Rare orbital tumor in a child: diagnostic and therapeutic challenge

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Patient’s history

- 9 years-old girl
- redness inner canthus left eye
- corneal trauma eight months earlier
- limitation of mobility of the left eye
- closed left eyelid palpation revealed induration of nasal quadrant
Clinical suspicion of rhabdomyosarcoma

Left intraorbital mass (24mm)

*Surgical biopsy* was performed

*In sano* resection was not possible
Spindle cells
Mild/moderate atypia
Rare hyperchromasia
Rare mitose
Fibroblastic/myofibroblastic tumor without evidence of high grade malignancy, with a muscular and nervous immunophenotype
SOX10
CD34
ALK1

Pan-NTRK
Clone A7H6R
Cell signaling

negative

SMA
florid fusocellular tumor without evidence of high grade malignancy, with a muscular and nervous immunophenotype, associated with \textit{LMNA-NTRK1} rearrangement.
What is NTRK?

- Neurotrophic tropomyosin-related kinases (NTRK)
- Receptor tyrosine kinase family of neurotrophin receptors involved in neuronal development
- Mainly expressed in the nervous system
- Can be found in multiple tissue types

- 3 TRK family members
  - NTRK1 (TRKA)
  - NTRK2 (TRKB)
  - NTRK3 (TRKC)

Activation of NTRK results into cell proliferation, differentiation and survival
what role NTRK plays in the cancerogenesis process?

- Oncogenic **fusions** involving NTRK = key mechanism of oncogenic TRK activation

- Chimaeric genes in which the 3’ region of the NTRK gene is joined with a 5’ sequence of a fusion partner gene

- Constitutively activation of the MAPK and PI3K/AKT pathways
Where NTRK fusions can be found in practice?

2 groups:

1/ Tumors that are very rare and are defined by a specific NTRK-fusion, often diagnostic (ETV6-NTRK3 fusion)

2/ Many different tumors that are partly very common but harbor NTRK fusion very rarely

- Both in adults and children

- NTRK fusion genes are mutually exclusive with other mitogenic drivers like KRAS, NRAS and BRAF.
Where NTRK fusions can be found in practice?

- Also recently in adult and pediatric soft tissue tumors

Original Article

Recurrent NTRK1 Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors

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Original Article

Expanding the Spectrum of Pediatric NTRK-rearranged Mesenchymal Tumors

Jessica L. Davis, MD,*† Christina M. Lockwood, PhD,‡ Bradley Stohr, MD, PhD,† Carolin Boecking, MD,† Alyaa Al-Ibraheemi, MD,§ Steven G. DuBois, MD,∥ Sara O. Vargas, MD,§ Jennifer O. Black, MD,¶ Michael C. Cox, PharmD,# Mark Luquette, MD,** Brian Turpin, DO,†† Sara Szabo, MD,‡‡ Theodore W. Laetsch, MD,§§ Catherine M. Albert, MD,¶¶ David M. Parham, MD,¶¶ Douglas S. Hawkins, MD,¶¶ and Erin R. Rudzinski, MD##

Am J Surg Pathol, 2019
Variable morphologic features

- Haphazardly arranged primitive mesenchymal cells in a variably myxoid stroma
- Spindled cells arranged in fascicles
- Infiltrative/fibromatosis-like growth
- Fascicular/herringbone growth
-...

- Monomorphic population of cells with plump oval to elongated nuclei
- Minimal to mild pleomorphism

Immunohistochemistry

- Variable expression of S100, SMA, CD34 and CD30
- panTRK 100% positive
How should NTRK fusions be investigated in practice?

In situ assays

In vitro nucleic acid-based assays

1. IHC
2. FISH
3. RT-PCR
4. RNA next-generation sequencing
5. DNA next-generation sequencing

Complexity Costs
How should NTRK fusions be investigated in practice?

1. IHC
   - Highest availability
   - Rapid
   - Relatively inexpensive
   - Easy to establish

1. panTRK antibody
   - Sensitivity 75-97%
   - Specificity 95-100%

2. Specific TRK antibodies
How should NTRK fusions be investigated in practice?

2. FISH

- Fusion or break-apart probes
- Very effective at identifying the presence of the ETV6-NTRK3 fusion gene in the tumour types where it is prevalent
### 3. RNA next-generation sequencing assays

- Approach for detection of fusion genes that are transcribed

**BUT**

- RNA quality assessment is a crucial step (false negative) in FFPE samples

### 4. Next-generation DNA sequencing assays

Some of the commercially available targeted sequencing panels offer the possibility to detect fusion genes

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**How should NTRK fusions be investigated in practice?**
How should NTRK fusions be investigated in practice?

ESMO recommendations for NTRK fusion investigation

1. Sample to be investigated for the presence of NTRK fusions
   - As a confirmatory technique, use FISH, RT-PCR or targeted RNA NGS assays with specific probes for the fusion involving the known NTRK gene
   - Is the histologic tumour type known to harbour highly recurrent NTRK fusions?
     - YES
     - NO*

   2. Is there a sequencing platform available?
     - NO
     - YES
       - Use front line NGS reliably detecting NTRK fusions, preferably including RNA testing when possible

   - NO TRK expression
   - Detection of TRK expression

Annals of Oncology, Marchio C et al. 2019
Why should NTRK anomalies be investigated?

**NTRK1/2/3 gene fusions = new targets for cancer therapy**

- successfully inhibited by targeted kinase inhibitors
- responses irrespective of the 5’ gene partner
- in a “age- and histology-agnostic” fashion

• Multi-kinase inhibitors (activity against a range of target including TRK)
• More selective TRK inhibitors (Larotrectinib, Entrectinib)

• Acquired resistance to TRK inhibition have been described
  – Next-generation TRK inhibitors to overcome acquired resistance to first generation TKI are already in development
Consequences to NTRK inhibition

Selective TRK inhibitors have favourable overall safety profile.
When should NTRK fusions be investigated in practice?

- There is no clear indication of which patients should be tested for NTRK fusion, and NTRK fusion should be considered in a wide patient population.
- Systematic analyses of large cohorts of metastatic cancer patients for the presence of NTRK1/2/3 fusion genes across cancer types have yet to be carried out.
- Phenotypic features of cancers harboring NTRK1/2/3 fusion genes have to be fully characterised.
- Some guidelines on non small cell lung cancer have already included a recommendation for NTRK gene fusion testing in patient with metastatic disease.
• The population to be tested should be represented by «any malignancy at an advanced stage, in particular if it has been proven wild type for other known genetic alterations tested in routine practice, and especially if diagnosed in young patient»
Our patient’s clinical evolution

- the tumor was not surgically resectable *in sano*
- Currently treated in Paris (Curie institute) with a NTRK inhibitor.
- The last news: totally reduction of the tumor.
Thank you for your attention