REPRINTED FROM FEBRUARY 2026

CAP TODAY

WHERE THE WORLD OF THE CLINICAL LABORATORY COMES TOGETHER

NTRK1-rearranged spindle cell sarcoma in an unusual location: molecular confirmation resolving a high-grade pediatric sarcoma differential

CAP TODAY and the Association for Molecular Pathology have teamed up to bring molecular case reports to CAP TODAY readers. AMP members write the reports using clinical cases from their own practices that show molecular testing's important role in diagnosis, prognosis, and treatment. The following report comes from Westchester Medical Center/New York Medical College. If you would like to submit a case report, please send an email to the AMP at amp@amp.org. For more information about the AMP and all previously published case reports, visit www.amp.org.

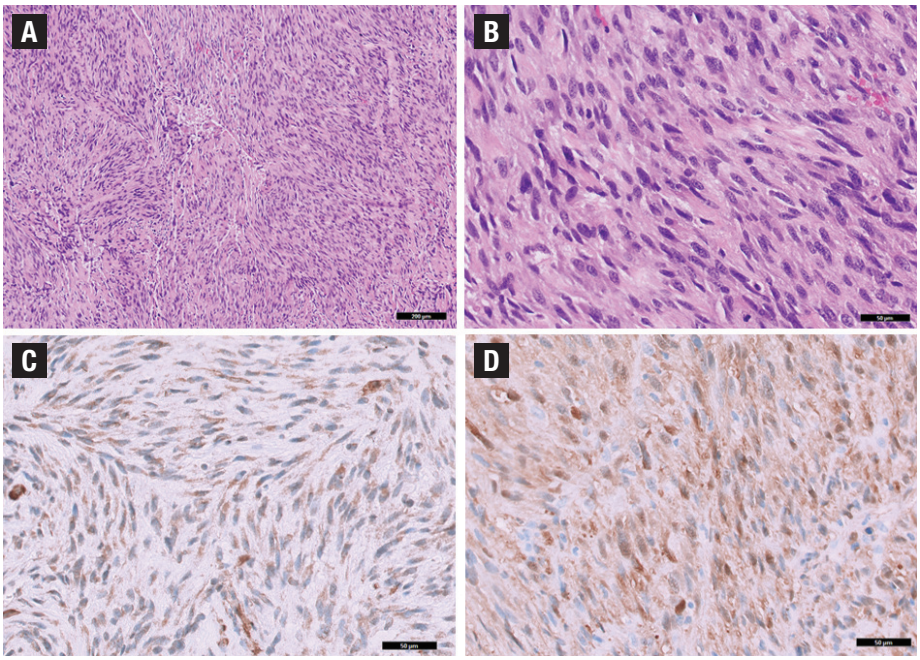
Haiyan Qiu, MD, PhD
Kotaro Takeda, MD, PhD

We report the case of a six-year-old boy with no significant past medical history who presented with a two-month history of intermittent left flank and abdominal pain. Initial abdominal radiography performed by his primary care provider demonstrated a moderate stool burden, and the patient was started on a two-week course of polyethylene glycol with minimal relief. Five days prior to admission, he developed daily tactile fevers, one episode of non-bloody, non-bilious emesis, and non-bloody diarrhea. Two days before presentation, the abdominal pain acutely worsened, became diffuse, and was associated with decreased oral intake, fatigue, and occasional night sweats.

The patient initially presented to the emergency department, where magnetic resonance imaging of the abdomen revealed small-volume free pelvic fluid without evidence of appendicitis. Subsequent review identified a partially visualized left pleural effusion, prompting dedicated chest imaging. Computed tomography of the chest demonstrated a bulky, lobulated, heterogeneously enhancing left posterior mediastinal mass measuring 7.7×8.0×8.7 cm (AP×TV×CC), crossing the midline and causing rightward mediastinal shift, without associated hilar or axillary lymphadenopathy. The thyroid was unremarkable.

Biopsy of the mediastinal mass revealed a highly cellular spindle cell neoplasm composed of uniform primitive spindle cells arranged in intersecting fascicles with hemangiopericytoma-like vasculature (**Fig. 1A** and **1B**). Brisk mitotic activity and focal

Fig. 1. Histologic and immunohistochemical features of the mediastinal mass



A) Low-power view showing a highly cellular spindle cell neoplasm arranged in intersecting fascicles with hemangiopericytoma-like vasculature (H&E, ×40). **B)** High-power view highlighting uniform spindle cells with scant cytoplasm and elongated nuclei (H&E, ×200). **C)** Diffuse cytoplasmic positivity for smooth muscle actin in tumor cells (IHC, ×200). **D)** Nuclear and cytoplasmic positivity for S100 in tumor cells (IHC, ×200).

necrosis were present. Immunohistochemistry demonstrated diffuse cytoplasmic smooth muscle actin positivity (**Fig. 1C**) and nuclear/cytoplasmic S100 expression (**Fig. 1D**), with negativity for cytokeratin, desmin, CD45, CD34, and p16 (not shown). The Ki-67 proliferation index was approximately 40 percent.

The morphologic and immunophenotypic features favored infantile fibrosarcoma (IFS), but the patient's age, tumor location, and marker profile prompted consideration also of malignant peripheral nerve sheath tumor, synovial sarcoma, and spindle cell rhabdomyosarcoma. IFS is most commonly driven by *ETV6::NTRK3* fusions; by contrast, *NTRK1* fusions are relatively rare in the pediatric IFS spectrum and broader pediatric mesenchymal tumors, underscoring the value of directed testing in diagnostically ambiguous cases.[1,2]

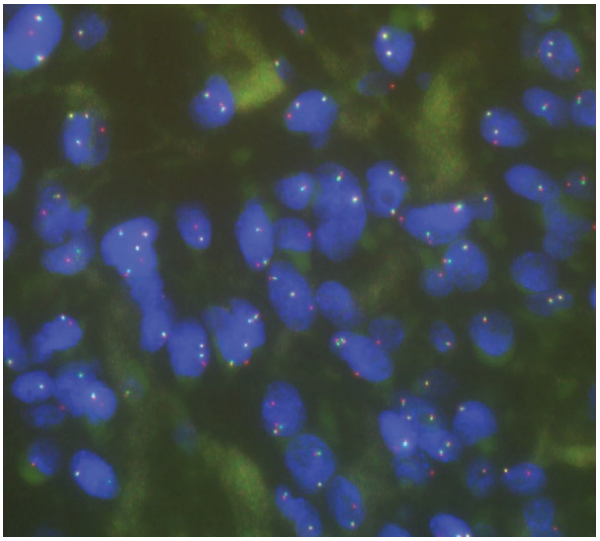
Given the diagnostic uncertainty, fluorescence in situ hybridization for *NTRK* gene rearrangements demonstrated separation of red and green signals consistent with an *NTRK1* rearrangement (**Fig. 2**). This established the diagnosis of *NTRK1*-rearranged spindle cell sarcoma, IFS-like—an entity now recognized within the spectrum of kinase fusion-driven spindle cell neoplasms.[3,4] Although RNA-based fusion testing was not available, targeted DNA-based next-generation sequencing using the genomic sequencing panel on the Illumina MiSeq identified an in-frame *TPR::NTRK1* fusion (*TPR* exon 10, NM_003292; *NTRK1* exon 10, NM_002529), providing molecular confirmation of the FISH finding.

NTRK-rearranged spindle cell neoplasms frequently show S100 expression with variable coexpression of myoid or CD34 markers and often feature hemangiopericytoma-like vasculature and stromal hyalinization, aligning with our histology and IHC pattern.[5] While most *NTRK* fusions in IFS are *ETV6::NTRK3*, several series highlight the relative scarcity of *NTRK1* fusions in pediatric mesenchymal tumors, including IFS-like lesions.[1,2]

Clinically, identification of an *NTRK* fusion is therapeutically actionable. TRK inhibitors such as larotrectinib and entrectinib have demonstrated high response rates across tumor types and ages, including children, with durable benefit in pooled analyses and basket trials. This supports consideration of targeted therapy in advanced or unresectable disease settings.[6–8]

In conclusion, this case highlights the critical role of molecular testing in resolving morphologically ambiguous pediatric spindle cell sarcomas, particularly when arising in unusual anatomic locations such as the posterior mediastinum. The identification of an *NTRK1* rearrangement not only confirmed the diagnosis and excluded morphologic mimics but also uncovered a targetable alteration with potential implications for future therapy. Contemporary guidelines and reviews emphasize broad fusion testing in pediatric spindle cell tumors with overlapping histology or atypical presentations.[1–5] □

Fig. 2. *NTRK1* rearrangement by fluorescence in situ hybridization



Break-apart FISH using dual-color probes demonstrates separation of red and green signals in tumor cell nuclei, consistent with *NTRK1* gene rearrangement (×1,000, oil immersion). An abnormal FISH result of ≥1R, 0G, ≥1F (62.0 percent of nuclei, normal cutoff 16.2 percent), consistent with deletion of the 5′ region of NTRK1 and suggestive of an *NTRK1* rearrangement.

1. Kang J, Park JW, Won JK, et al. Clinicopathological findings of pediatric *NTRK* fusion mesenchymal tumors. *Diagn Pathol*. 2020;15(1):114.

2. Tauziède-Espariat A, Duchesne M, Baud J, et al. NTRK-rearranged spindle cell neoplasms are ubiquitous tumors of myofibroblastic lineage with a distinct methylation class. *Histopathol*. 2023;82[4]:596–607.

3. Sbaraglia M, Bellan E, Dei Tos AP. TRK-rearranged spindle cell neoplasm (emerging). In: WHO Classification of Tumours Editorial Board, eds. *Soft Tissue and Bone Tumours*. Vol. 3. IARC Press; 2020:287–289. *WHO Classification of Tumours*; 5th ed.

4. Suurmeijer AJH, Dickson BC, Swanson D, et al. A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes. *Genes Chromosomes Cancer*. 2018;57(12):611–621.

5. Brčić I, Godschachner TM, Bergovec M, et al. Broadening the spectrum of *NTRK* rearranged mesenchymal tumors and usefulness of pan-TRK immunohistochemistry for identification of *NTRK* fusions. *Mod Pathol*. 2021;34(2):396–407.

6. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in *TRK* fusion–positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731–739.

7. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731–747.

8. Rosa K. FDA expands entrectinib indication in pediatric patients with NTRK+ solid tumors. OncLive. Oct. 20, 2023.

Dr. Qiu is a pathology resident and Dr. Takeda is attending pathologist—both in the Department of Pathology, Westchester Medical Center and New York Medical College.

See 'Test yourself' questions, next page.

Test yourself

Here are three questions taken from the case report. Answers are online now at www.amp.org/casereports *and will be published next month in* CAP TODAY.

1. Which of the following statements is most accurate regarding the infantile fibrosarcoma-spectrum tumor?

a. *NTRK1* rearrangements are the most common genetic event in infantile fibrosarcoma.
b. These tumors typically lack targetable molecular alterations.
c. Mediastinal location is uncommon for this tumor type.
d. The immunophenotype usually includes strong desmin positivity.

2. Which histologic and immunohistochemical profile is most characteristic of *NTRK*-rearranged spindle cell sarcoma?

a. Spindle cells in fascicles, hemangiopericytoma-like vasculature, S100 and SMA coexpression.
b. Epithelioid cells with abundant eosinophilic cytoplasm, keratin positivity.
c. Storiform spindle cell proliferation, CD34 positivity only.
d. Primitive small round cells, CD99 and FLI1 positivity.

3. Which of the following statements regarding the clinical implications of detecting an *NTRK1* rearrangement in a pediatric spindle cell sarcoma is true?

a. The finding has diagnostic value only and no therapeutic relevance.
b. TRK inhibitors have shown high response rates in both pediatric and adult *NTRK*-fusion tumors.
c. *NTRK1* fusions are present in more than 50 percent of pediatric sarcomas.
d. Identification of the fusion rules out malignant potential.