Spindle cell sarcoma with KIAA1549-BRAF resembling infantile fibrosarcoma morphologically: A case report and literature review

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Abstract. Infantile fibrosarcoma (IFS) commonly harbors ETS variant transcription factor 6 (ETV6)-neurotrophic receptor tyrosine kinase 3 (NTRK3) fusion. However, the recent accessibility to clinical next-generation sequencing (NGS) has revealed ETV6-NTRK3 negative spindle cell sarcomas resembling IFS morphologically, involving NTRK1/2, MET, RET and BRAF. The present report describes a pediatric case of spindle cell sarcoma with KIAA1549-BRAF resembling IFS morphologically. A 20-month-old female patient was referred to Kobe Children's Hospital (Kobe, Japan) for the treatment of intrathoracic spindle cell sarcoma. Pathologically, the intrathoracic tumor cells were composed of spindle cells with focal hemangiopericytomatous pattern. In immunohistochemistry analysis, the intrathoracic tumor cells focally expressed desmin and WT-1 and were negative for pan-tropomyosin receptor kinase (TRK), S100 and CD34. Fluorescence in situ hybridization analysis for ETV6 and capicua transcriptional repressor revealed negative split signals. Although the patient was initially diagnosed with IFS morphologically, KIAA1549-BRAF fusion transcript was detected by comprehensive genomic profiling with NGS using intrathoracic tumor tissues and confirmed by reverse transcription-PCR. Chemotherapy induced a reduction in the tumor size. At present, the patient is alive with the disease and has been receiving therapy for 8 months since the initiation of chemotherapy. Review of BRAF-altered spindle cell sarcomas resembling IFS morphologically revealed the inconsistency in immunohistochemical expression patterns and the diversity of BRAF fusion genes and mutations. Therefore, the elucidation of genomic profiling by NGS may assist in making an appropriate diagnosis and selecting novel alternative therapies in ETV6-NTRK3-negative spindle cell sarcomas resembling IFS morphologically.

Introduction

Infantile fibrosarcoma (IFS) is a malignant fibroblastic tumor and occurs in younger children under the age of 2 years (1,2). IFS occurs most frequently in the extremities or trunk and less frequently in the abdomen or the retroperitoneum. Metastasis at diagnosis is uncommon (<4%) (1,2). IFS is pathologically described as hypercellular tumors comprising monomorphic spindle cells with scant cytoplasm, including a hemangiopericytoma-like vascular pattern (3). The immunohistochemistry demonstrates the variable expression patterns of smooth muscle actin (SMA), CD34, S100, and CD30 (4,5). Most cases of IFS harbor an ETV6-NTRK3 gene fusion, resulting in the expression of pan-TRK in the immunohistochemistry (2,6). The recent accessibility to clinical next-generation sequencing (NGS) revealed ETV6-NTRK3 negative spindle cell sarcomas resembling IFS morphologically. The spindle cell sarcomas described above involve other kinase genes such as NTRK1/2, RET, MET, and BRAF, each with various gene partners (7-11).

BRAF encodes a serine/threonine RAF kinase, regulates the MAP kinase/ERK signaling pathway, and causes tumorigenesis. In some solid tumors and hematological malignancies, the activating mutations in BRAF, typically resulting in V600E were identified and emerged as potential therapy targets (12,13). However, the biological and clinical characteristics of BRAF-altered spindle cell sarcomas resembling IFS morphologically remain to be elucidated. Herein, we report a pediatric case of spindle cell sarcoma with KIAA1549-BRAF resembling IFS morphologically.

Key words: infantile fibrosarcoma, KIAA1549-BRAF, spindle cell sarcoma, sarcoma, next-generation sequencing

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Case report

A 20-month-female was transferred to our hospital for the treatment of an intrathoracic tumor. She had no remarkable family history. At the age of 3 weeks, a subcutaneous tumor in the right buttock was incidentally noted by a family doctor. Because the tumor gradually increased in size, the total resection of the tumor was performed at the age of 12 months. She was diagnosed with IFS and followed up care without any additional therapies. However, she relapsed as left intrathoracic tumors at the age of 20 months. The enhanced computed tomography (CT) at transfer showed left intrathoracic tumor of 5x4 cm with severe mediastinal shift, as well as right intrathoracic tumor of 1.5x1.5 cm (Fig. 1A and B). Enhanced CT with 5 mm slice thickness was performed using 640-multislice CT scanners (Aquilion ONE, Canon Medical Systems Corpotion, Otawara, Japan). Iopamiron® (Bayer, Osak, Japan) was used as iodinated contrast medium. No other metastatic diseases were detected. The biopsy of the left intrathoracic tumor revealed the presence of IFS. The VDC-IE chemotherapy containing vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide, induced a significant reduction in tumor size. She was alive with disease receiving therapy for 8 months since the initiation of chemotherapy.

The tumor cells were composed of spindle cells, arranged into intersecting fascicules with focal hemangiopericytomatous pattern (Fig. 2A). The mitoses in the tumor were counted at 10 per 10 high-power fields (Fig. 2B). The procedure of H&E pathological staining was as follows. Resected specimens were immediately fixed with 10% formalin neutral buffer solution for 48 h at room temperature. Fixed sections were embedded in paraffin and 4-µm-thick tissue sections were stained with hematoxylin and eosin solutions (Sakura, Tokyo, Japan). Immunohistochemical staining was performed on 4-µm-thick sections using a fully automated systems (Bench Mark GX System (Roche, Rotkreuz, Switzerland) or Leica Bond-max (Leica Biosystems, Buffalo Grove, IL, USA)) and the following primary antibodies; desmin (clone D3; prediluted) (IR606; Dako, Calpinteria, CA, USA), Wilms tumor gene 1 (WT-1) (6F-H2; dilution 1:1) (41386; NICHIREI, Osaka, Japan), pan-TRK [VENTANA Pan-TRK (EPR17341) Assay] (790-7026; Roche, Rotkreuz, Switzerland) or Leica Bond-max. Appropriate positive control sections were performed using ultraView Universal DAB detection kit and following DAB (3,3′-Diaminobenzidine) reaction were confirmed by reverse transcription-polymerase chain reaction (RT-PCR) (Fig. 4A). While several types of KIAA1549-BRAF fusion transcripts were previously reported (14), the transcript composed of KIAA1549 exon 10 fused to BRAF exon 9 was exclusively detected in our case (Fig. 4B). The procedure of sanger sequence was as follows. DNA was extracted from FFPE tissue of the right buttock tumor using The RNAstorm™ kit (Cell Data Science, CA, USA). RT reaction, cDNA polymerase (Promega, WI, USA) with KIAA1549-forward (5'-GAATGTGGTGTATCCCTACTGG-3') and BRAF-reverse (5'-CCTTACATACACGAAATCCTTT-3') primers. PCR conditions were initial denaturation at 95°C for 1 min, 40 cycles.
Figure 3. IHC staining (magnification, x400). (A) Weak positive expression of desmin. (B) Cytoplasmic expression of WT-1. Negative IHC staining results for (C) pan-TRK, (D) S-100, (E) SMA, (F) CD34, (G) CD99, (H) NKX2.2, (I) MyoD1 and (J) pan-cytokeratin. IHC, immunohistochemistry; WT-1, Wilms tumor gene 1; pan-TRK, pan-tropomyosin receptor kinase; SMA, smooth muscle actin; NKX2.2, NK2 homeobox 2; MyoD1, myogenic differentiation 1.

Figure 4. KIAA1549-BRAF fusion protein. (A) RT-PCR of KIAA1549-BRAF fusion transcript. RT-PCR was performed with KIAA1549-forward (5'-GATTGTTGTCATCCTCTACTGG-3') and BRAF-reverse (5'-CCTCCATCACCAGAAATCCTT-3') primers. (B) RT-PCR followed by sequencing analysis revealed that exon 10 of KIAA1549 was fused to the sequence within exon 9 of BRAF. RT-PCR, reverse transcription-PCR.
of 95°C for 30 sec, annealing at 51°C for 30 sec, 72°C for 30 sec, and a final extension at 72°C for 5 min. PCR products were electrophoresed on 2.0% agarose gel and purified with Wizard® SV Gel and PCR Clean-up System (Promega, WI, USA). BigDye Terminator v3.1 Cycle Sequencing kit (Thermo Scientific, USA) was used for terminator cycling sequencing reactions for Sanger sequencing of purified PCR products on the 3730xl DNA Analyzer (Thermo Fisher Scientific, USA).

Discussion

Herein, we reported a pediatric case of spindle cell sarcoma with KIAA1549-BRAF resembling IFS morphologically. Although the present case was initially diagnosed with IFS morphologically, a comprehensive genomic profiling with NGS led to a more precise diagnosis. Because sarcomas in pediatrics are rare and heterogenous, the elucidation of genomic profiling in pediatric sarcomas using NGS can contribute to an appropriate diagnosis and targetable therapies.

The characteristics of BRAF-altered spindle cell sarcomas resembling IFS morphologically are not well understood (10,11,15-18). To identify the clinical characteristics of BRAF-altered spindle cell sarcomas resembling IFS morphologically, we conducted a literature search of all reports. A literature search of all reports was conducted. The following keywords were used in the electronic databases PubMed with no date of publication limitations: ‘infantile fibrosarcoma’ OR ‘spindle cell sarcoma’ OR ‘spindle cell neoplasm’ combined with ‘BRAF’. From the titles and abstracts, we excluded non-English language studies, meeting presentations, and commentaries. The article titles, abstracts, and full papers were examined, and the reports not containing BRAF-altered IFS, spindle cell sarcoma, or spindle cell neoplasm were excluded. URL was as follows: https://pubmed.ncbi.nlm.nih.gov/?term=((infantile%20fibrosarcoma)%20OR%20(spindle%20cell%20sarcoma)%20OR%20(spindle%20cell%20neoplasm))%20AND%20(BRAF)&sort=date

We identified 24 cases of spindle cell sarcoma with BRAF-rearrangement or mutation. The median age at diagnosis was 5.5 months (range: 0-69 years). Seven of 24 cases (30%) were diagnosed over 2 years of age and in three cases over 20 years of age. The most common site of tumors was extremities (6 cases, 25%). Immunohistochemical identification of expression of CD34 was observed in 8 (47%) cases, S-100 in 4 (21%) cases, and SMA in 6 (40%) cases. The expression of pan-Trk was present in one (9.0%) case. BRAF-rearrangements, including fusions of BRAF kinase domain, were detected in 17 cases (68%). The fusions were as follows: KIAA1549-BRAF, AGAP3-BRAF, CUX1-BRAF, DAAM1-BRAF, EPB41L2-BRAF, MCC-BRAF, NPF1-BRAF, OSBP-BRAF, PDE10A-BRAF, SEPT7-BRAF, TEX4-BRAF, FOXN3-BRAF, and TRIP11-BRAF (10,11,15-18). KIAA1549-BRAF fusion was detected in two cases in our case (10,19). BRAF point mutations were present in four cases and BRAF-intrernal duplication (ID) in three cases (10,16,17). One case contained BRAF point mutation and BRAF-rearrangement. The identification of ETV6-NTRK3 transcript was performed in 12 cases by FISH for ETV6 or whole genome sequencing. In two cases, ETV6-NTRK3 fusion and BRAF-ID coexisted (17). One case harbored two distinct BRAF fusions (FOXN3-BRAF and TRIP11-BRAF) (10). Three of 13 cases (23%) had metastasis at diagnosis. All the three cases occurred in adults and were refractory to the conventional chemotherapy. Median follow-up period was 10 months (360 months) and 2 patients (8%) died of disease. In our review of BRAF-altered spindle cell sarcomas resembling IFS morphologically, most cases occurred in younger children under the age of 2 years, showed nonspecific patterns of immunohistochemistry staining, and harbored a BRAF fusion. These results were consistent with our case.

KIAA1549-BRAF fusion is considered as a recurrent oncogenic driver in pilocytic astrocytoma (19). KIAA1549-BRAF fusion leads to loss of N-terminal regulatory domain of BRAF and subsequent activation of the kinase domain, thereby resulting in constitutive activation of BRAF (20). Although different fusion variants were identified in KIAA1549-BRAF, the transcript detected in our case was composed of KIAA1549 exon 10 fused to BRAF exon 9 and contained the intact BRAF kinase domain. Trametinib, a MEK inhibitor has recently been demonstrated to be effective in low-grade glioma with BRAF fusions including KIAA1549-BRAF (21,22). Subbiah et al (15) reported the effectiveness of the combination therapy of sorafenib, temsirolimus, and bevacizumab for a spindle cell sarcoma with KIAA1549-BRAF, which was refractory to the conventional chemotherapies. Because of limited data, further studies are needed to determine the effectiveness of BRAF-targeted therapy including MEK inhibitor for BRAF-altered spindle cell sarcomas morphologically resembling IFS.

In conclusion, we report a pediatric case of spindle cell sarcoma with KIAA1549-BRAF morphologically resembling IFS. The elucidation of genomic profiling by NGS may assist us in making an appropriate diagnosis and selecting new therapeutic options for ETV6-NTRK3 negative spindle cell sarcomas morphologically resembling IFS.

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Availability of data and materials

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

Authors’ contributions

TF, SU, MY, DH and YK participated in the conception and design of the study. MY, SH, AK, AS, KK, TI, AU, KM, TH, MK, and TS were involved in the analysis and interpretation of the data for the pathological diagnosis. MY, TM, AT, NY, MK and TS were involved in the analysis and interpretation of data for comprehensive genomic profiling using NGS. AU, KM and TH performed surgery. MY and MK performed the
histological examination of the tumors. TF and SU drafted the initial manuscript. TF, SU, MY, KK, MK, DH and YK critically revised the article for important intellectual content. TH, TS, DH and YK confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Kobe Children's Hospital (R3-62; Kobe, Japan). Written informed consent was obtained from the patient's parents.

Patient consent for publication

The patient's parents provided written informed consent for the publication of any associated data.

Competing interests

The authors declare that they have no competing interests.

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