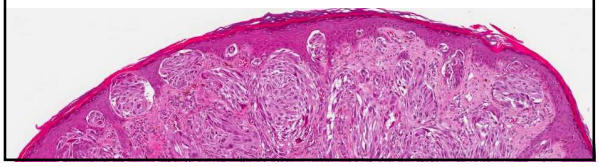
FISH in Spitz Nävi. Ein ungelöstes Problem

L. Mazzucchelli
Istituto cantonale di patologia,
Locarno, Schweiz

5. FISH-Anwenderforum 2011, Wiesbaden-Delkenheim



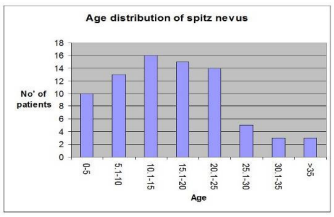
Spitz nevus

- Until the late 1940s, Spitz nevus was commonly diagnosed as melanoma
- The original termed used by S. Spitz was „juvenile melanoma“
- A variety of other names have been proposed (spindled and epitheloid cell nevus)
- Spitz nevus came into use in the late 1960

Spitz S. Melanomas of childhood. Am J Pathol 1948, 24:591-609

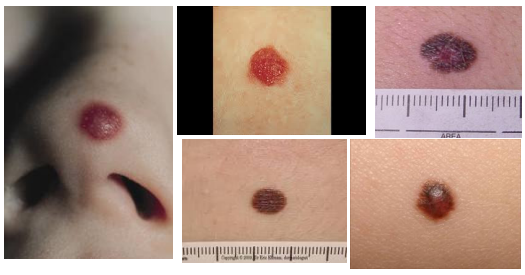
Spiz nevus

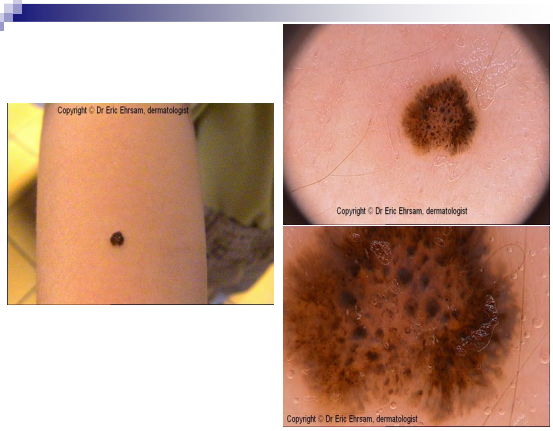
- Mainly in caucasian
- Most Spitz nevi are diagnosed in childhood and adolescence
- No marked sex preponderance (female>male?)



Site	All skin and some mucous membranes; preferred site are face, ear in childhood; extremities and trunk in adulthood
Size	Generally under 1 cm, but exceptional reported cases up to several centimeters
Shape	Symmetrical, papillomatous or smooth dome shaped
Color	Skin colored, reddish or light brown; rarely dark brown
Variants	Multiple, pruritic, combined with congenital nevus

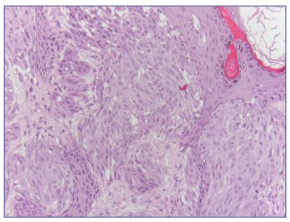
Pathology of Melanocytic disorders. WJ Mooi and T Krausz 2nd edition





Histological features

- Symmetrical
- Proliferation of large epitheloid or sipndle shaped melanocytes
- Spindel cells tend to be vertically oriented
- Shrinkage artifacts with clefts between the cells and around the cells
- Infiltrative growth at the base
- Kamino bodies
- Associated epidermal hyperplasia



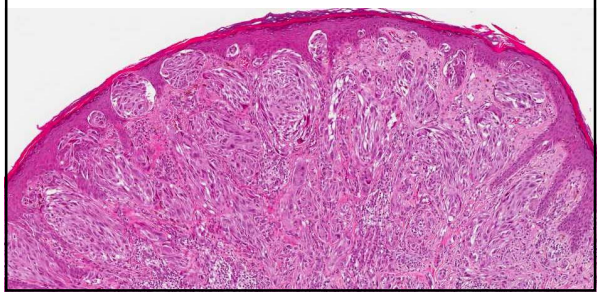
Spitz Nevus/Tumor and variants

- Spitz nevus: junctional, compound, dermal
- Desmoplastic Spitz nevus
- Pigmented spindle cell nevus
- Plexiform pigmented spindle cell nevus
- Spitz nevus, halo variant
- Recurrent Spitz nevus
- Spitz tumor with atypical features
  - **Pagetoid Spitz nevus/tumor**
  - **Spitz nevus/tumor with architectural disorder and cytologic atypia**
- Spitz nevus/tumor with atypical features and indeterminate biological potential (STUMP „Spitzoid tumor of uncertain malignant potential")
- „Spitzoid melanoma"

Adv Anat Pathol 2010, 17:73

„Among the melanocytic lesions we receive in consultation, over half concern the differential diagnosis of Spitz Nevus versus Melanoma"

Pathology of Melanocytic disorders. WJ Mooi and T Krausz 2nd edition



Special techniques

Immunohistochemistry	Molecular biology	DNA gain/loss
HMB-45	BRAF	Aneuploidy
Ki67 (MIB1)	H-RAS	CGH
P53	N-RAS	FISH
p16		
E-Cadherin		
Cyclin D1		

Immunohistochemical Evaluation of p16^{INK4A}, E-Cadherin, and Cyclin D1 Expression in Melanoma and Spitz Tumors

Evan George, MD,[1] Nayak L. Polissar, PhD,[2] and Mark Wick, MD[3]

Am J Clin Pathol 2010, 133:370-379

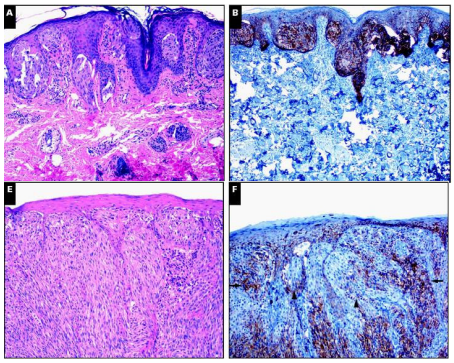
RESULTS

Cyclin D1:	no statistical significant differences
E-Cadherin:	subtle and focal qualitative differences
p16:	dermal p16 was the best discriminator

E-Cadherin

Spitz

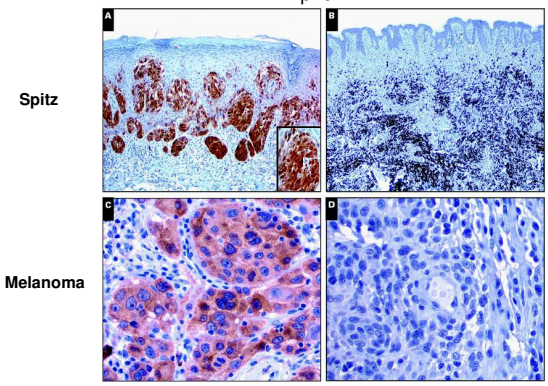
Melanoma

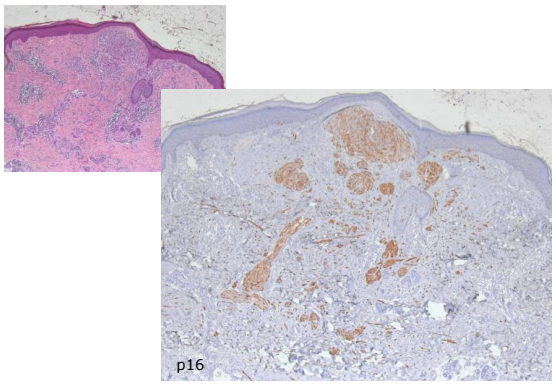


p16

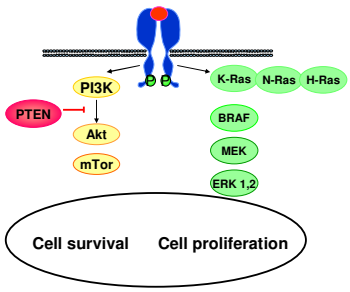
Spitz

Melanoma





Molecular biology

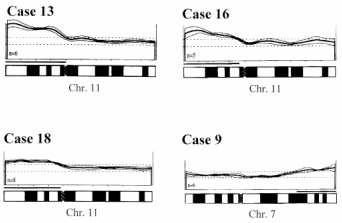


Frequencies of mutations

Lesion Type	BRAF	NRAS	HRAS
Common acquired nevus	Up to 87%	0?	0
Dysplastic or atypical nevus	52-62%	Up to 71%	0
Blue nevus	0-12%	0	ND
Spitz nevus	0	0	Up to 29%
Congenital nevus	30-88%	64%	0

Blokx WAM. Histopathology 2010, 56:121-132

Chromosomal gains or losses



Copy number increas of 11p in 20% Spitz nevi

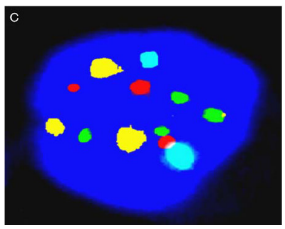
Bastian BC. J Invest dermatol 1999, 113:1065
Bastian BC. Am J pathol 2000, 157:967-972

Chromosomal gains or losses

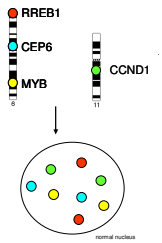
Melanoma subtype	*BRAF* mutation	*NRAS* mutation	Chromosomal aberrations
Skin NCSD	59%	22%	Increased copy no: 6p, 7,8q, 17q, 20q
			Reduced copy no: 9p, 10, 21q
Skin CSD	11%	15%	Increased copy no: 6p, 7,8q, 17q, 20q
			Reduced copy no: 9p, 10, 21q
Mucosal	11%	5%	Increased copy no: 1q, 6p, 7, 8q, 11q13, 17q, 20q
			Reduced copy no: 3q, 4q, 6q, 8p, 9p, 10,11p, 11q, 21q
			Amplification: 1q13, 4q12, 12q14
Acral	23%	10%	Increased copy no: 6p, 7,8q, 17q, 20q
			Reduced copy no: 6q, 9p, 10,11q, 21q
			Amplification: 5p15, 5p13, 11q13, 12q14

Nevus versus Melanoma: to FISH, or not to FISH

Adv Anat Pathol 2011, 18 (May):229



Melanoma FISH assay



FISH REGISTRATION FORM

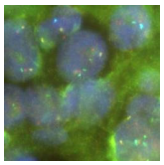
Nucleus	RREB1 signals	MYB signals	CCND1 signals	CEP6
1	3	2	2	2
2	3	2	3	2
3	4	3	3	3
4	4	4	4	4
5	5	3	4	3
6	4	3	5	3
7	3	2	3	2
8	2	1	2	2
9	2	1	1	1
10	3	1	4	1
11	2	2	2	2
12	1	1	2	1
13	2	2	2	2
14	3	3	3	3
15	2	3	2	2
16	2	1	4	2
17	4	3	4	4
18	4	2	2	2
19	4	4	4	4
20	6	3	5	3
21	2	4	3	3
22	3	2	1	2
23	2	2	3	2
24	2	2	3	2
25	1	2	2	2
26	3	2	1	1
27	2	1	1	1
28	4	5	2	2
29	4	3	4	4
30	4	4	3	3

Criteria	Value	Result
Average CCND1 signals per nucleus >2,5	2,63	POSITIVE
Average MYB signals per nucleus >2,5	2,20	negative
Percent loss of MYB relative to CEP6 >31%	20,0%	negative
Percentage of Abnormal nuclei for RREB1 > 63%	66,7%	POSITIVE

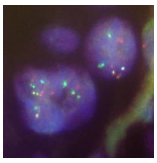
Interpretation
POSITIVE

- 1990-2008 → 82 Spitz nevi
  - Median FU >8 years
  - FISH evaluable in 51 cases

32 (63%) FISH-



19 (37%) FISH+



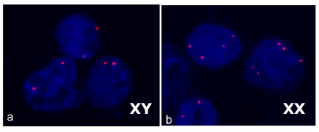
FISH and SPITZ

- In a series of ambiguous cases with long-term clinical follow-up (about five years), Gaiser and colleagues were able to investigate three cases with FISH. One Spitz nevus with a FISH+ status and one Spitz nevus with a FISH- status had a benign follow-up, whereas one FISH- Spitz nevus was found in a patient with malignant evolution
- In a second study, on a large series of 41 definitely diagnosed Spitz nevi with a median follow up of two years, Isaac and colleagues identified a FISH+ profile in four cases (10%), three of which were from the same patient. The authors hypothesised that the FISH+ profile in Spitz nevi reflected a polyploid state rather than true clonal aberrations, as is the case in malignant tumours, and they confirmed and supported this thought by the detection of chromosome X polysomy in all cases

Gaiser T *et al.*. *Mod Pathol.* 2010;23;413-9.
Isaac AK et al *Am J Dermatopathol*. 2010;32;144-8.

19 FISH+ → Test for polysomy

4 POLY- 14 POLY+

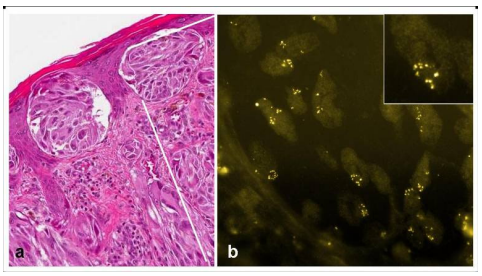


Spitz	FISH- (n=10)		FISH+ (n=18)	
	%	# of patients	%	# of patients
POLY-	100%	10/10	22%	4/18
POLY+	0%	0/10	78%	14/18

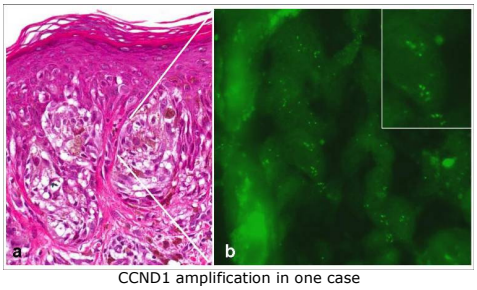
Melanomas (n=12)	FISH-		FISH+	
	%	# of patients	%	# of patients
POLY-	0%	0/12	67%	8/12
POLY+	0%	0/12	33%	4/12

Nevi (n=11)	FISH-		FISH+	
	%	# of patients	%	# of patients
POLY-	100%	11/11	0%	0/11
POLY+	0%	0/11	0%	0/11

Martin V et al: submitted



MYB amplification in one case

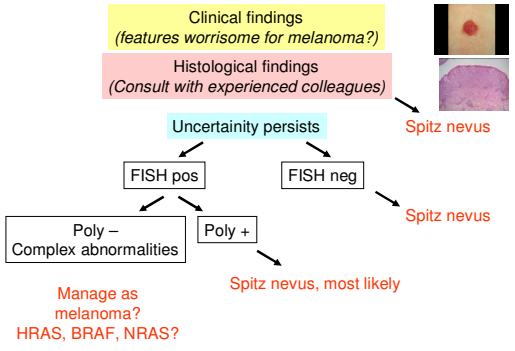


CCND1 amplification in one case

Conclusions

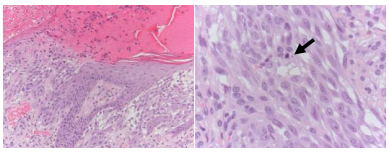
- **The presence of gene copy number changes in Spitz nevi as detected by FISH analysis with probes targeting 6p25, 6q23, CEP 6, and 11q13 is higher than expected**
- **The presence of cytogenetic abnormalities in Spitz nevi may not be solely explained by a polyploid state**
- **FISH- or FISH+/POLY+ Spitz nevi are most likely "true" benign lesions, whereas additional studies are warranted to clarify the biological significance of Spitz nevi bearing gene amplifications or a FISH+/POLY- profile**

Proposal for diagnostic algorithm



Patient 1

- 12 years old boy, scalp, diameter 1 cm

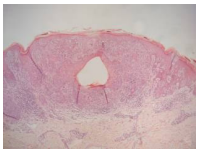

Ulceration > 6 mitoses

FISH neg.

Spitz nevus

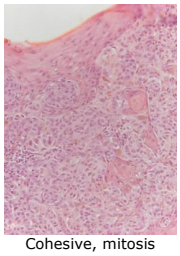
Patient 2

- 29 years old man, right knee, diameter 0,8 cm



FISH pos.

Favor Melanoma



Cohesive, mitosis

Institute of Pathology

Locarno
Switzerland
www.ti.ch/ICP

V. Martin
S. Leoni-Parvex
M. Frattini
A. Camponovo
M. Ghisletta
S. Banfi
L. Lunghi
L. Mazzucchelli

Abbott Corinne Beringer