The International Society of Dermatopathology

17th Summer Academy of Dermatopathology

Childhood, adolescence and young adults melanoma

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Pediatric Melanoma

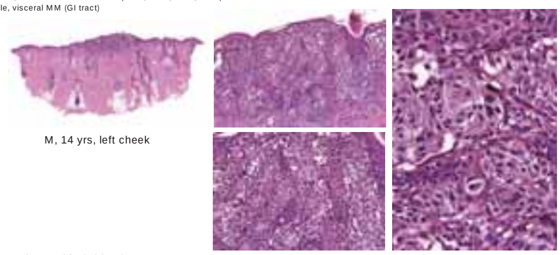
Childhood (≤10 yrs) incidence of 1.6/mln (1% of all cancers)
Adolescence (11-19 yrs) incidence of 8.2/mln (3% of all cancers)

(National Cancer Institute, updated September 8th 2023)

2

Pediatric familial MM

mother, two SSM/Low-CSD MM (1996, 2005)
brother, four SSM/Low-CSD MM (2011, 2013, 2014, 2015)
uncle, visceral MM (GI tract)

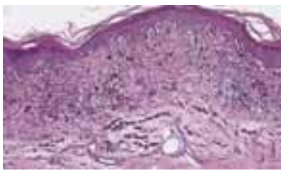


M, 14 yrs, left cheek

patient: c715>C (p-R24P) CDKN2A mut
mother: c715>C (p-R24P) CDKN2A mut
brother: c715>C (p-R24P) CDKN2A mut

3

Pediatric adult-type MM



F, 12 yrs, left thigh

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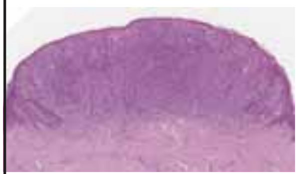
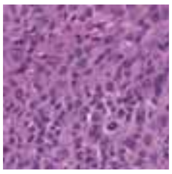
Pediatric Spitz MM





F, 16 yrs, right leg

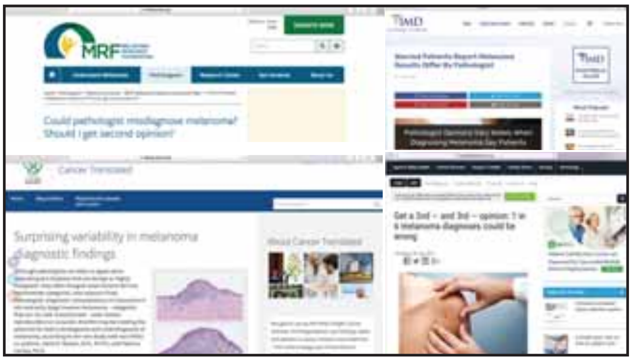
5

Pediatric nevoid MM

pT3aN1a
BRAFV600E mut

M/14 yrs, retroauricular region

6



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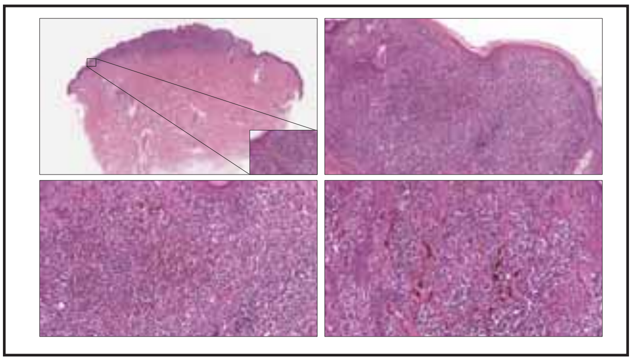
CLINICAL CASE

F, 20 yrs
Pigmented skin lesion on the trunk

8



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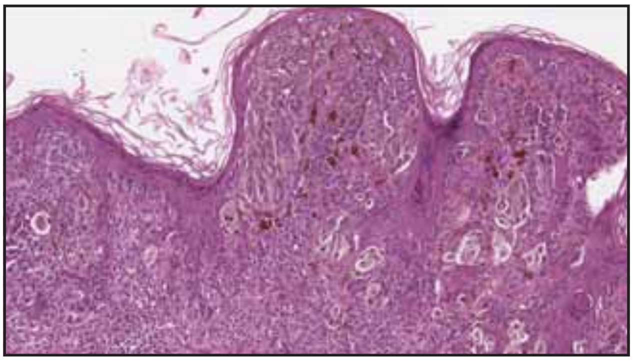

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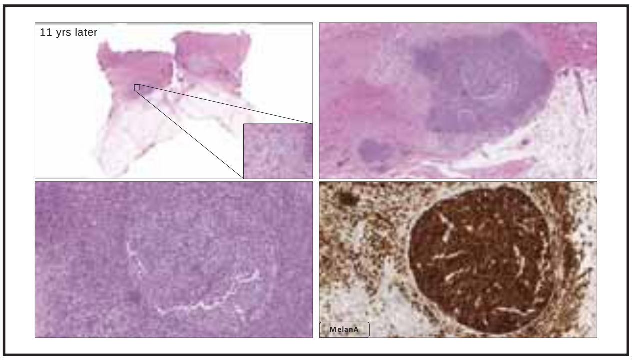

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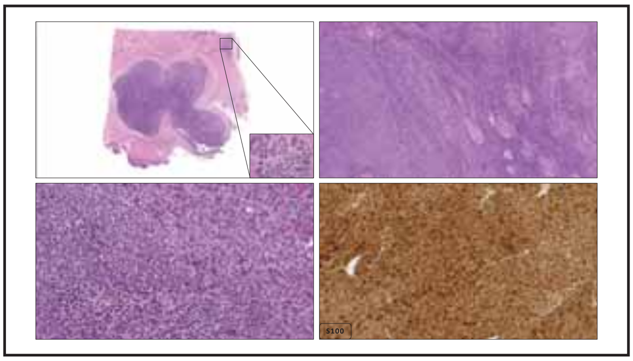

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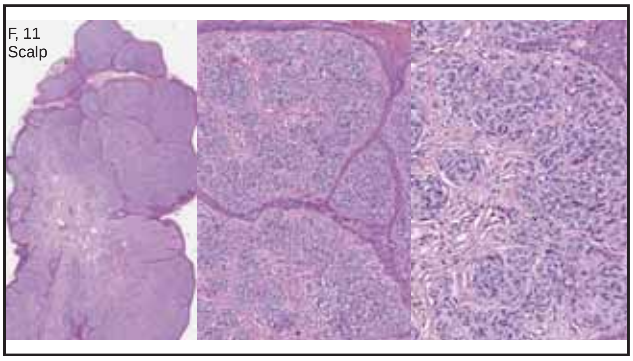

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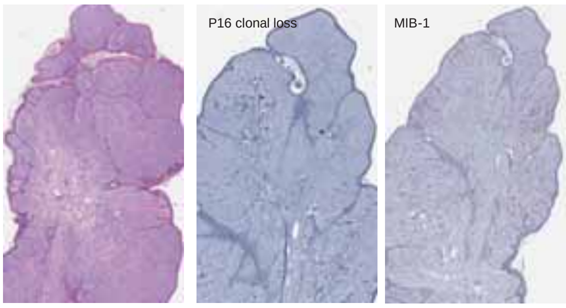

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Naevoid Melanoma (<0.5% of all melanomas)

Papillomatous	Maturing	Nodular	Large nested
• Exophytic nodule • Elongated thin rete ridges separating the melanocytic component into compartments • Scant cytoplasm, hyperchromatic nuclei • Mitoses often at the periphery of the compartments	• Superficial melanoma component merges with small melanocytes in the deep dermis • Small hyperchromatic cells are usually arranged in nests • Nests tend to become larger with depth	• Nodular dermal tumour mimicking Miescher's naevus • Lack of in situ • Cells are small to medium in size, without prominent atypia • Sheet-like hypercellular pattern (expansile growth) • Filiform elongation of the rete ridges • Mitotic figures (1-4/mm^2)	• Large, irregular junctional melanocytic (nests, may have an invasive dermal component • Junctional nests may be confluent • Variable cytological atypia

The diagnostic molecular pathology is similar to that of low-CSD melanoma

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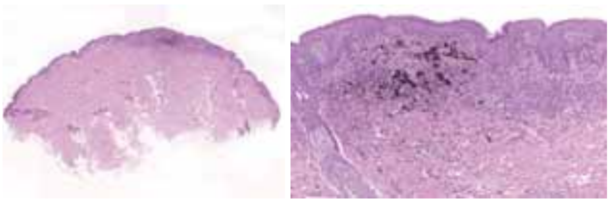
CLINICAL CASE

F, 11 yrs
Pigmented skin lesion on the right clavicle (2019)



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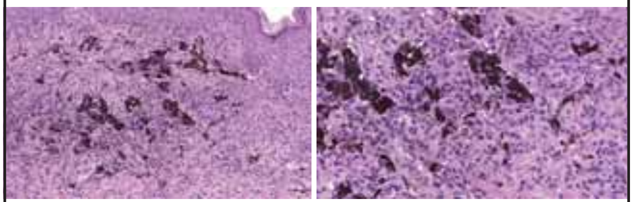

2 dermal mitoses

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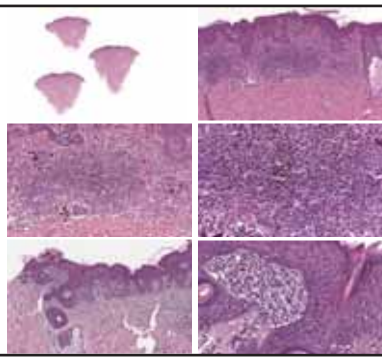
4 years later (2023)
right scapular region



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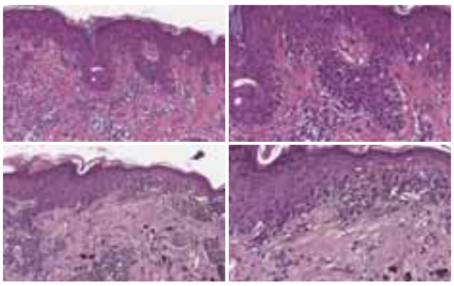

Nevus-associated MIS, re-excised

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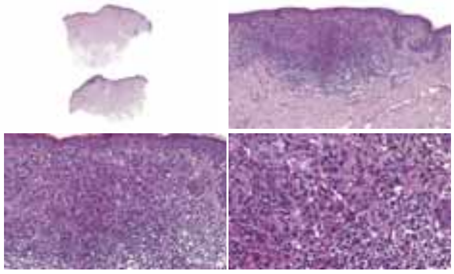
1 year later (2024)
Pigmented lesion on the scar of the clavicular region from previous excision (2019)



pT1a SSM/Low CSD MM (0.4 mm, 1 mitosis/mm2) with adiacent scar

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Clinical Case - What is your diagnosis?

1. Congenital nevus
2. Combined congenital nevus (with WNT-activated DPN component)
3. WNT-activated deep penetrating melanocytoma (nevus)
4. Melanoma arising in nevus/melanocytoma

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CLINICAL CASE

F, 33 yrs
Pigmented skin lesion on the right interscapular region

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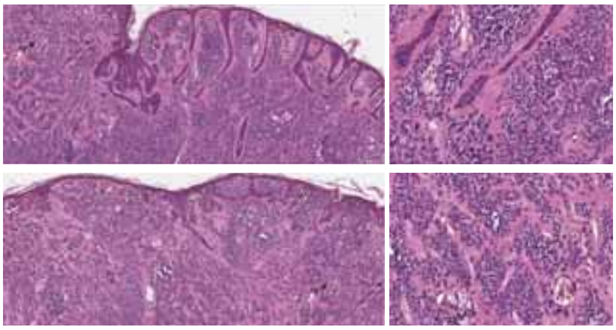

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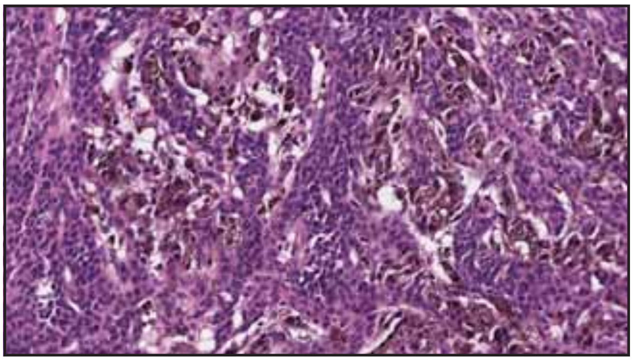

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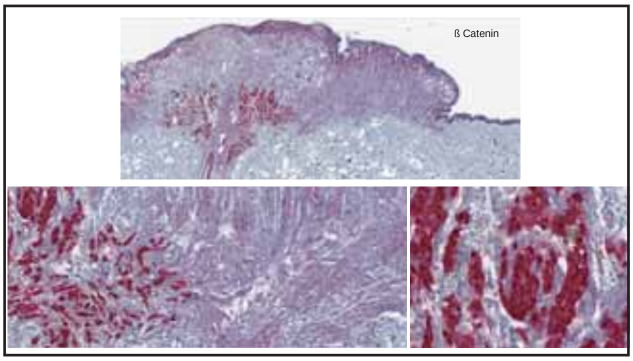
ß Catenin

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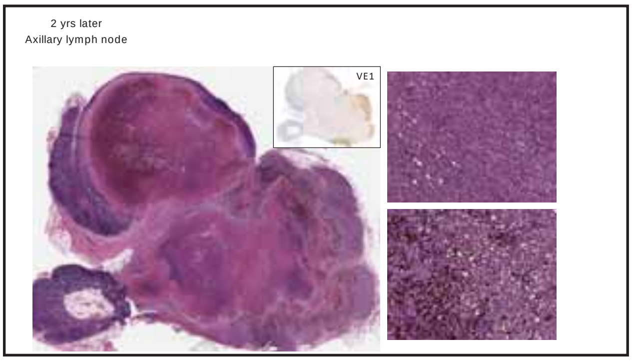
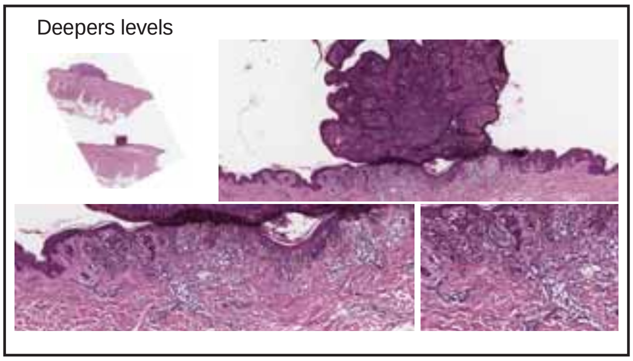

2 yrs later
Axillary lymph node
VE1

27


Deepers levels

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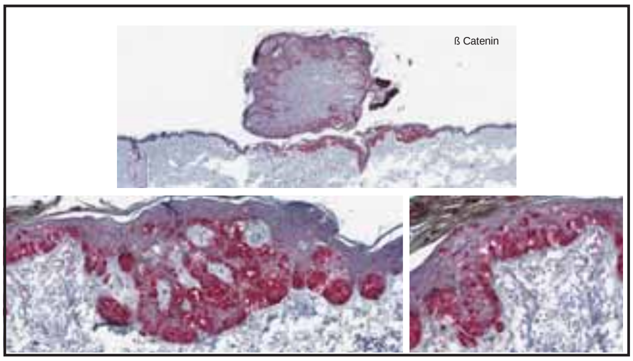

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Clinical Case - What is your diagnosis?

1. Congenital nevus
2. Combined congenital nevus (with WNT-activated DPN component)
3. WNT-activated deep penetrating melanocytoma (nevus)
4. Melanoma arising in nevus/melanocytoma

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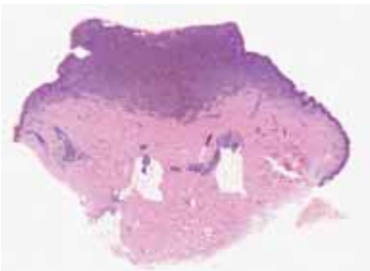
CLINICAL CASE

- M, 9 yrs
- Trunk



MELCAYA – Case provided by Lucia Alos – Hospital Clínic Barcelona

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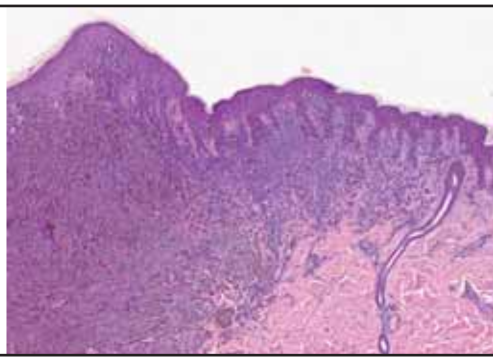

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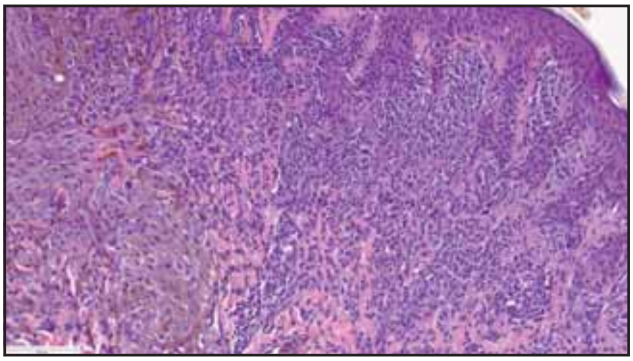

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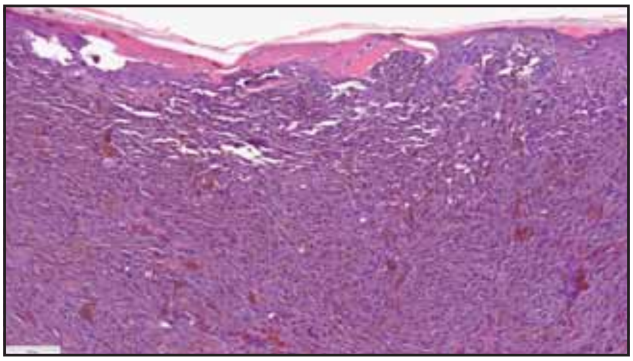

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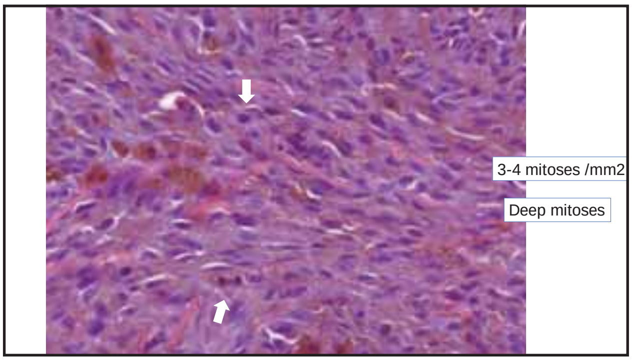

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Clinical Case - What is your diagnosis?

1. Congenital nevus
2. SSM/Low-CSD MM on a nevus
3. WNT-activated deep penetrating nevus/melanocytoma
4. Melanoma arising in WNT-activated deep penetrating nevus/melanocytoma

- *BRAF* exon 15; c.1799T>A; p.Val600Glu
- *CTNNB1* mutation exon 3; c.134C>T; p.Ser45Phe
- *NRAS* wt, c-KIT wt
- *pTERT*: not performed

- SLNB+
- Adjuvant therapy: Dabrafenib+Trametinib
- Follow-up: 5 years, alive, no recurrences

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Pathway of tumor progression?

Malignant

Melanocyte	Melanocytic nevus	WNT-activated deep penetrating/plexiform melanocytomas (naevus)	Atypical WNT-activated deep penetrating/plexiform melanocytomas (naevus)/MELTUMP	Melanoma in WNT-activated deep penetrating/plexiform melanocytomas (naevus)
	BRAF	*BRAF, MAP2K1 or NRAS, CTNNB1 or APC, HRAS, BRAF fusion*	*CDKN2A heterozygous loss, ARID1A, TET2, IDH1 p.R132C, KIT,* 1-2 CNVs	*TERTp, TP53, CDKN2A homozygous loss,* ≥3 CNVs

"In difficult cases, molecular analysis can be performed to confirm the presence of a CTNNB1 or APC mutation and rule out the presence of additional mutations such as TERT promoter mutations or CDKN2A inactivation, or DNA copy number changes typical of melanoma. More than two copy number variations have been proposed to be indicative of melanoma" (WHO 5th Edition)

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WHO Skin5 - The challenges

- The concept of melanocytic tumor progression
- The term *melanocytoma*
- Genetic trasversality within WHO pathways
- Clinical «unrecognition» and therapeutic implications for intermediate lesions

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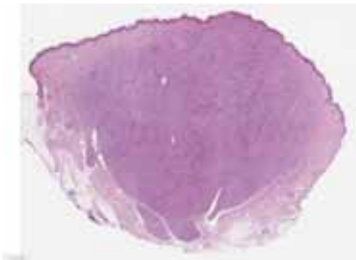
Clinical Case

- Female, 12 yrs
- Right arm



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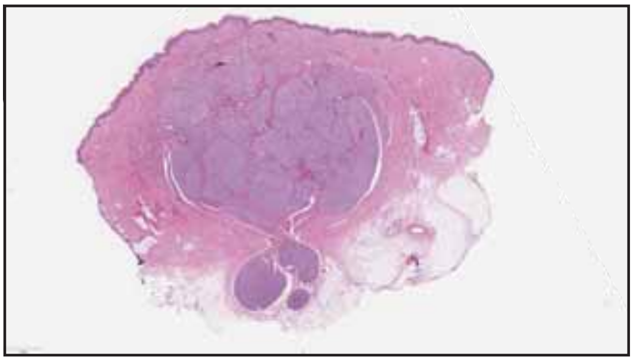

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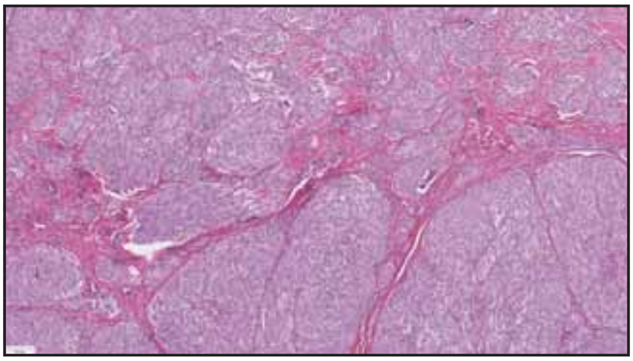

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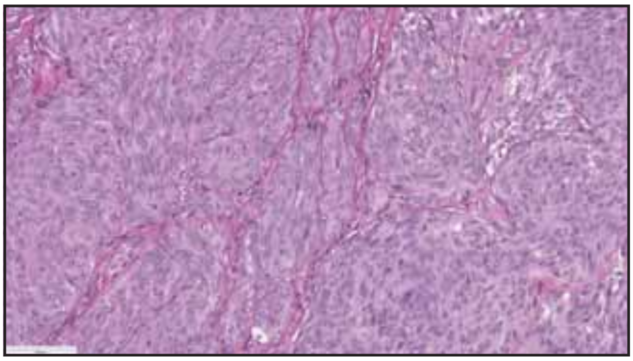

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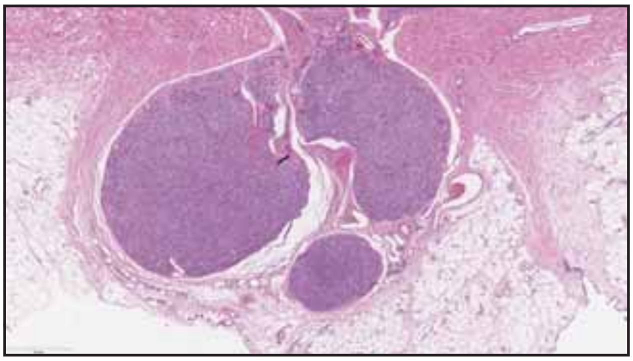

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Clinical Case – What is your diagnosis?

1. Spitz melanoma
2. Atypical Spitz Tumor/Spitz melanocytoma
3. Cellular blue nevus
4. Malignant blue nevus

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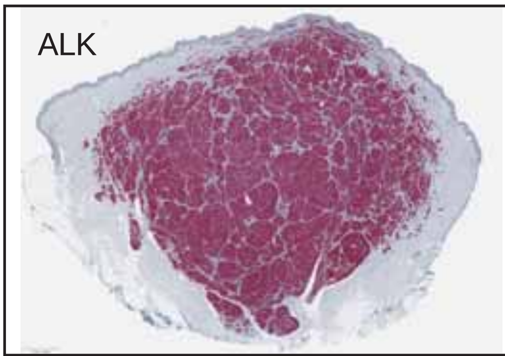

- P16: pos
- BRAF: neg
- pNTRK: neg
- HMB45: neg
- BRAFwt
- NRASwt
- KITwt
- p-TERTwt

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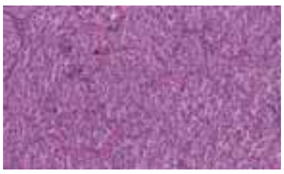
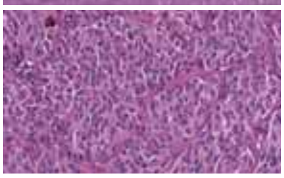
F/18 yrs,
left buttock

2.9 mm
Mitotic rate/mm²: 5





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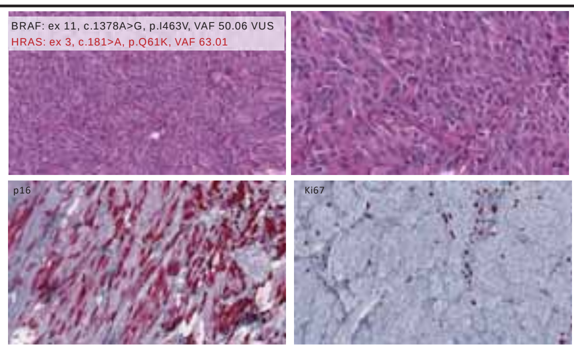

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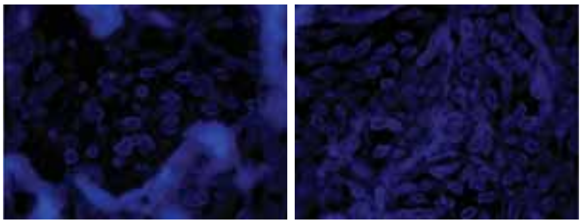
CDKN2A (9p21) 12%, Negative (cut-off >29%);
Heterozygous deletion in 69% of cells



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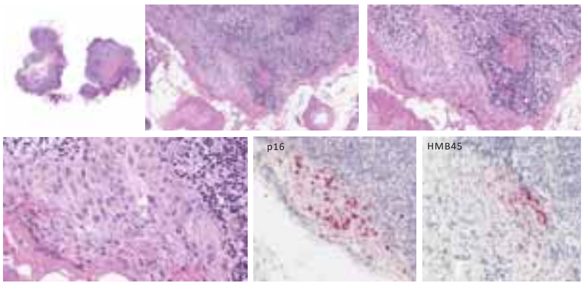
Positive SLNB (1/1), left inguinal region, subcapsular and parenchymal, 0.7 mm



FU 15 months

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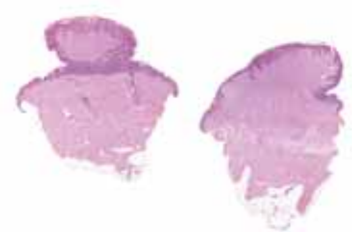
CLINICAL CASE

M, 29 yrs
Left buttock



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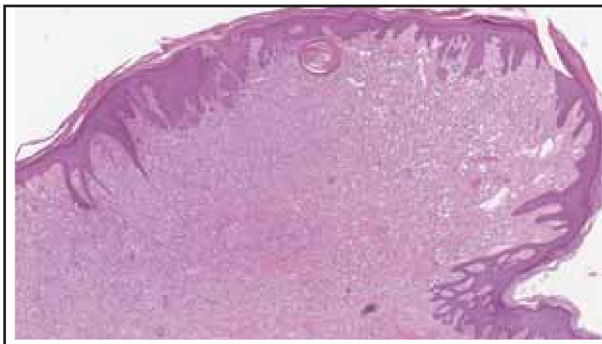

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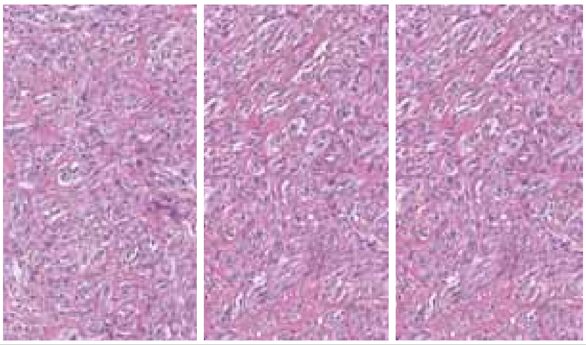

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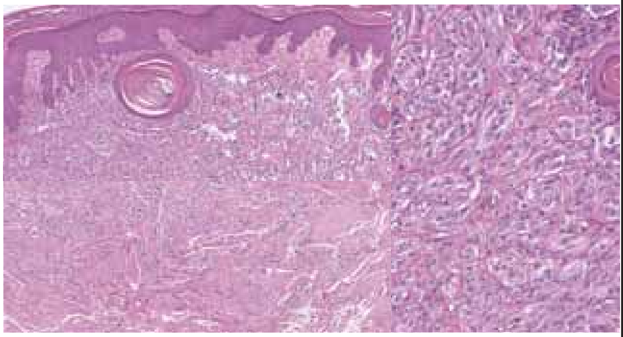

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Clinical Case – What is your diagnosis?

1. Spitz nevus
2. Atypical Spitz Tumor/Spitz melanocytoma
3. Spitz melanoma
4. Spitzoid melanoma

Original diagnosis: (Polipoid) dermal Spitz Nevus

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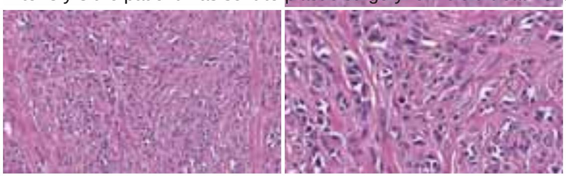
Upon excision

After 3 yrs the patient was sent to plastic surgery for keloid treatment



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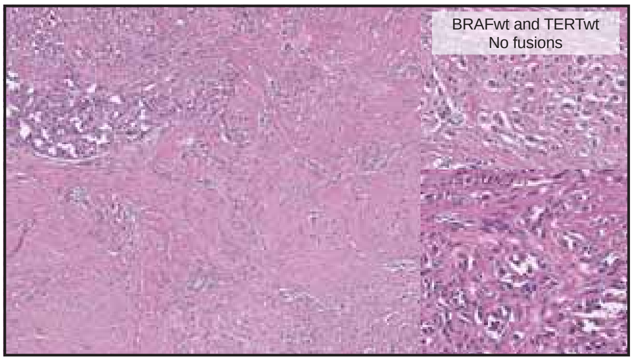
BRAFwt and TERTwt
No fusions

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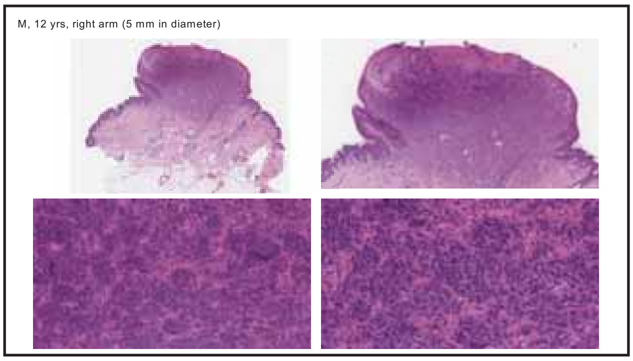
M, 12 yrs, right arm (5 mm in diameter)

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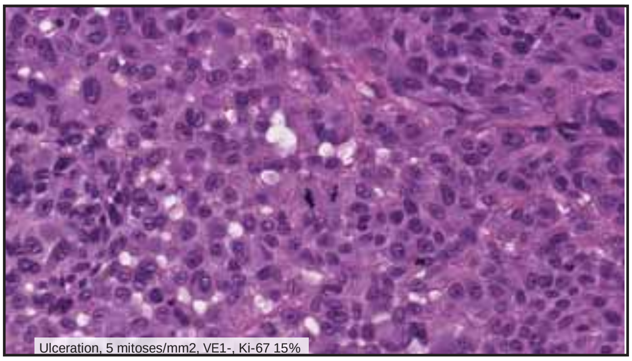
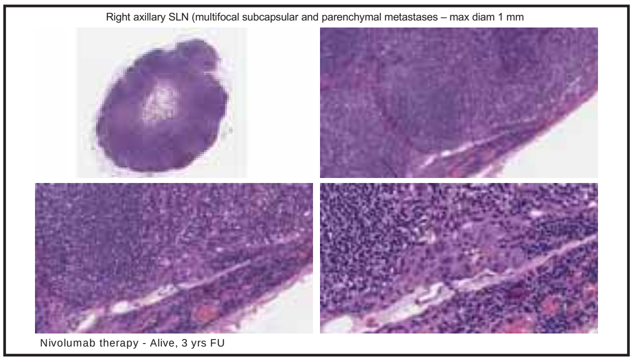
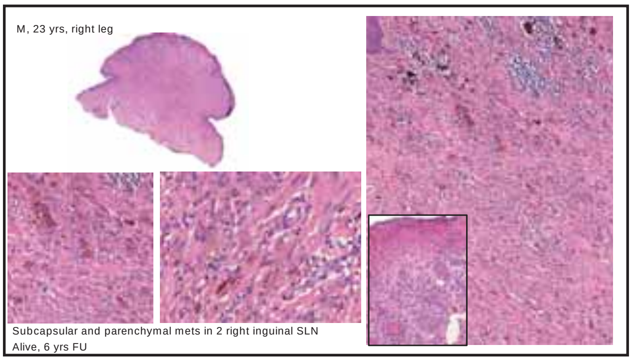

Ulceration, 5 mitoses/mm2, VE1-, Ki-67 15%

59


Right axillary SLN (multifocal subcapsular and parenchymal metastases – max diam 1 mm
Nivolumab therapy - Alive, 3 yrs FU

60


M, 23 yrs, right leg
Subcapsular and parenchymal mets in 2 right inguinal SLN
Alive, 6 yrs FU

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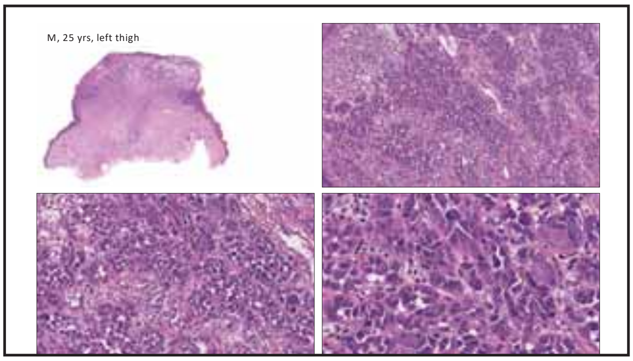
M, 25 yrs, left thigh

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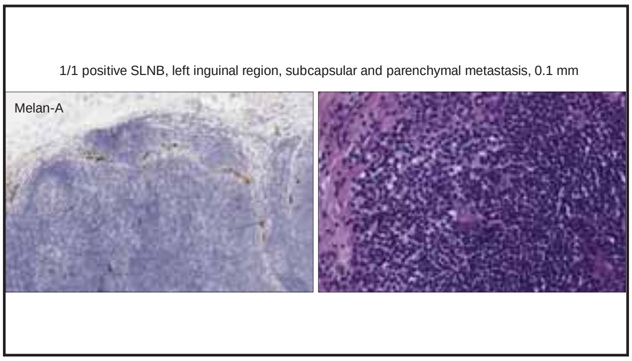
1/1 positive SLNB, left inguinal region, subcapsular and parenchymal metastasis, 0.1 mm
Melan-A

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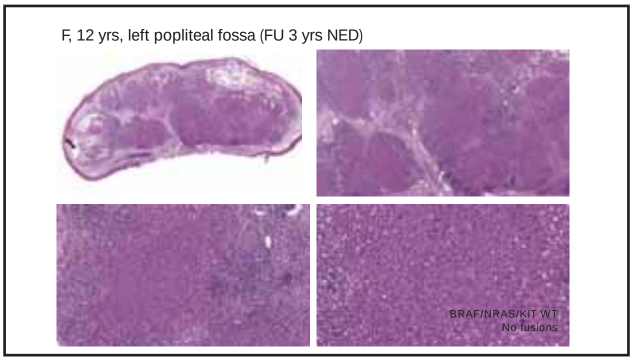
F, 12 yrs, left popliteal fossa (FU 3 yrs NED)
BRAF/NRAS/KIT WT
No fusions

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CLINICAL CASE

M, 6 yrs
Cutaneous erythematous partly pigmented lesion on the left thigh.

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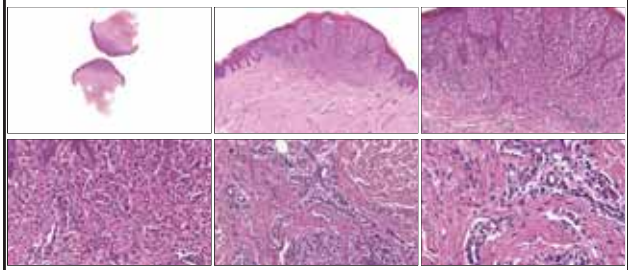

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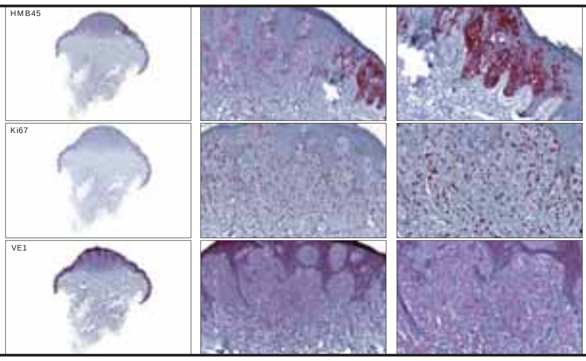

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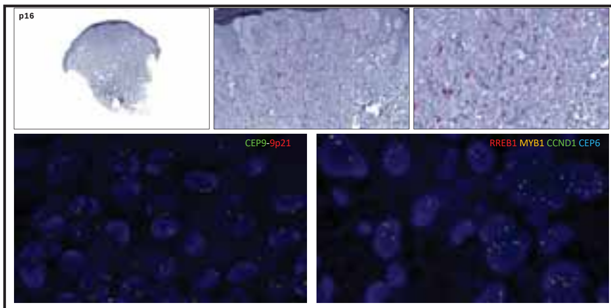

Homozygous CDKN2A deletion (9p21): Result 15%, Negative (Cut-off >29%)

RREB1 gain: 20% Negative (Cut-off >29%);
RREB1/CEP6 gain: 10% Negative (Cut-off >55%);
CCND1 gain: 17% Negative (Cut-off >38%);
MYB/CEP6 loss: 27% Negative (Cut-off >40%)

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RNA Fusions: Absent

Total Tumor Mutational Burden (TMB): 0

Gene Amplifications: Absent

Microsatellites Instability (MSI): 0

Mutated Genes	Wild Type Genes				
BRAF; p.V600E c.1799T>A	p-TERT	NRAS	CDKN2A	HRAS	PTEN

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What is your diagnosis?

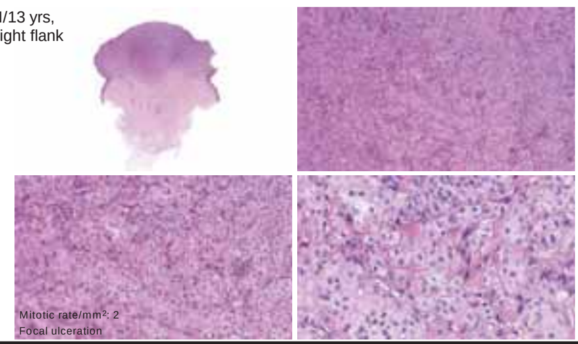
1. Spitz nevus
2. Atypical Spitz Tumor/Spitz melanocytoma
3. Spitz melanoma
4. Spitzoid melanoma
5. Atypical melanocytic tumor with spitzoid features and BRAF mutation

BRAFV600E mut (Real Time/NGS)

Alive NED, 3 years FU

70

M/13 yrs,
Right flank



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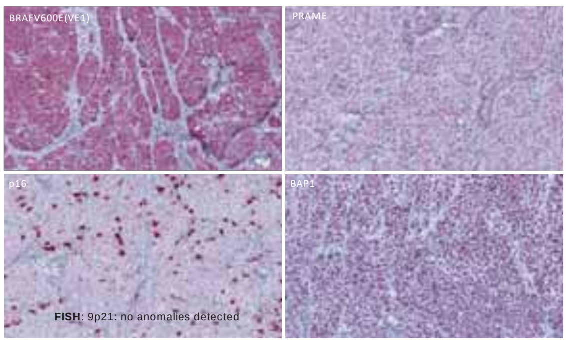

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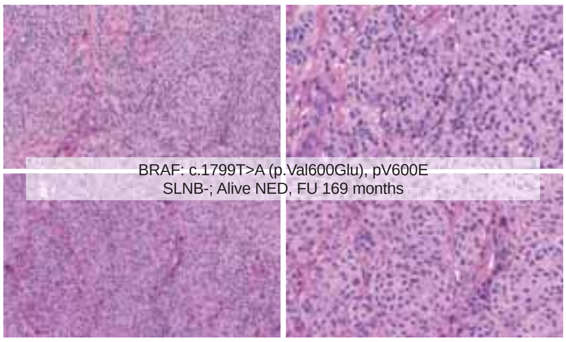

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CLINICAL CASE

- F, 3 yrs
- Back

MELCAYA – Case provided by Rita Alaggio & Sabrina Rossi - Ospedale Pediatrico Bambino Gesù Roma

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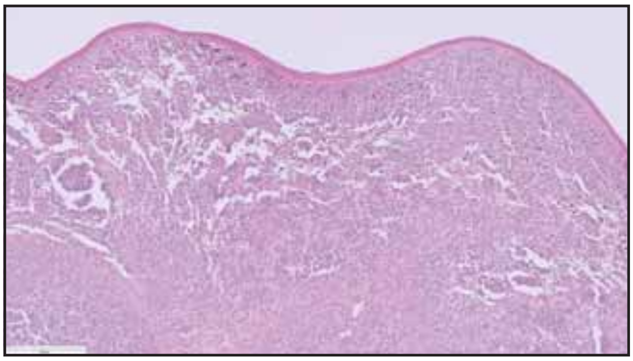

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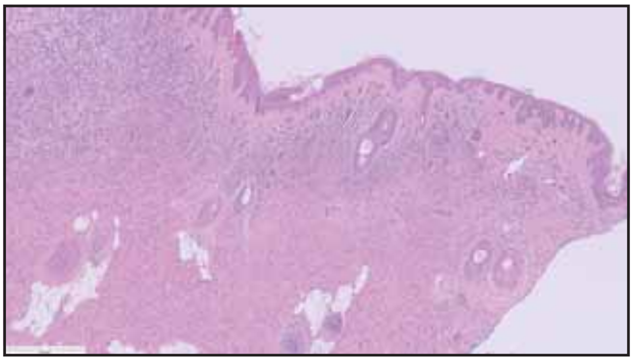

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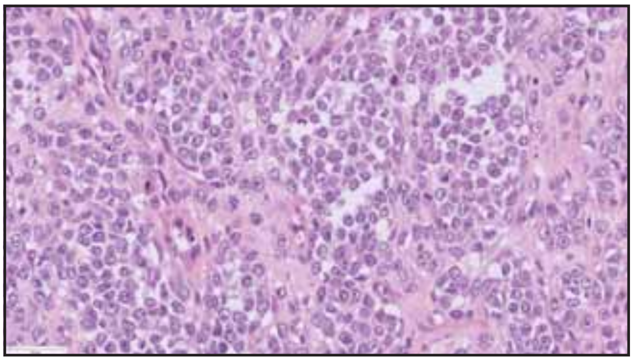

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What is your diagnosis?

1. Congenital nevus
2. Proliferative nodule on congenital nevus
3. Melanoma on congenital nevus
4. Nodular melanoma

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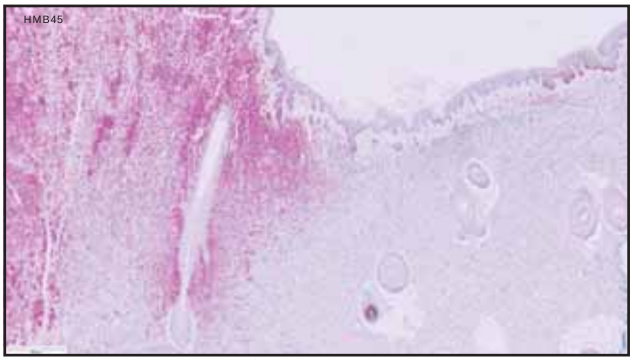

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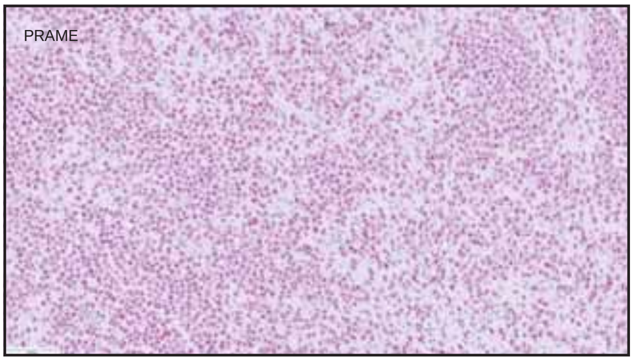

81

What is your diagnosis?

1. Congenital nevus
2. Proliferative nodule on congenital nevus
3. Melanoma on congenital nevus
4. Nodular melanoma

Molecular studies not performed
SLNB: not performed
Adjuvant therapy: Nivolumab
FU: 2 years, deceased

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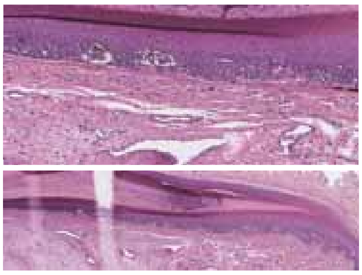
CLINICAL CASE
F, 16 yrs



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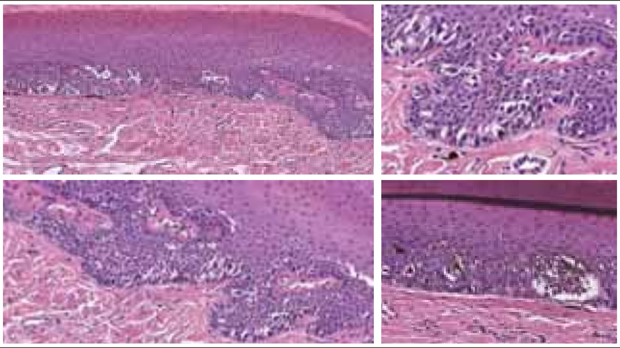

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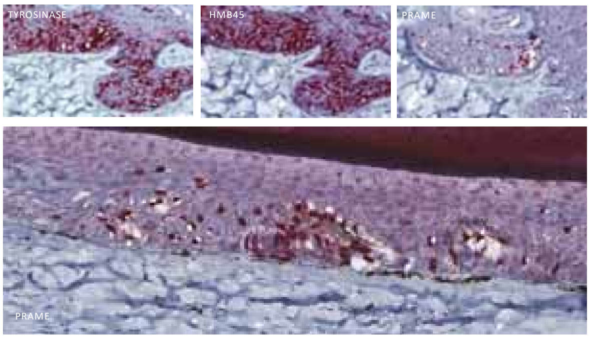

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What is your diagnosis?

1. Nevus
2. In situ melanoma
3. Lentigo
4. In situ melanoma arising on a nevus

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Melanonychia: Differential Diagnosis

Functional melanonychia	Lentigo/Lentigines (nail matrix)	Nevus (under and around the nail unit)	Melanoma (under or around the nail unit)
Increase in pigmentation, normal number of melanocytes	Obvious increase in pigmentation, increased number of markedly pigmented (slender) dendritic melanocytes. Melanophages may be present. The most frequent cause of longitudinal melanonychia in fair-skinned young patients	Obvious increase in pigmentation, increased number of dendritic melanocytes, some nests. Mostly junctional, rarely compound, congenital and blue.	Variable pigmentation, cellular atypia; melanocytes with plump dendrites, increased number of melanocytes

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Melanoma of the nail unit

- Age (40-70 yrs)?
- Streak is wider than 5 mm
- Anatomical site: thumb, big toe, index, middle finger (a single digit)
- Widening proximally (growth in the matrix)
- Associated with nail distrophy
- Hutchinson sign (periungueal pigmentation)
- Develops a tumefaction

Exception: Nail bed melanomas are not associated with longitudinal streak (as matrix melanoma) and are often amelanotic

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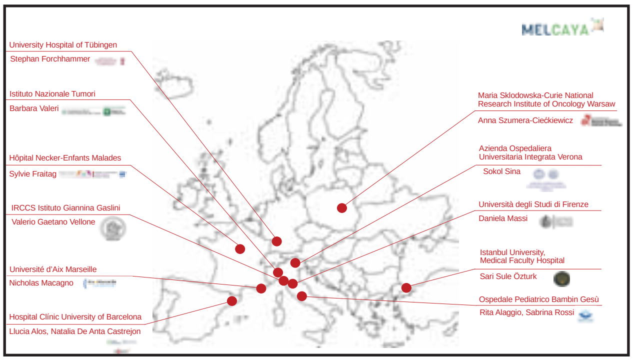

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Thank You

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New York University

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