Wolf in sheep’s clothing and vice versa?

Jean-Michel Coindre - Institut Bergonié - Bordeaux France
Case 5
Case 5
Clinical information

- 6 day-old girl
- Tumor of the thigh
- Involving muscles and subcutaneous fat
- 30 mm in size.
Case 5 – Proposal diagnosis

Juvenile fibromatosis
Lipofibromatosis type
Case 5 - Immunohistochemistry

- SMA
- H-Caldesmon
- S100 protein
- CD34
- Pan TRK
- Desmin
- Myogenin
Case 5

**Molecular analysis - Full RNA sequencing**

*VGLL2-NCOA2* gene fusion

**Final diagnosis**

Congenital spindle cell rhabdomyosarcoma with a *VGLL2-NCOA2* gene fusion
Spindle cell rhabdomyosarcoma
(WHO 2013)

- Rare subtype (5 – 10% of RMS)
- M>>F (6:1)
- Children – mainly paratesticular
  Good prognosis
- Adult – mainly head and neck
  Poor prognosis
- Sclerosing subtype– mainly extremities
Recent advances on rhabdomyosarcoma

- Spindle cell RMS with mutation of $MYOD1$
- Spindle cell RMS with $NCOA2 / VGLL2$ gene fusion
- Spindle cell RMS with no recurrent molecular lesion
Recurrent NCOA2 Gene Rearrangements in Congenital/Infantile Spindle Cell Rhabdomyosarcoma

Juan Miguel Mosquera,\textsuperscript{1,} Andrea Sboner,\textsuperscript{1,} Lei Zhang,\textsuperscript{2} Naoki Kitabayashi,\textsuperscript{1} Chun-Liang Chen,\textsuperscript{3} Yun Shao Sung,\textsuperscript{3} Leonard H. Wexler,\textsuperscript{4} Michael P. LaQuaglia,\textsuperscript{5} Morris Edelman,\textsuperscript{6} Chandrika Sreekantaiah,\textsuperscript{7} Mark A. Rubin,\textsuperscript{1} and Cristina R. Antonescu\textsuperscript{3,}\textsuperscript{8}

A Molecular Study of Pediatric Spindle and Sclerosing Rhabdomyosarcoma

Identification of Novel and Recurrent VGLL2-related Fusions in Infantile Cases

Rita Alaggio, MD,\textsuperscript{*} Lei Zhang, MD,\textsuperscript{†} Yun-Shao Sung, MSc,\textsuperscript{†} Shih-Chiang Huang, MD,\textsuperscript{†} Chun-Liang Chen, MSc,\textsuperscript{†} Gianni Bisogno, MD,\textsuperscript{‡} Angelica Zin, PhD,\textsuperscript{§} Narasimhan P. Agaram, MD,\textsuperscript{†} Michael P. LaQuaglia, MD,\textsuperscript{∥} Leonard H. Wexler, MD,\textsuperscript{¶} and Cristina R. Antonescu, MD\textsuperscript{†}

NCOA2 and VGLL2 in infantile RMS

- VGLL2-CITED, TEAD1-NCOA2, VGLL2-NCOA2
- Children before 5 years
- Spindle cell morphology
- Good prognosis (no death so far)
Transactivating mutation of the MYOD1 gene is a frequent event in adult spindle cell rhabdomyosarcoma

Karoly Szuhai,1* Daniëlle de Jong,1 Wai Yi Leung,2 Christopher DM Fletcher3 and Pancras CW Hogendoorn4

- Exome capture sequencing (NGS) on an adult-type spindle cell RMS
- MYOD1 mutation exon 1 (c.365 T>G, p.L122R)
- Sanger sequencing on 17 other adult cases: 7 (41%) with MYOD1 mutation
Spindle cell RMS with \textit{MYOD1} mutation

- Kohsaka et al. Nat Genet 2014;46:595-600
- In adults and children
- In both spindle cell RMS and sclerosing RMS
- Concurrent \textit{PIK3CA} mutations in \textit{MYOD1}-mutant sclerosing RMS
- \textit{MYOD1}-mutated RMS followed an aggressive clinical course
Case 5 - Differential diagnosis

- Lipofibromatosis
- Lipofibromatosis-like neural tumor
- Dermatofibrosarcoma protuberans
- Fibrous hamartoma of infancy
A Clinicopathologic Study of 45 Pediatric Soft Tissue Tumors With an Admixture of Adipose Tissue and Fibroblastic Elements, and a Proposal for Classification as Lipofibromatosis

John F. Fetsch, M.D., Markku Miettinen, M.D., William B. Laskin, M.D., Michal Michal, M.D., and Franz M. Enzinger, M.D.

- Infantile fibromatosis
- 0 – 12 years (median 1 year)
- 3M / 1F
- Extremities 90% (hand and foot 50%)
- 1 – 7 cm
- Local recurrence 65%
• Abundant adipose tissue (>50%)
• Bland spindle fibroblastic cells
• Involving the septa of fat
• Entrapping vessels and nerves
• IHC: SMA+
  Desmin, CD34, S100 protein, TRK –
Case 5 - Differential diagnosis

- Lipofibromatosis
- Lipofibromatosis-like neural tumor
- Dermatofibrosarcoma protuberans
- Fibrous hamartoma of infancy
14 cases aged 4 to 38 years (median 13.5 y)
Subcutaneous lesions of various locations
Size from 1.3 to 5.4 cm
Local recurrence in 42% (when positive surgical margins)
No metastasis
Histology looks like lipofibromatosis or DFSP
IHC
- S100 and CD34 positive
- SOX10 and melanocytic markers negative
- Pan TRK and NTRK1 positive
Molecular biology
- NTRK1 rearrangement (10/14) with LMNA, TPM3, TPR
- ROS1 rearrangement (1/14)
- ALK rearrangement (1/14)
Potential importance for target treatment
• 6 month old boy
• Scalp tumor
• Initial diagnosis: DFSP
• Case referred for FISH DFSP
Dermatofibrosarcoma Protuberans, Giant Cell Fibroblastoma, and Hybrid Lesions in Children: Clinicopathologic Comparative Analysis of 28 Cases With Molecular Data
A Study From the French Federation of Cancer Centers Sarcoma Group

Marie-Josée Terrier-Lacombe, M.D., Louis Guillou, M.D., Georges Maire, M.Sc., Philippe Terrier, M.D., Dominique Ranchère Vince, M.D., Nicolas de Saint Aubain Somerhausen, M.D., Françoise Collin, M.D., Florence Pedeutour, Pharm.D., Ph.D., and Jean-Michel Coindre, M.D.

**DFSP in children**
- 2% of cases in the French sarcoma network (<15 years)
- 3/1000 neonatal
- Mainly trunk
Fibrous hamartoma of infancy: a clinicopathologic study of 145 cases, including 2 with sarcomatous features


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- 2M/1F
- 0 - 14 years (mean 15 months)
- Site: axilla, back, upper arm, scrotum (50%)
- Subcutaneous mass, .4 – 17 cm (mean 3 cm)
- Local recurrence < 5%, no metastasis
- IHC: SMA, CD34


_EGFR_ exon 20 insertion/duplication mutations
Case 5 – Take-home messages

- Importance of diagnosing RMS (Treatment – chemotherapy)
- Importance of subtyping RMS (Prognosis)
- IHC for diagnosis and molecular analysis for subtyping
- RNA sequencing for selected cases of children mesenchymal tumors