought to have a more indolent clinical course than Ewing sarcoma, despite poor responses to Ewing sarcoma chemotherapy regimens (7); therefore, metastatic *EWSR1::NFATC2* sarcoma is very rare. Thus, there is insufficient information regarding chemotherapeutic treatments for metastatic *EWSR1::NFATC2* sarcoma. Herein, we report a case of a man with *EWSR1::NFATC2* sarcoma, initially diagnosed as Ewing-like adamantinoma, who received a series of chemotherapy treatments of for Ewing sarcoma, including eribulin, trabectedin, and pazopanib.

Case report

A 55-year-old male patient with Ewing-like adamantinoma, who had a durable response with trabectedin monotherapy as third-line therapy, was recently definitively diagnosed as having *EWSR1::NFATC2* sarcoma using direct sequencing. The patient was admitted to Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research (Tokyo, Japan) in July 2022. He initially experienced pain in his left lower leg and consulted a local clinic at 38 years of age. The patient also exhibited disc space narrowing and osteolytic changes in the proximal tibia. The patient had no significant medical history. One month later, he underwent biopsy of the tumor in the proximal part of the left tibia at our hospital. The pathological diagnosis was 'epithelioid malignant tumor of the left tibia suggesting Ewing-like adamantinoma'. A month thereafter, he underwent wide excision of the tumor in his left tibia with left total knee arthroplasty and a medial gastrocnemius muscle flap. The patient survived with no evidence of recurrent or metastatic disease. However, five years after surgery, the patient underwent right thyroid lobectomy and lymph node dissection for papillary thyroid cancer. In addition, 14 years after surgery, multiple new lesions were detected radiographically in the left lung, left pleural dissemination, and mediastinal, left hilar, and juxtaesophageal lymph nodes. The lesion, which was biopsied by transbronchial lung biopsy (TBLB), was diagnosed as 'Ewing-like adamantinoma'. At 52 years of age, he started systemic chemotherapy with five cycles of vincristine, doxorubicin, and cyclophosphamide (VDC) combination chemotherapy, with the maximum doxorubicin dosage, resulting in stable disease (SD). Next, he received eight cycles of vincristine, actinomycin D, and cyclophosphamide (VAC) combination chemotherapy. In addition, he received radiation therapy (60 Gy/30 fractions) for the tumor in the left lower lobe. However, he developed radiation pneumonitis and steroid therapy was initiated at a dose of 40 mg prednisolone per day. The prednisolone dosage was gradually reduced, and once a dosage of 5 mg/day was reached, the patient started receiving eribulin monotherapy as second-line therapy. Prednisolone was administered until the completion of 16 cycles of eribulin. Microsatellite instability (MSI) tests using the TBLB specimens yielded negative results. In addition, a *BCL2L1* amplification, previously reported in *EWSR1::NFATC2* sarcoma, was identified using FoundationOne® CDx (12). Although *EWSR1* rearrangement was not detected using FoundationOne® CDx, FISH analysis using an *EWSR1* break apart probe revealed amplification of the 5'-end of *EWSR1*, indicating the rearrangement of the *EWSR1* gene, compatible with *EWSR1::NFATC2* sarcoma. Reverse transcription-polymerase chain reaction (RT-PCR) using a pair of primers (forward: 5'-GAGAGAACC GGAGCATGAGTG-3' and reverse: 5'-CTTGGGCTGCAC CTCGATCCGC-3') followed by direct sequencing revealed an in-frame *EWSR1::NFATC2* fusion where exon 8 of *EWSR1* (ENST00000397938.7) was fused to exon 3 of *NFATC2* (ENST00000371564.8), as previously shown by Sadri *et al* (9). We also used a pair of primers for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (forward: 5'-GAAGGTGAAGGT CGGAGTC-3' and reverse: 5'-GAAGATGGTGATGGGATT TC-3') as internal control for RT-PCR. In addition, the tumor mutational burden (TMB) was found to be 1 Mut/Mb. Three months later, he had progressive disease (PD): left pleural dissemination progressed, left pleural effusion increased, and peritoneal dissemination in the left paracolic gutter was suspected. The next treatment was trabectedin monotherapy. Although he also had a bone infection in the postoperative region of the left tibia, he continued the trabectedin monotherapy with concurrent oral antibiotics. The patient remained stable for 16 months, however, after 18 cycles of trabectedin monotherapy, the patient developed PD. He was subsequently administered pazopanib (800 mg/day). After 2 months, he once again had PD due to the progression of the pleural effusion.

Discussion

In recent years, *EWSR1::NFATC2* sarcoma has become recognizable using various pathological and genetic tests. Our patient was diagnosed by additional immunohistochemical

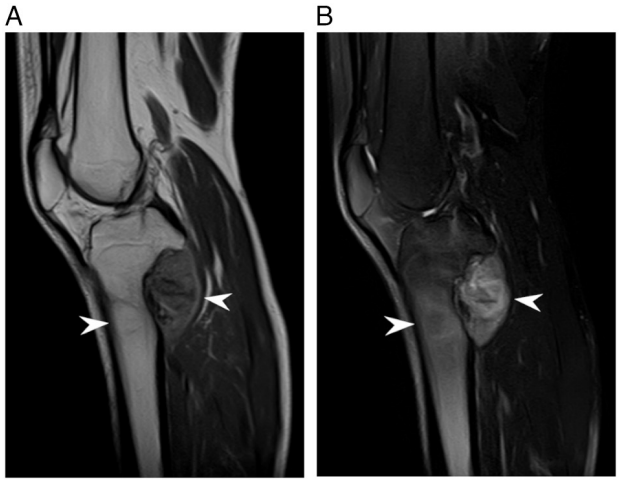

Figure 1. Sagittal magnetic resonance imaging of the primary tibial tumor. The tumor was present in proximal site of the metaphysis of the left tibia. The periosteal or intracortical envelopes from the tibial metaphysis to the epiphysis show (A) a lytic lesion of vague low intensity on T1-SE and (B) mild hyperintensity on T2-FSE (arrow heads pointing to the right), involving soft tissue mass protruding to the dorsal side of the lytic lesion (arrow heads pointing to the left).

staining for NKX3-1, FISH, and RT-PCR followed by direct sequencing. *EWSR1::NFATC2* sarcoma is classified as *ESWR1::non-ETS* sarcoma, a wastebasket diagnosis; however, it comprises the majority of this class of Ewing-like sarcomas, and the number of case reports and studies have been accumulating.

EWSR1::NFATC2 sarcoma often occurs in the diaphyseal medulla of long bones, similar to Ewing sarcoma. In the present case, the tumor was located at the proximal site of the metaphysis of the left tibia (Fig. 1A and B). Notably, no tibial tumors, including those in our case, occurred on the anterior side of the cortex, which is the most common site of classic adamantinoma of the long bones, as shown in Table SI (4,8,13-17). *EWSR1::NFATC2* sarcomas tend to grow slowly and are relatively indolent in nature. The metastatic tumors in our case were also characteristic because of their slow growth.

Ewing-like adamantinoma is composed of relatively uniform, small round or epithelioid cells arranged in nests, cords, or trabeculae with fibrous or myxoid stroma. Our patient had an epithelioid malignant tumor of the left tibia, suggesting a Ewing-like adamantinoma 19 years previously. This case was similar to the *EWSR1::NFATC2* sarcoma case reported by Makise *et al* (11).

When we reanalyzed the tissue samples, hematoxylin and eosin staining revealed relatively uniform round cells in a trabecular arrangement within a fibrous background (Fig. 2A) and epithelioid tumor cells with abundant clear cytoplasm, forming nests or trabeculae (Fig. 2B). Immunohistochemical staining revealed that the tumor cells were weakly and focally positive for AE1/AE3 (Fig. 2C), weakly positive for CD99 (Fig. 2D), and diffusely positive for NKX3.1 (Fig. 2E).

The main radiological characteristics of *EWSR1::NFATC2* sarcoma are as follows: tendency to arise at the diaphysis of long bones, cortical expansion with buttressing-type thickening, and frequent bone surface involvement with saucer-like erosion without cortical destruction. Adamantinoma is a primary low-grade malignant bone tumor of epithelial origin (18). Although predominantly localized in the mid-tibial diaphysis, cases of synchronous or isolated lesions in the fibula have been reported. It is a rare neoplasm, comprising only 0.1-0.5% of all primary bone tumors (19). Our tibial *EWSR1::NFATC2* sarcoma case is very rare and appears to be different from classic adamantinomas in terms of localization.

EWSR1::NFATC2 sarcoma carries a t(20;22)(q13;q12) chromosomal translocation (3). This type of sarcoma is translocation sarcoma (TRS). In 2015, trabectedin was approved in Japan for the treatment of patients with soft tissue sarcoma (STS) after a clinical trial targeting TRS (20). We previously demonstrated that the median progression-free survival was been 7.3 months in our single-institution cohort (21). Kobayashi *et al* (22) reported an overall median progression-free survival (PFS) of 3.7 months in a cohort of 140 patients who underwent trabectedin treatment at 29 Japanese Musculoskeletal Oncology Group institutions. With respect to the histological type in their study, the median PFS was 17.4 months for myxoid liposarcoma, 4.9 months for leiomyosarcoma, 5.6 months for synovial sarcoma, and 3.7 months for dedifferentiated liposarcoma, respectively. As the PFS was 16.4 months in our patient during trabectedin administration, he showed a noteworthy response to trabectedin without any severe adverse events. However, he developed PD after 18 cycles of trabectedin as the left pleural lesion grew bigger and the pleural effusion increased (Fig. 3A and B), and received best supportive care. Notably, the patient also had stable disease for more than a year with eribulin treatment. A future trial with eribulin in these patients may therefore be worthwhile.

With regard to drug therapy, several reports have suggested pazopanib as an effective treatment (18). A summary of metastatic cases treated with chemotherapy is presented in Table I. Seligson *et al* (12) demonstrated the mammalian target of rapamycin (mTOR) pathway as a potential therapeutic target in *EWSR1::NFATC2* sarcomas using multiscale-omic assessment. They also presented the case of a 58-year-old male patient with metastatic *EWSR1::NFATC2* sarcomas who achieved 47 months of disease stabilization when treated with a combination of the mTOR inhibitor, everolimus, and the vascular endothelial growth factor receptor-tyrosine kinase inhibitor, pazopanib. *EWSR1::NFATC2* sarcomas are molecularly distinct entities with an overactive mTOR signaling pathway that may be therapeutically targetable. Gouda *et al* (18) reported a case of a patient with *EWSR1::NFATC2* sarcoma in which exceptional tumor control was achieved using pazopanib and surgery, for an overall duration exceeding 5 years. In addition, Machado *et al* (23) suggested the possibility of exploring an immunotherapy approach because the transcriptomes of *EWSR1::NFATC2* sarcomas should be enriched in genes associated with inflammatory and immune responses (13).

In conclusion, we described a case of metastatic *EWSR1::NFATC2* sarcoma that was initially diagnosed as a Ewing-like adamantinoma arising from the left tibia. Reconsideration during the durable response to trabectedin revealed a definitive diagnosis of a translocation-related sarcoma, *EWSR1::NFATC2* sarcoma. Accordingly, physicians should consider *EWSR1::NFATC2* sarcoma in patients who have been previously diagnosed with Ewing-like adamantinoma with a slow clinical course. It is important to

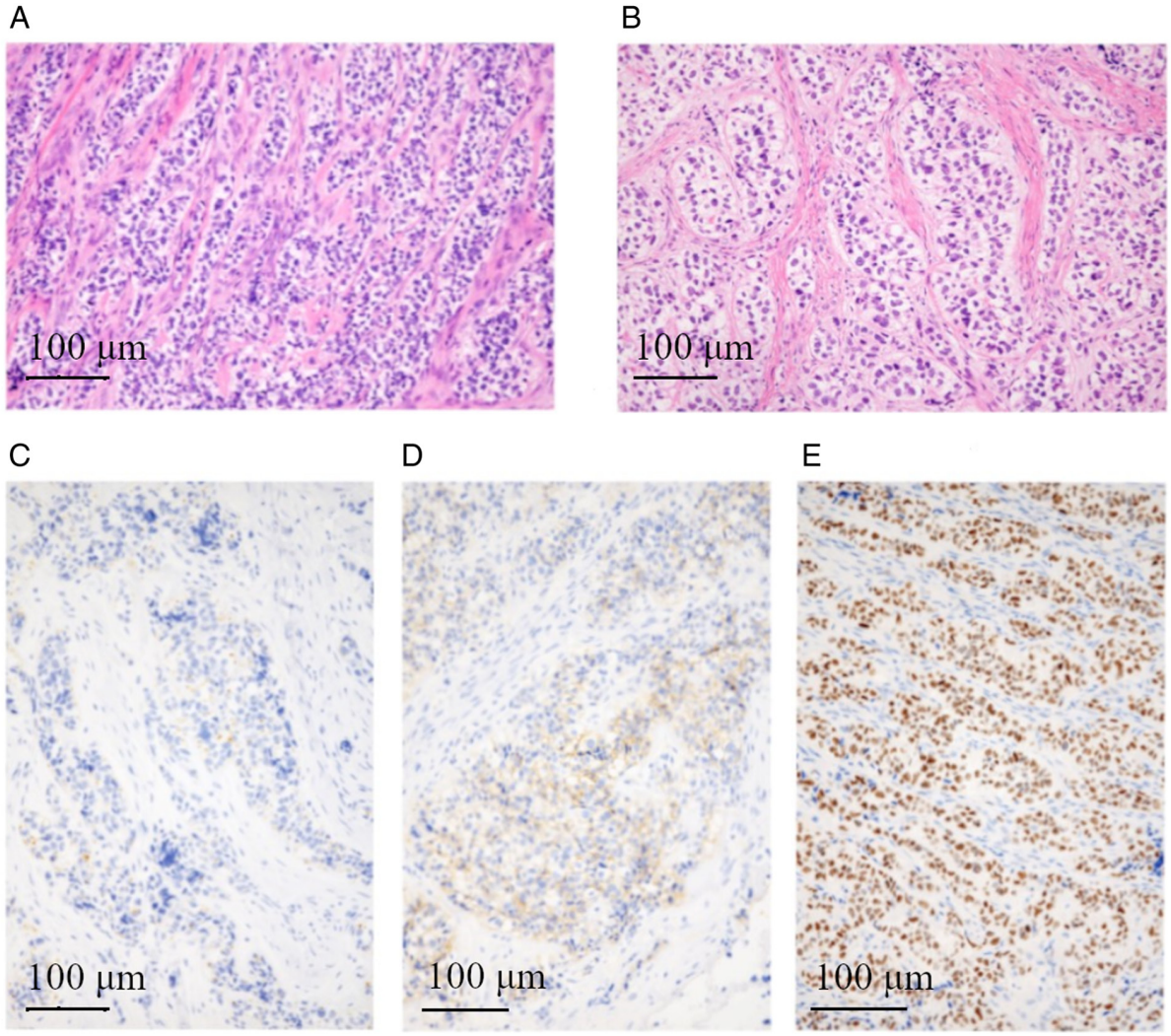

Figure 2. (A and B) Histopathological examination and (C-E) immunohistochemical examination of the tissue samples. Hematoxylin and eosin staining shows (A) relatively uniform round cells in a trabecular arrangement within a fibrous background and (B) epithelioid tumor cells with abundant clear cytoplasm also forming nests or trabeculae (scale bars, 100 μm). Immunohistochemical staining shows the tumor cells are (C) weakly and focally positive for AE1/AE3, (D) weakly positive for CD99 and (E) diffusely positive for NKX3.1 (scale bars, 100 μm).

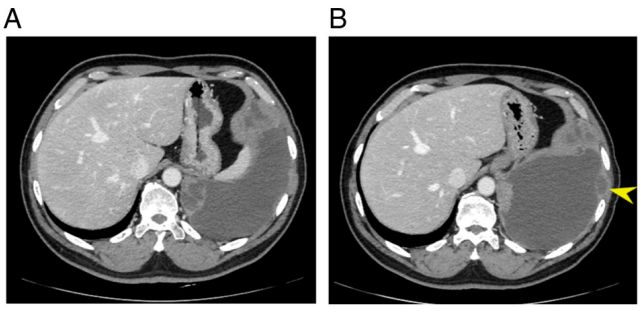

Figure 3. Computed tomography imaging of the left metastatic lung and pleural lesions. The left metastatic pleural lesions have shrunk slightly and newly developed (yellow arrowhead) between the period (A) before start of trabectedin monotherapy and (B) after 18 cycles of trabectedin monotherapy. An increase in pleural effusion was observed.

diagnose it *via* FISH analysis using an *EWSR1* break-apart probe. Amplification of the 5'-end of *EWSR1* indicates the rearrangement of the EWSR1 gene, which is consistent with *EWSR1::NFATC2* sarcoma. In addition, this sarcoma may have a prolonged response to eribulin and trabectedin in preventing or delaying the progression of additional metastasis after adriamycin-based chemotherapy. Further research is required to identify additional active agents or sequences for chemotherapy for this type of sarcoma.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Table I. Clinicopathological features of reported cases of metastatic *EWSR1::NFATC2* sarcoma.

First author, year	Age, years/Sex	Primary site	Surgery	Metastatic site	Gene alteration	Chemotherapy	Outcome/duration or follow-up	(Refs.)
Seligson ND, 2021	58/M	Intraperitoneal mass	Surgical excision of the mass	Retroperitoneum, lung	SPV in *FANCE*	ACT (VDC followed by IE)	Little benefit	(12)
						Pazo alone	Little CB	
						Pazo + CPT-11	Little CB	
						Pazo + Eve	SD/26 mo	
						Pazo + Pembro	SD/10 mo	
						Nivo + Ipi	SD/4 mo	
						Pazo + Eve (re-challenge)	SD/21 mo	
Gouda MA, 2023	30s[a]/M	Left leg	Wedge resection; surgical resection of the cardiac metastasis	Lung, heart	*mTOR* E1799K mut, *TOP1* amp	PCT (VDC/IE)	NA	(18)
						ACT (high-dose IFM alternating with ADR and CDDP)	NED/24 mo	
						TMZ + CPT-11	MR	
Present study	38[a]/M	Metaphyseal cortex of tibia (left)	Wide resection	Lung, LNs, pleura (RT 60 Gy/30 fr after VDC/VAC)	*BCL2L1* amp	VDC/VAC	SD/9 mo	-
						Eribulin	SD/15 mo	
						Trabectedin	SD/16 mo	
						Pazopanib	PD/2 mo	

[a]Age at initial diagnosis. ACT, adjuvant chemotherapy; ADR, adriamycin; amp, amplification; CB, clinical benefit; CDDP, cisplatin; CPT-11, irinotecan; IFM, ifosfamide; fr, fractions; LN, lymph node; M, male; mo, months; mut, mutation; MR, minimal response; NA, not applicable; NED, no evidence of disease; PCT, preoperative chemotherapy; RT, radiation therapy; SD, stable disease; SPV, single pathogenic variant; VAC, vincristine, actinomycin D, and cyclophosphamide; VDC, vincristine, doxorubicin, and cyclophosphamide.

Authors' contributions

TU drafted the manuscript. TU, MO, TT and AO contributed to the management of the clinical case. TU, MO, KY, TT, KT, SM and KA contributed to conception and design, and analysis and interpretation of clinical data. KY performed histological assessment and immunohistochemistry. KY and YT performed RT-PCR and direct sequencing. HS, RO, XW, NF, YS, KN and JT contributed to the patient's care and acquisition of data. TN, MS and KH contributed to the acquisition of data. MO, KY, TT and ST contributed to interpretation of clinical data and reviewed the manuscript. TU and MO confirm the authenticity of all the raw data. KT, SM, KA and ST supervised this study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare that they have no competing interests.

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