Case 4.

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• A mass of the left thigh in a fetus detected on US exam in the 13th week of pregnancy

• A FTD boy born in Feb 2012 (cesarean section), deep-seated tumor 60x76x125 mm involving soft tissues from the dorsal and medial sides, extending from the pre-trochlear region to the proximal tibia. No infiltration of bone and big blood vessels
Biopsy 2012

• Cellular-rich spindle cell tumor with infiltrative diffuse and whorly pattern of growth; low mitotic activity. IHC: CD34 focal +, SMA focal +, CD99 focal+, Ki67 up to 10%, Desmin(-), MyoD1 (-), S100(-)
The first diagnosis - Infantile Fibrosarcoma
Consultations

• 1) Infantile fibromatosis / myofibromatosis

• 2) Molecular genetic analysis did not show a break in the *ETV-6* gene (*ETV-NTRK3*) (lack of t(12; 15) (p13;q25).

**Diagnosis** ➔ **Infantile fibromatosis, diffuse type.**

• Chemotherapy Feb - July 2012: 6 VAC courses (CWS 2006)

• Tumor volume stable

• Sub-total tumor resection
Histopathology 2012

- Low grade spindle cell lesion, collagen production. Immunophenotype the same as in a chemonaive tumor.
Immunohistochemistry

- SMA
- Beta catenin
- CD99
- Desmin, S100, MyoD1, CD117
- CD34
Continuation of the chemotherapy

- Vinblastin + Methotrexate (Sep 2012 - April 2013) – Methotrexat, Vinblastine; residual **tumor stabilization for 4.5 years**
January 2018

Slow regrowth of the tumor since two months before admission; heterogenous mass 104 x 81 x 95 mm
Biopsy 2018

• Highly cellular tumor made of small and medium-sized epithelioid cells with prominent mitotic activity and necrotic foci. Immunophenotype: SMA focal+, S100+, CD34+, PGP9.5(-), NSE(-), SOX10(-), Ki67 up to 25%

• The diagnosis ➔ **Fibromatosis with signs of atypization**

Recommendation for a wide genomic analysis of the tumor tissue
Gross-total tumor resection

- April 2018
- The densely cellular, heterogenous tumor with high mitotic activity, fields of atypization, spindle and epithelioid cells, fields of fibrosarcoma pattern; collagen production. Multifocal necrosis, also geographic
- Immunophenotype: strong S100 positivity, in part loss of CD34 expression, SMA very low
Final diagnosis

• The genetic study (Illumina; Archer Dx) ➔ **TMP3-NTRK1** fusion

• Histological picture + clinical history + results of a genetic study = diagnosis of:

**Aggressive Lipofibromatosis-like Neural Tumor**

Therapy 2018/2019

- Multicenter consultations in Europe and US on optimal therapeutic approach; because of localized stage and subtotal tumor resection, observation was suggested (May 2018)

- July 2018- local progression of the disease and lung metastases. Chemotherapy- VAC, CEV

- August 2018 - the boy was enrolled in the phase I/II trial LOXO-TRK-15003, started LOXO-101 ➔ partial local and lung response Nov 2018.

- CT of the lungs 01.2019 - one lung lesion progressive, whereby all others are more or less stable.
Progressing lung metastasis

• Biopsy for molecular analysis and resistance mutations

• *TPM3 (7)-NTRK1(10)* fusion

• *NTRK1 G595R* acquired solvent front resistance mutation (decreases binding of LOXO-101)

• New drug LOXO-195 administration with increasing doses (since three months local progression and pulmonary dissemination)
Pulmonary metastasis
Lipofibromatosis-like neural tumor

- Infantile / congenital- single cases (altogether 20)
- Highly infiltrative, cellular, primitive ovoid- spindle cell low grade lesions, collagenous or myxoid stroma
- No consistent IHC: variable expression CD34, S100, SMA, (CD30)
- Differential diagnosis: Congenital Infantile Fibrosarcoma (CIFS), Myofibroma/ Myofibromatosis group of tumors, Infantile Fibromatosis / Lipofibromatosis, Spindle cell RMS; DFSP

- Fusions: \textit{LMNA-NTRK1; TPM3-NTRK1;} \textit{(EML4-NTRK3)}
- \textit{TRK immunoreactivity}

- Conception/ nomenclature:
  - NTRK-associated mesenchymal tumors
  - NTRK- fusion sarcomas (together with CIFS \textit{(ETV-NTRK3)})
**TMP3-NTRK1 fusion**

- Chromosome 1
  - Close-up, normal
  - Inversion
  - Deletion
  - q21.3
  - q23.3

- Fusion by inversion:
  - TPM3
  - 3' end of TPM3
  - LMNA
  - 5' end of NTRK1
  - NTRK1
  - Fusion by removal:
    - LMNA-NTRK1
    - Cut out section
    - Fuse ends
    - Removed

- Genes involved:
  - TPM3
  - NTRK1
  - LMNA

- Chromosome 12 and 15:
  - der(12)
  - der(15)
  - NTRK3
  - 12 (der)
  - 15 (der)
TRK fusions are rare but recurrent oncogenic drivers in a variety of adult and pediatric cancers

- Beyond the embryo, tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC are primarily limited to the nervous system
  - TRK is uncommonly expressed in normal tissues
- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers
References:

- Infantile NTRK-associated Mesenchymal Tumors. Davis JL et al. , Pediatr Dev Pathol. 2018
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- Fibroblastic and myofibroblastic tumors of children: new genetic entities and new ancillary testing. Parham DM; F1000Res. 2018