

# Lesioni mucose: aspetti clinici e dermoscopici

**Angela Ferrari**

UOSD di Dermatologia  
Oncologica e Prevenzione

Responsabile: Dott. Pasquale Frascione

Università Cattolica del Sacro Cuore  
Fondazione Policlinico Universitario A. Gemelli  
Università degli studi di Roma Tor Vergata  
Fondazione Policlinico Tor Vergata  
Università degli studi dell'Aquila  
Ospedale Regionale S. Salvatore



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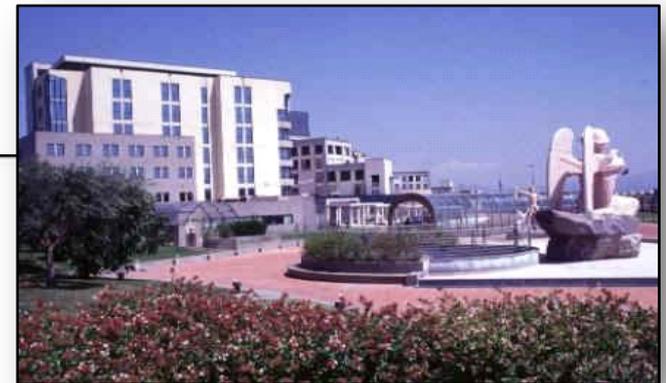


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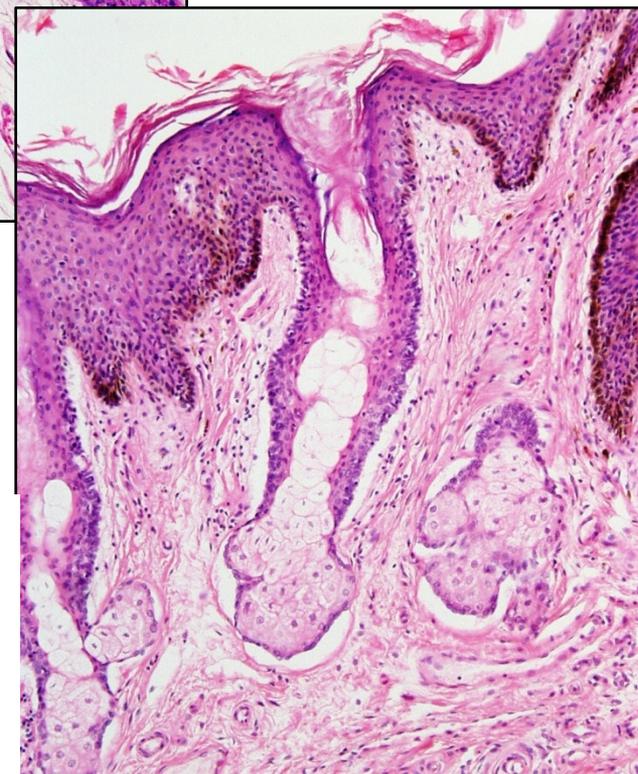
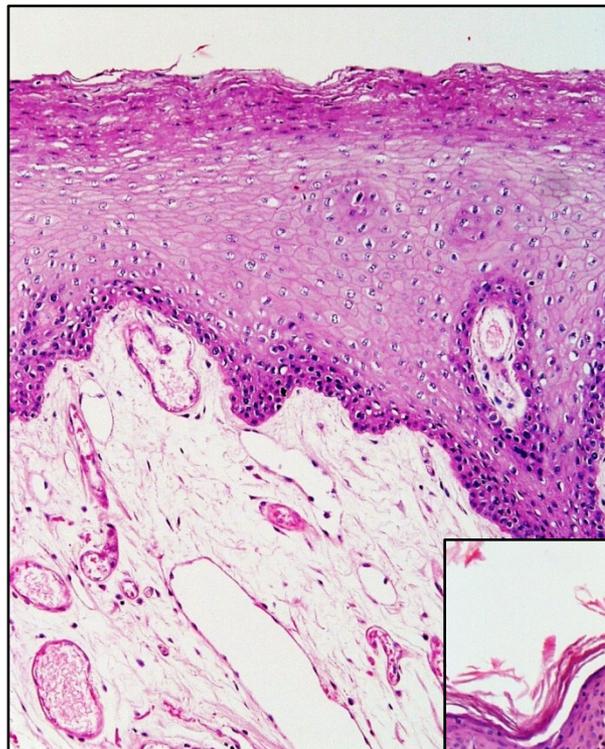
ISTITUTO DERMATOLOGICO

**SAN GALLICANO**

ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO



# AREE GENITALI



Melanosi

Melanosi/Melanoma

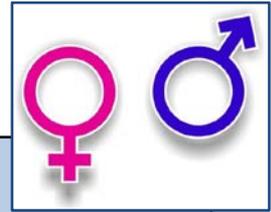
Nevo



M



# Lesioni osservate in sede genitale: Diagnosi differenziale



**Melanosi**

Nevi

Melanoma

Altro

# Pattern dermoscopic delle melanosi: Guida alla diagnosi



**Ring-like**



**Parallelo**



**Rail tracks**



**Impronta  
digitale**



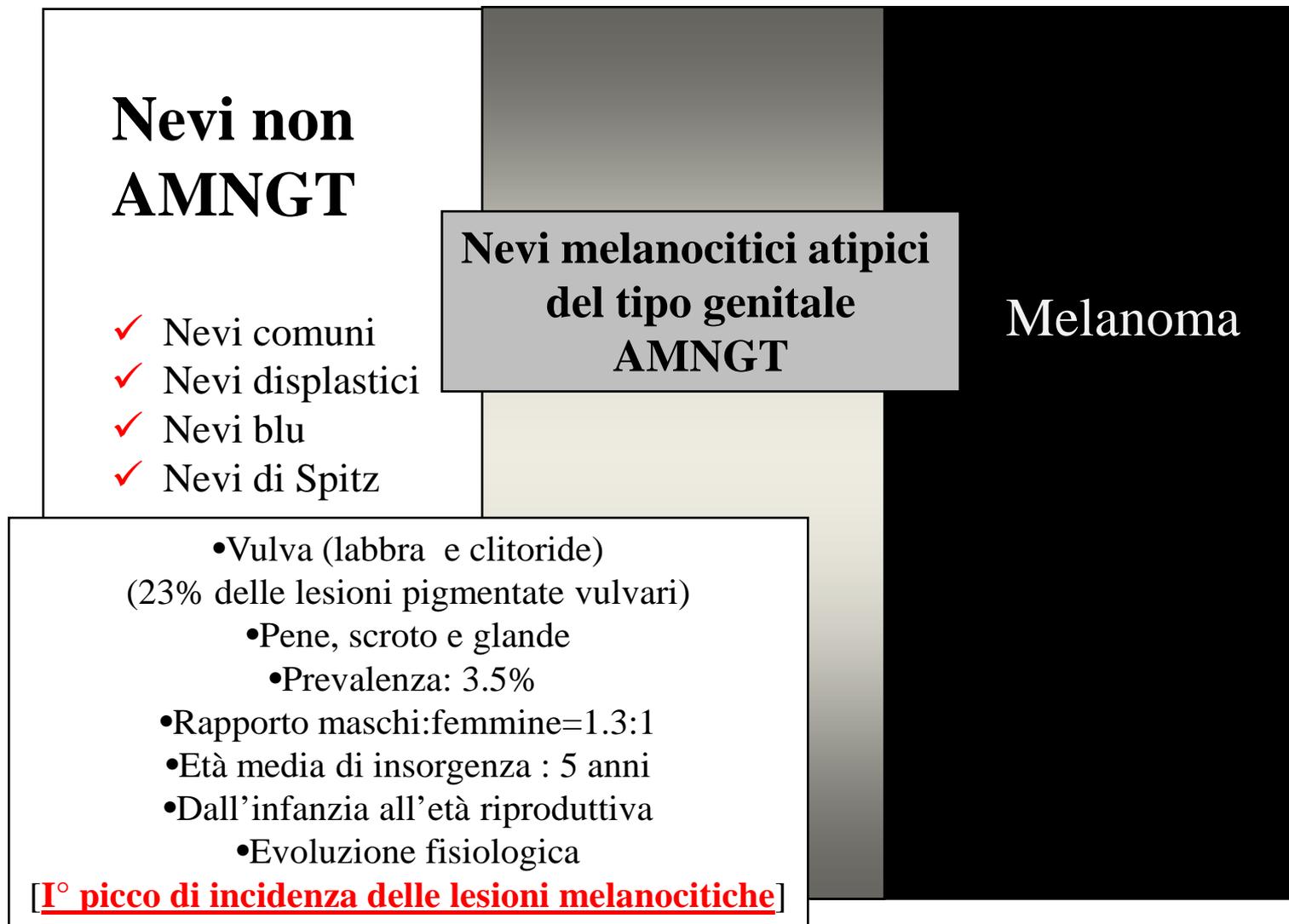
**Omogeneo**



**Misto**

- ✓ *Carli P, et al. Eur J Dermatol 1996; 6: 434-6*
- ✓ *de Giorgi V, et al. Oral Oncology 2003;39:534-535*
- ✓ *Mannone F, et al. Dermatol Surg 2004; 30:1118-23*
- ✓ *Ferrari A, et al. Arch Dermatol 2008;144(8):1030-34*
- ✓ *Olszewska M, et al. J Dermatol Case Reports 2008;3:43-48*
- ✓ *Lin J, et al. BJD 2009;161:1255-61*
- ✓ *Ferrari A, et al. Dermatology DOI:10.1159/000323409; 2011*
- ✓ *Ronegr-Savle S, et al. BJD 2011;164:54-61*
- ✓ *Blum A, et al. Arch Dermatol. DOI:10.1001/archdermatol.2011.55*
- ✓ *Hofmann-Wellenhof R, et al. Dermatol Clin 2013;31:625-36*

# Lesioni melanocitarie: diagnosi differenziale



✓ Hunt RD, et al. Genital melanocytic nevi in children; experience in a pediatric dermatology practice. *JAAD* 2014;70:429-34

✓ Murzaku EC, et al. Vulvar nevi, melanosis, and melanoma: an epidemiologic, clinical, and histopathologic review. *JAAD* 2014;71:1241-9

# Lesioni melanocitarie: Aspetti clinici e dermoscopic



## Genital melanocytic nevi in children: Experience in a pediatric dermatology practice

Raegan D. Hunt, MD, PhD,<sup>a</sup> Seth J. Orlow, MD, PhD,<sup>a,b</sup> and Julie V. Schaffer, MD<sup>a,b</sup>  
*New York, New York*

**Table II.** Clinical characteristics of genital nevi (total n = 44) in children

Characteristic	n (%)
<b>Color</b>	
Pink-brown	4 (9.1)
Tan to light brown	4 (9.1)
Medium to dark brown	19 (43.2)
Not recorded	17 (38.6)
<b>Elevation</b>	
Macule	10 (22.7)
Papule	18 (40.9)
Not recorded	16 (36.4)
<b>Other features</b>	
Eclipse (lighter center)	3 (6.8)
Fried egg (darker and more elevated center)	2 (4.5)
Speckled	2 (4.5)
Irregular pigmentation	1 (2.3)
Halo	1 (2.3)

# Management dei nevi melanocitici non AMNGT

- ✓ Pattern globulare/cobblestone
  - ✓ Pattern omogeneo
  - ✓ Pattern reticolare
- ✓ Assenza di caratteristiche dermoscopiche atipiche



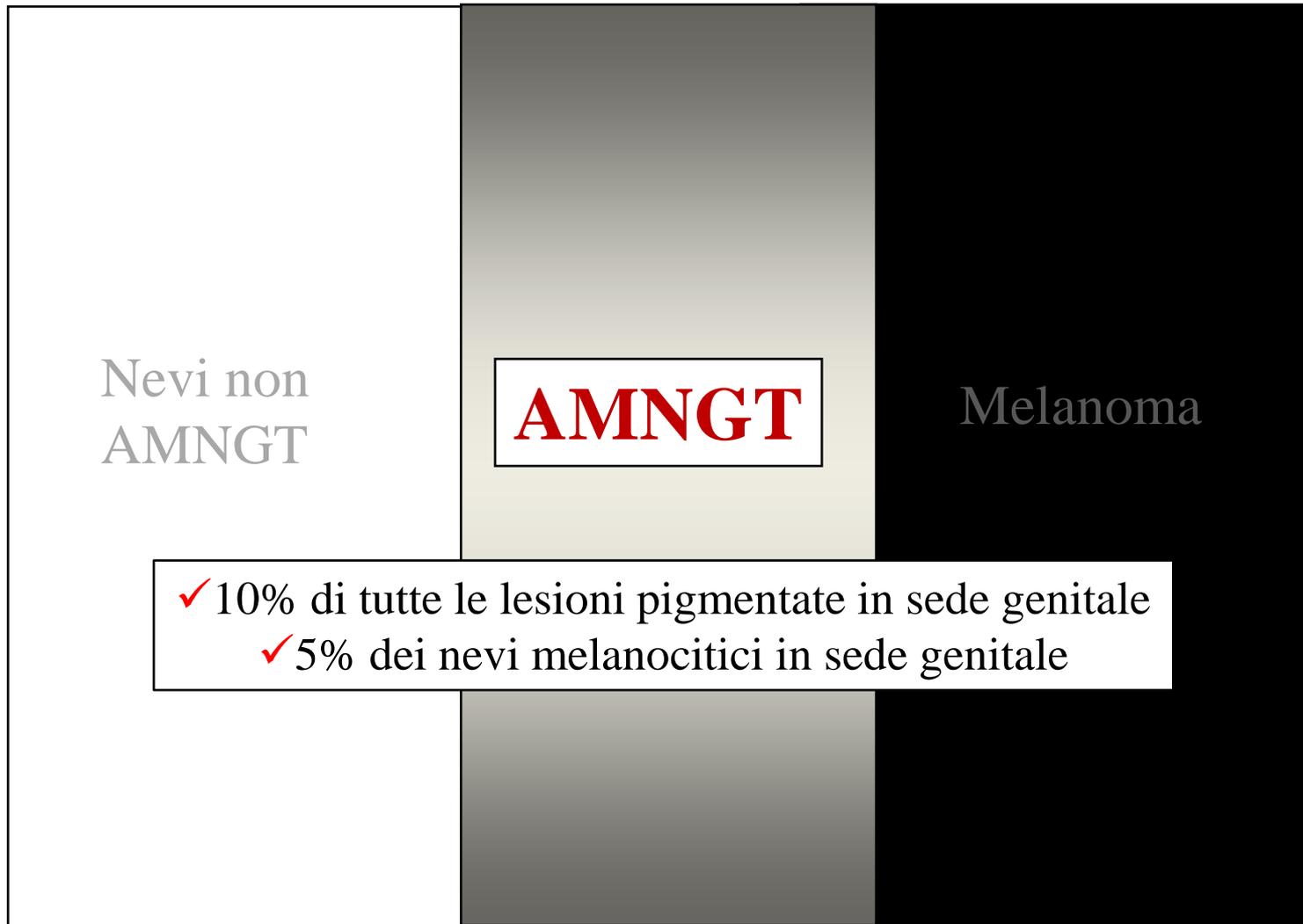
**NO**

Asportazione chirurgica

**SI**

Follow-up

# Lesioni melanocitarie: Aspetti clinici e dermoscopici



# Nevi melanocitici atipici del tipo genitale (AMNGT/AGN)

- Entità clinico-patologica distinta
- Più frequente in sede vulvare
- *Infanzia/adolescenza*
- Lesioni con caratteristiche istologiche diverse da quelle dei nevi displastici e sovrapponibili, per alcuni aspetti, a quelle del melanoma
- **Potenziale biologico ancora non ben definito** (assenza di ricorrenze o metastasi dopo asportazione completa in pochi studi e con follow-up medio di 3.5 anni)
- *Origine sconosciuta della atipicità di tale subset di lesioni rispetto alla maggior parte dei nevi in tale sede: (probabili specifici pathway molecolari che spieghino l'effetto di influenze ormonali, embriologiche e fisiche)*
- *Possibile link tra AMNGT e rischio incrementato di melanoma (?)*
- *Pattern mutazionale differente da quello del melanoma genitale*

- Clark WH Jr, et al. Atypical melanocytic nevi of the genital type with a discussion of reciprocal parenchymal-stromal interactions in the biology of neoplasia. *Hum Pathol* 1998;29:S1-24

- Makino E et al. Melanocytic nevi clinically simulating melanoma. *J Dermatol* 2007;34(1):52-7

- Gleason BC, et al. Atypical genital nevi. A clinicopathologic analysis of 56 cases. *Am J Surg Pathol* 2008;32(1):51-7

- Ribè A. Melanocytic lesions of the genital area with attention given to atypical genital nevi. *J Cutan Pathol* 2008;35(2):24-27

- Tseng D, et al. Oncogenic mutations in melanomas and benign melanocytic nevi of the female genital tract. *JAAD* 2014;71(2):229-236

- Yelamos O, et al. Nonoverlapping clinical and mutational patterns in melanomas from the female genital tract and atypical genital nevi. *J Invest Dermatol* 2016;136:1858-65

# Special Criteria for Special Locations 2

## Scalp, Mucosal, and Milk Line

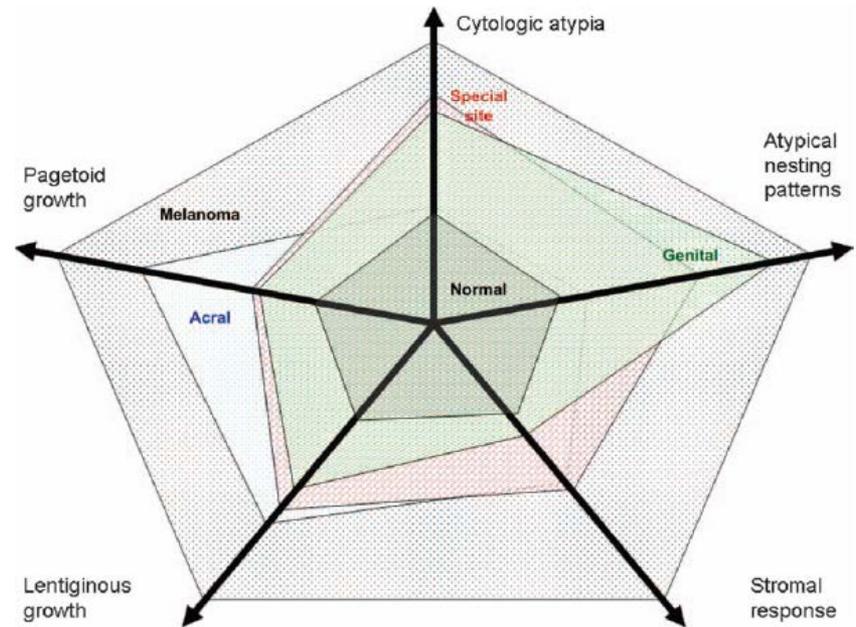
Rainer Hofmann-Wellenhof, MD

Dermatol Clin 2013

AMNGT/AGN



Nevi with site-related atypia



Hosler GA, et al. J Cutan Pathol 2008

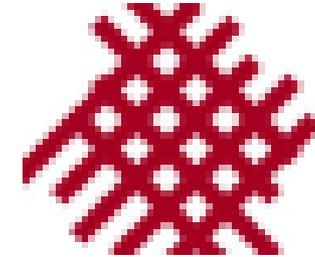
# Pattern dermoscopicci dei nevi genitali: Guida alla diagnosi



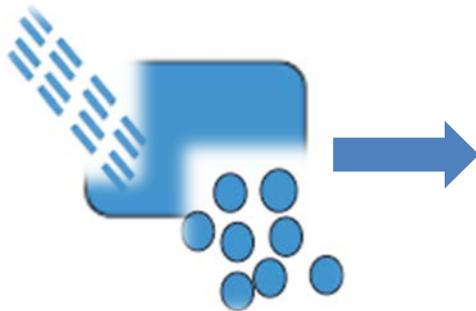
**Globulare/cobblestone**



**Omogeneo**



**Reticolare**



**Misto**

## AMNGT

- ✓ *Lin J, et al. BJD 2009;161:1255-61*
- ✓ *Virgili A, et al. Dermatology 2010;221:55-62*
- ✓ *Ferrari A, et al. Dermatology DOI:10.1159/000323409; 2011*
- ✓ *Ronegr-Savle S, et al. BJD 2011;164:54-61*
- ✓ *Blum A, et al. Arch Dermatol. DOI:10.1001/archdermatol.2011.55*
- ✓ *Hofmann-Wellenhof R, et al. Dermatol Clin 2013;31:625-36*
- ✓ *Hunt RD, et al. JAAD 2014;70:429-34*
- ✓ *Murzaku EC, et al. JAAD 2014;71:1241-49*
- ✓ *Cengiz FP, Hofmann Wellenhof RH. An Bras Dermatol 2015;90(2):178-83*

## Summary of the Salient Clinical and Histologic Features of Atypical Genital Nevus in Comparison With Vulvar Melanoma

Feature	Atypical Genital Nevus	Vulvar Melanoma
Age	Premenopausal	Postmenopausal
Size, cm	<1	>1
Borders	Distinct, circumscribed	Indistinct, ill-defined
Symmetry	Preserved	Absent
Shoulder	Small or absent	Extensive
Lentiginous growth	Minor component	Prominent
Pagetoid spread	Rare, focal and central	Prominent
Ulceration	Absent	Frequently present
Dermal atypia	Superficial	Confluent and deep
Dermal mitoses	Rare, superficial	Abundant and deep
Dermal maturation	Preserved	Absent

AMNGT



- ✓ *Yelamos O, et al. J Invest Dermatol 2016;136:1858-65*
- ✓ *Brenn T. Arch Pathol Lab Med 2011;135:317-320*

## Genital Melanocytic Nevus Arising in a Background of Lichen Sclerosus in a 7-Year-Old Female: The Diagnostic Pitfall With Malignant Melanoma. A Literature Review

Andre Pinto, MD,\* Son H. McLaren, MD,† Dix P. Poppas, MD,‡ and Cynthia M. Magro, MD†

### CASI DI AMNGT SU LICHEN SCLERO-ATROFICO

*Pinto et al*

*Am J Dermatopathol • Volume 34, Number 8, December 2012*

TABLE 2. Atypical Genital Nevi Arising on a Background of LS

Case #	Age	Sex	Site	Pathologic DX	Treatment/Follow-Up	Reference
1	9	F	Penileum	ACMN	No additional treatment, no recurrence (24 m)	Carlson et al <sup>3</sup>
2	8	F	Periclitiorial	AJMN	Primary excisional Bx, no recurrence (12 m)	Carlson et al <sup>3</sup>
3	11	F	Labia minora	ACMN	Reexcision with 5-mm margins, no recurrence (19 m)	Carlson et al <sup>3</sup>
4	14	F	Labia majora	ACMN	Re-excision with 5 mm margins, no recurrence (4 m)	Carlson et al <sup>3</sup>
5	6	F	Vulva (nonspecified)	CMN	Reexcision (no margins mentioned), no recurrence (12 m)	El Shabrawi-Caelen et al <sup>4</sup>
6	11	M	Glans penis	JMN	Partial excision (shave biopsy, no margins mentioned), recurrence after 22 m. After 60 mos of F/U, the patient is well.	El Shabrawi-Caelen et al <sup>4</sup>
7	9	F	Mucocutaneous junction of the labia minora	AJMN	Reexcision (no margins mentioned), no recurrence (12 m)	Bussen <sup>5</sup>

- ❖ Infiltrato linfocitario lichenoidale e melanofagi con incontinenza pigmenti che mima il melanoma con regressione



## Management degli AMNGT/AGN

- In presenza di un PATTERN MISTO  
Stretto follow-up/Asportazione chirurgica completa a seconda dei casi (NO punch biopsy)
- In caso di conferma istologica, escissione completa se i margini sono positivi
- No ampliamento
- No biopsia del linfonodo sentinella



- ✓ Conoscenza e riconoscimento della tipologia di nevo
- ✓ Collaborazione clinico/patologo
- ✓ Evitare interventi mutilanti e traumi psicologici a giovani pazienti

# Lesioni melanocitarie: Aspetti clinici e dermoscopic



# Melanoma vulvare

- ✓ **Incidenza : 0.1-0.2 casi/100.000 donne/anno**
- ✓ **l'1%-7% di tutti i melanomi nel sesso femminile**
- ✓ **2%-10% delle neoplasie in sede vulvare**
- ✓ **E' la seconda neoplasia maligna della vulva dopo il carcinoma squamocellulare**
- ✓ **V-VIII decade di vita**
- ✓ **Grado di sopravvivenza a 5 aa: 8%-61%**
- ✓ **Prognosi infausta**

**➤ Aspetto multifocale al momento  
della diagnosi (20% dei casi)**

✓ Data l'aggressività del melanoma vulvare e la sua rapida crescita verticale, la lesione multifocale rappresenterà una malattia avanzata al momento della diagnosi e quindi con una componente palpabile

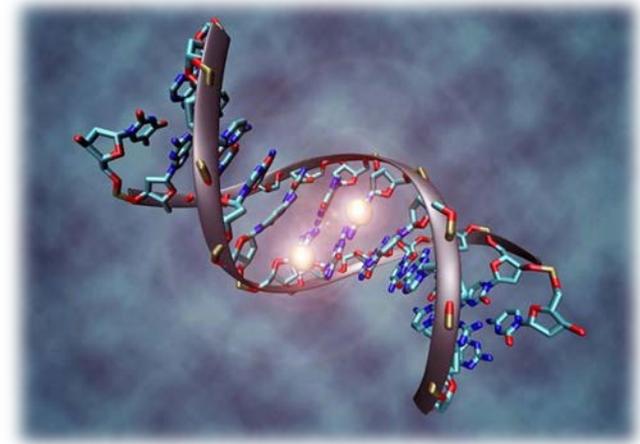
# Melanoma vulvare e mutazione del gene KIT

Analysis of c-KIT expression and *KIT* gene mutation in human mucosal melanoma

**British Journal of Cancer (2008) 99, 2065–2069**

I Satzger<sup>\*,1</sup>, T Schaefer<sup>1</sup>, U Kuettler<sup>1</sup>, V Broecker<sup>2</sup>, B Voelker<sup>1</sup>, H Ostertag<sup>3</sup>, A Kapp<sup>1</sup> and R Gutzmer<sup>1</sup>

<sup>1</sup>Department of Dermatology and Allergology, Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany; <sup>2</sup>Department of Pathology, Hannover Medical School, Hannover, Germany; <sup>3</sup>Department of Pathology, Klinikum Region Hannover, Hannover, Germany



## **Human Cancer Biology**

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### ***KIT* Gene Mutations and Copy Number in Melanoma Subtypes**

Carol Beadling,<sup>1</sup> Erick Jacobson-Dunlop,<sup>1</sup> F. Stephen Hodi,<sup>5</sup> Claudia Le,<sup>1</sup> Andrea Warrick,<sup>1</sup> Janice Patterson,<sup>1</sup> Ajia Town,<sup>1</sup> Amy Harlow,<sup>1</sup> Frank Cruz III,<sup>2</sup> Sharl Azar,<sup>1</sup> Brian P. Rubin,<sup>6</sup> Susan Muller,<sup>7</sup> Rob West,<sup>8</sup> Michael C. Heinrich,<sup>1,3,4</sup> and Christopher L. Corless<sup>1,2</sup>

*Clin Cancer Res* 2008;14:6821-6828.

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## **Human Cancer Biology**

### **KIT Pathway Alterations in Mucosal Melanomas of the Vulva and Other Sites**

Katarina Omholt, Eva Grafström, Lena Kanter-Lewensohn, Johan Hansson, and Boel K. Ragnarsson-Olding

*Clin Cancer Res* 2011;17:3933-3942.

Re



## Oncogenic mutations in melanomas and benign melanocytic nevi of the female genital tract

Diane Tseng, MD, PhD<sup>a,b</sup>, Julie Kim, MD<sup>c</sup>, Andrea Warrick, BS<sup>d</sup>, Dylan Nelson, BS<sup>d</sup>, Marina Pukay, BS<sup>d</sup>, Carol Beadling, PhD<sup>d</sup>, Michael Heinrich, MD<sup>e</sup>, Maria Angelica Selim, MD<sup>c</sup>, Christopher L. Corless, MD, PhD<sup>d</sup>, and Kelly Nelson, MD<sup>c</sup>

<sup>a</sup>Harvard University, Cambridge <sup>b</sup>Department of Medicine, Massachusetts General Hospital, Boston <sup>c</sup>Department of Dermatology, Duke University Medical Center, Durham <sup>d</sup>Knight Diagnostic Laboratories, Oregon Health and Science University, Portland <sup>e</sup>Division of Hematology and Oncology, Oregon Health and Science University, Portland



- ❖ 25 Melanomi
- ❖ 7 Nevi melanocitici comuni
- ❖ 4 Nevi genitali atipici

### Mutazioni osservate:

- ✓ **BRAF V600E**: 100% Nevi genitali senza atipia
- ✓ **BRAF V600E**: 75% AMNGT
- **KIT**: 16% Melanomi genitali
- **NRAS**: 16% Melanomi genitali
- **BRAF**: 8% Melanomi genitali

Dati emersi dalla review relativi al melanoma vulvare:

**KIT**: 26%; **NRAS**: 15%; **BRAF**: 5%

# Pigmented oral lesions

1275 pazienti  
386/1275 (30.3%):  
con pigmentazione orale

## Focal

**Foreign body tattoos, e.g. amalgam, graphite, carbon,,,**

Blue-grey small macule usually on gingivae or palate adjacent to amalgam filled teeth or at sites of previous trauma

**Melanotic macule**

Brown small macule usually on lip vermillion

**Melanocytic nevus**

Brown raised nodule usually on palate or buccal mucosa

**Melanoacanthoma**

Brown raised nodule, usually on buccal mucosa, develops rapidly and disappears spontaneously or after incomplete excision

**Melanoma**

Pigmented mass with irregular borders, color variation, and rapid growth

- ✓ Da pigmento melanico
- ✓ Da pigmento non melanico
- ✓ Di origine endogena
- ✓ Di origine esogena

## Diffuse/multifocal

**Racial/physiologic**

Diffuse brown patches mainly on the attached gingivae of dark skinned individuals, bilaterally symmetrical

**Smokers' melanosis**

Diffuse brown-grey patches mainly on the buccal and labia mucosa of smokers; asymmetrical distribution

**Drug induced melanosis**

Diffuse brown, blue-grey, or blue-black pigmentation mainly on the hard palate, tongue, or gingivae

**Heavy metals pigmentation**

Blue-black line along the gingival margin (Burton's line).

**Postinflammatory pigmentation**

Multiple brown-black pigmented areas adjacent to areas of chronic mucosal inflammation, particularly lichen planus

**Systemic disease associated**

**Endocrinopathies, e.g. Addison's, Nelson's, Albright, pregnancy, Graves**

Diffuse brown pigmentation on tongue lips and mucosae

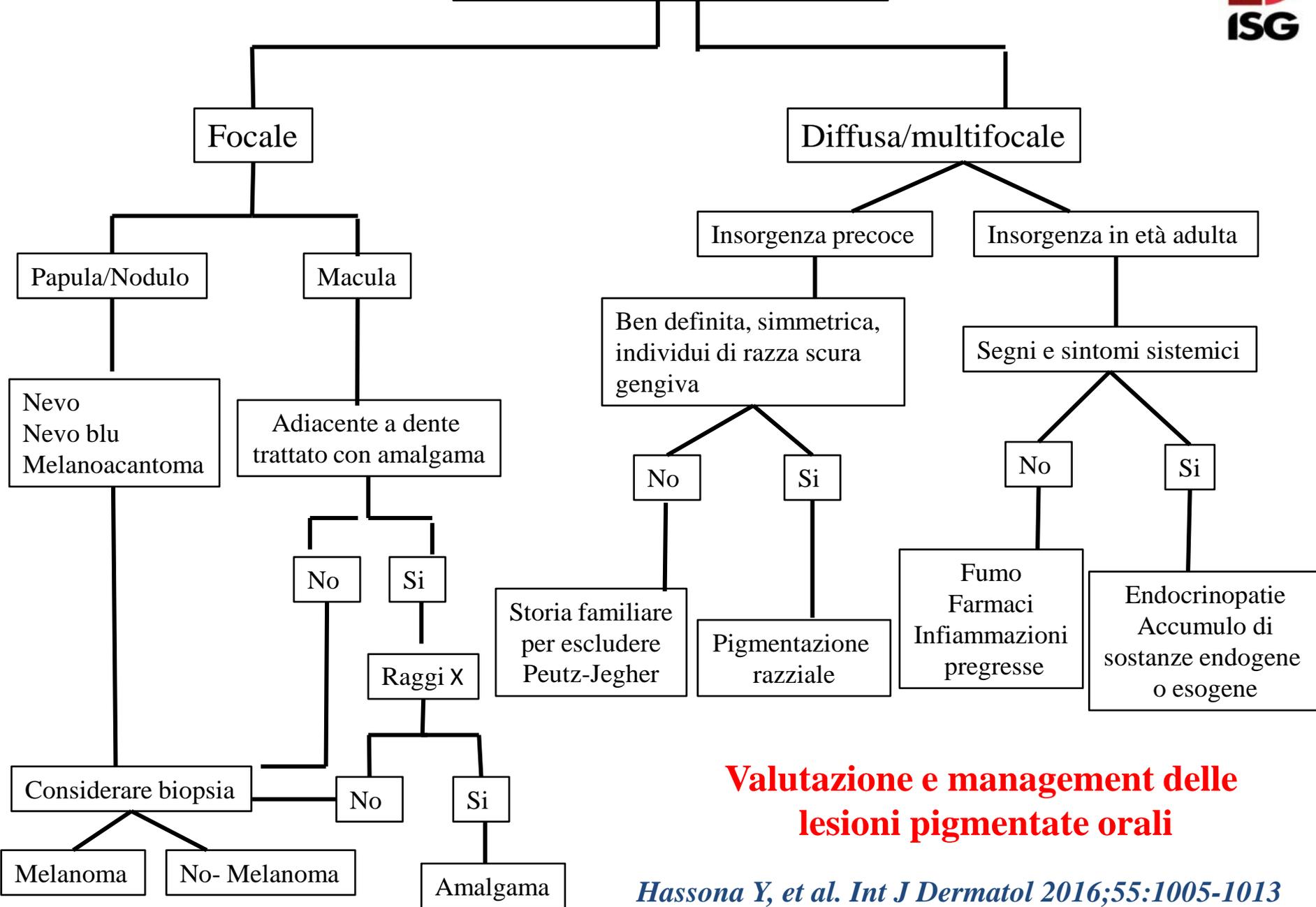
**Genetic disorders, e.g. Peutz-Jeghers, Laugier-Huuziker, Carney**

Brown circumoral macules, mucosal brown patches

**Others; HIV, hemochromatosis, Wilson disease**

Brown-blue pigmented patches

# Lesione pigmentata orale



## Valutazione e management delle lesioni pigmentate orali

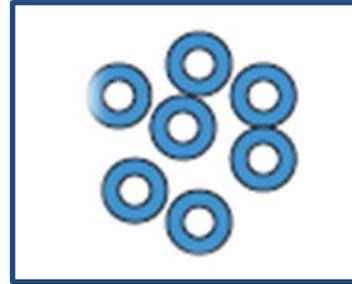
# Lentigo/melanosi labiale



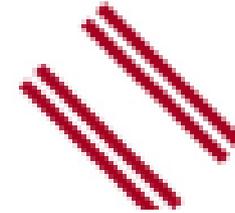
Parallelo



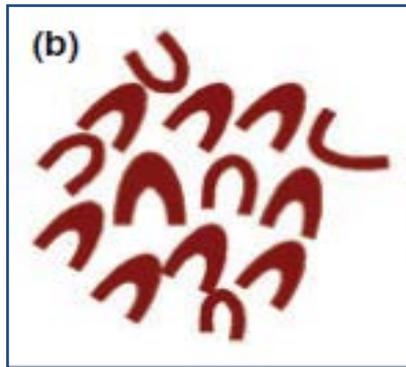
Fingerprint



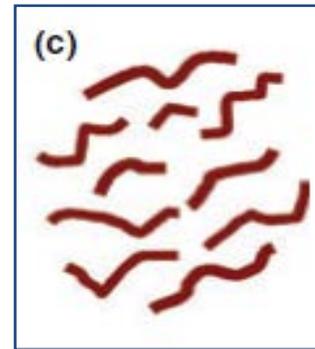
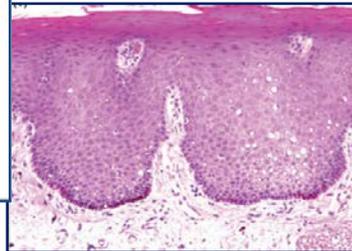
Ring-like



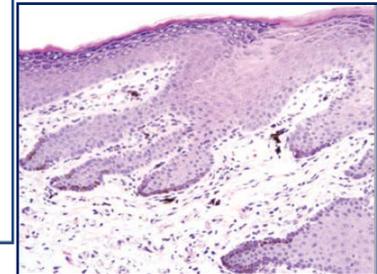
Rail Tracks



Fish-scale



Hyphal



- ✓ Gaeta GM, et al. *Oral pigmented lesions*. *Clin in Dermatol* 2002;20:286-288
- ✓ De Giorgi V, et al. *Dermoscopy in the management of pigmented lesions of the oral mucosa*. *Oral Oncol* 2003;39:534-35
- ✓ Tsunemi Y, et al. *Labial melanotic macule diagnosed by dermoscopy*. *Acta Dermato Venereol.* 2008;88:524-25
- ✓ Mannone F, et al. *Dermoscopic features of mucosal melanosis*. *Derm Surg* 2004;30:1118-23
- ✓ Lin J, et al. *Dermoscopy of pigmented lesions on mucocutaneous junction and mucous membrane*. *BJD* 2009;161:1255-61

# Melanoma Orale

- ❑ 0.5% di tutte le neoplasie orali
  - ❑ 1-2% di tutti i melanomi
  - ❑ Giappone, Africa, India
  - ❑ V-VII decade di vita
  - ❑ M:F=2:1
  - ❑ Palato duro, gengiva mascellare, labbro, lingua, pavimento buccale
  - ❑ Prognosi infausta
  - ❑ Sopravvivenza a 5 anni: 15%
  - ❑ Può non essere primitivo e quindi rappresentare una metastasi
- 
- ✓ *Olszewska M, et al. J Dermatol Case Reports 2008;3:43-48*
  - ✓ *Meleti M, et al. Oral Surg, Med, Pathol, Radiol, Endodontol 2008;105(5):606-16*
  - ✓ *Hajar-Serviinsky T, et al. J Dermatol Case Rep 2012;1:1-4*
  - ✓ *Alawi F. Dent Clin North Am 2013;57(4):699-710*
  - ✓ *Tarakji B, et al. Singapore Dental Journal 2014;35:39-46*
  - ✓ *Fernandes D, et al. Oral Surg, Med, Pathol, Radiol 2015;119:374-378*
  - ✓ *Hassona Y, et al. Int J Dermatol 2016;55:1005-1013*

# Melanoma orale: Criteri dermoscopic



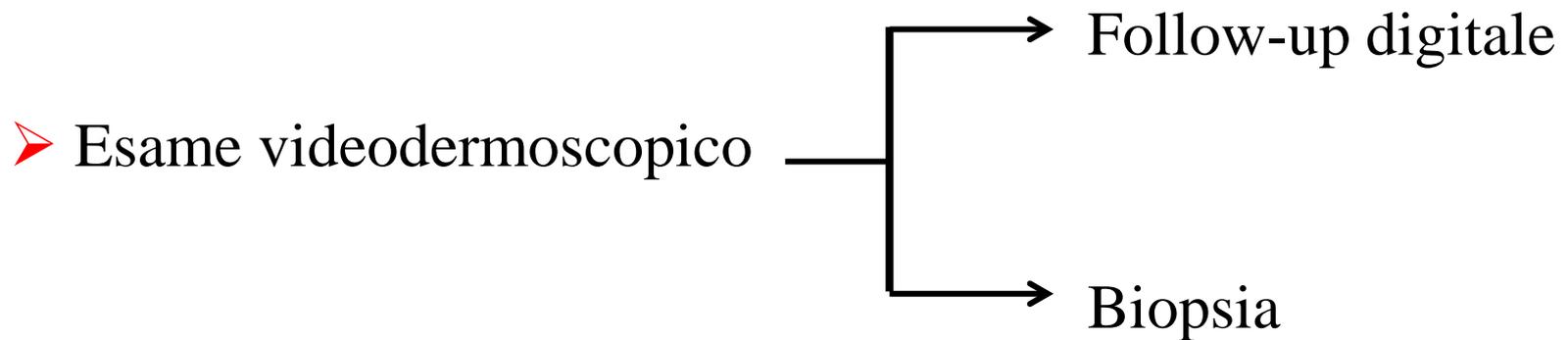
- ❑ Asimmetria di forma e strutture
  - ❑ Colori multipli
  - ❑ Aree grigio-blu
  - ❑ Velo bianco-blu
- ❑ Punti/globuli irregolari
- ❑ Pattern vascolare atipico

- ✓ *Olszewska M, et al. J Dermatol Case Reports 2008;3:43-48*
- ✓ *Lin J, et al. Br J Dermatol 2009;161:1255-61*
- ✓ *Blum A, et al. doi:10.1001/archdermatol. 2011.155*
- ✓ *Hajar-Seviansky T, et al. J Dermatol Case Rep 2012;1:1-4*

# Conclusioni



- Esame Total Body del paziente
- Anamnesi accurata (Età, storia clinica, familiare, occupazionale, precedenti traumi o interventi di tipo odontoiatrico, assunzione di farmaci, sintomatologia generale)
- Esami di laboratorio e strumentali (per le forme multifocali/diffuse)



- In casi sospetti o dubbi
- In caso di modifiche significative