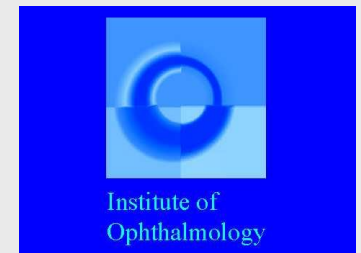


Oral and Genital Melanocytic Lesions

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Declaration of Interests

- » Senior visiting scientist, IARC, Lyon
- » Former Head of the WHO Classification of Tumours Programme and the Section of Evidence Synthesis and Classification at the International Agency for Research on Cancer, part of the World Health Organisation, Lyon, France.
- » Director, CanTech Ltd, Northamptonshire, UK
- » All opinions expressed are personal, and not those of any of the organisations above.

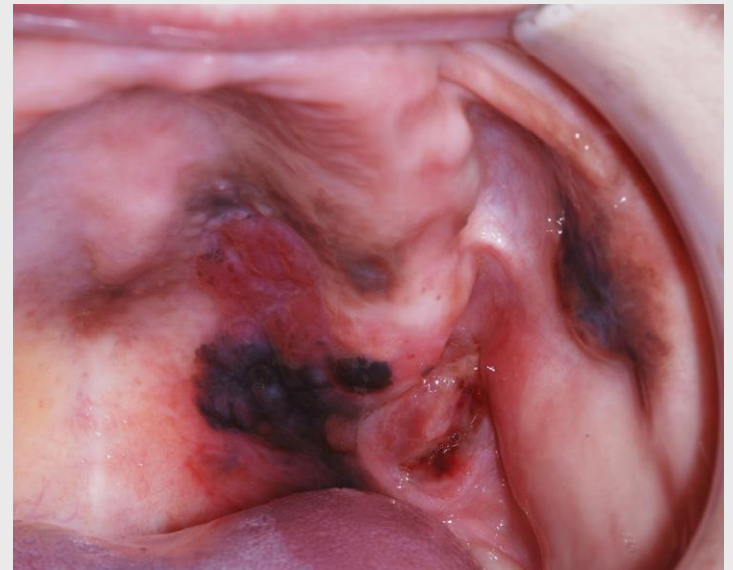
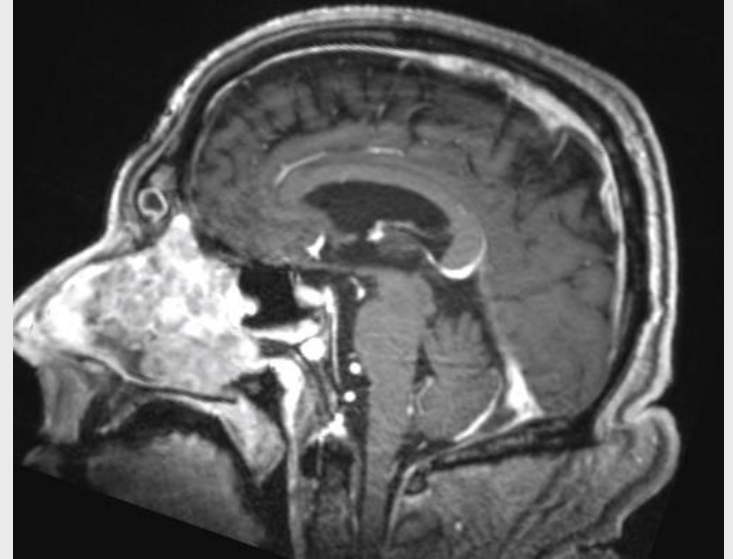
Introduction - oral tumours

- Mucosal melanomas arise in the sinonasal region, oral cavity, and larynx: naevi are rarely biopsied.
- They are biologically distinct from both cutaneous and uveal melanomas.
- Mucosal melanomas of the head and neck harbour distinct genetic alterations characterized by numerous chromosomal structural aberrations and copy-number alterations.
- The common MAPK activating mutations seen in cutaneous melanoma (*BRAF*, *NRAS*, *NF1*) are much less common, with only 28% of head and neck mucosal melanomas showing any of these mutations, whereas *KIT* mutations are more common
- Knowledge of the mutation landscape of head and neck mucosal melanoma is evolving, and potential therapeutic targets are being identified.

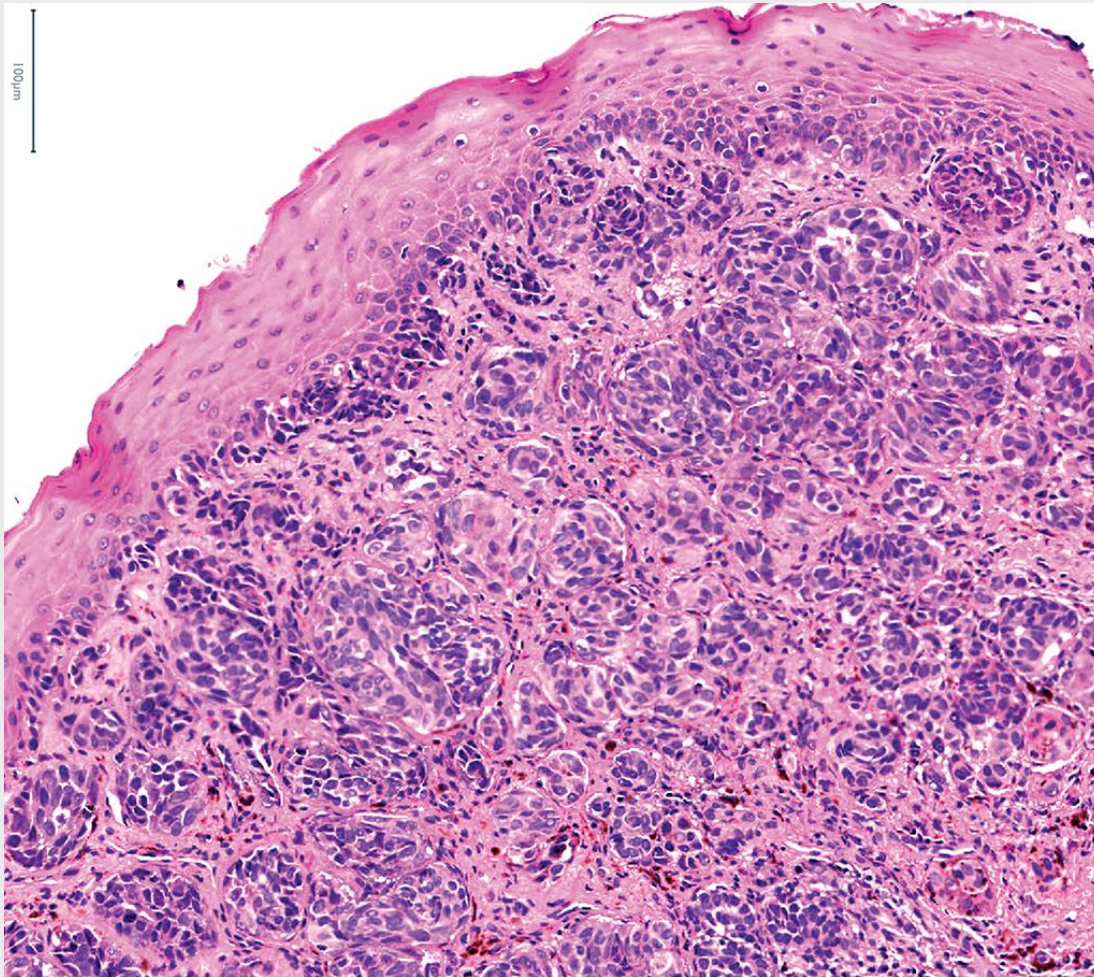
Oral Melanoma

Subtypes:

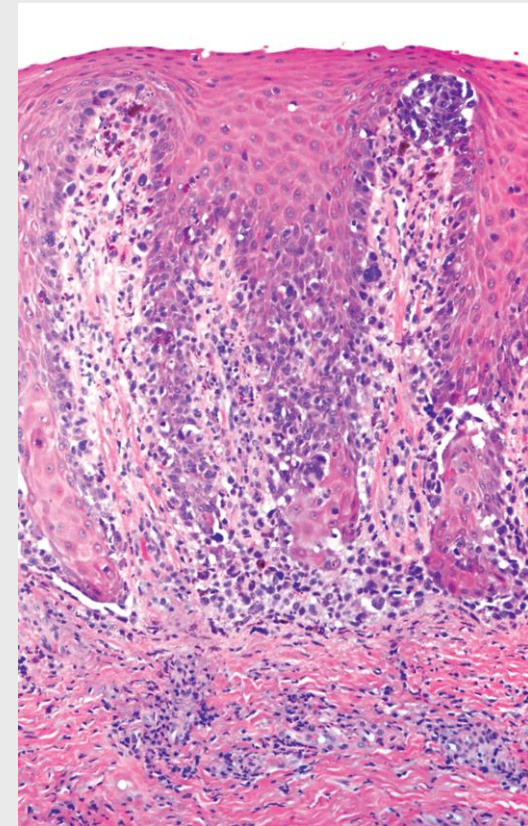
- Mucosal melanoma
- Desmoplastic mucosal melanoma
- Mucosal lentiginous melanoma
- Nodular melanoma



Oral Melanoma

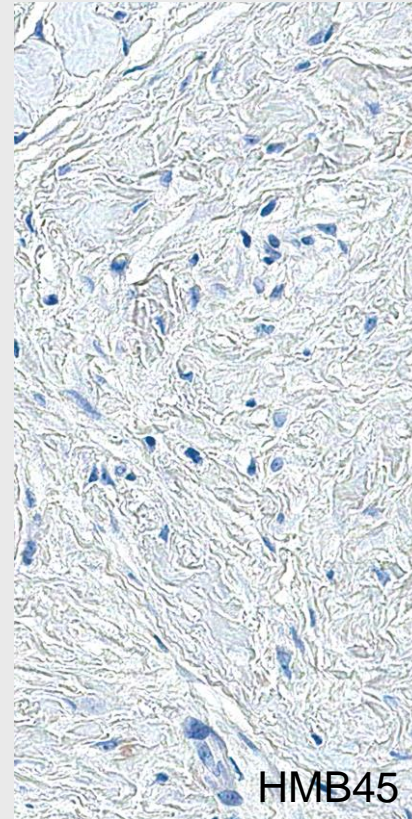
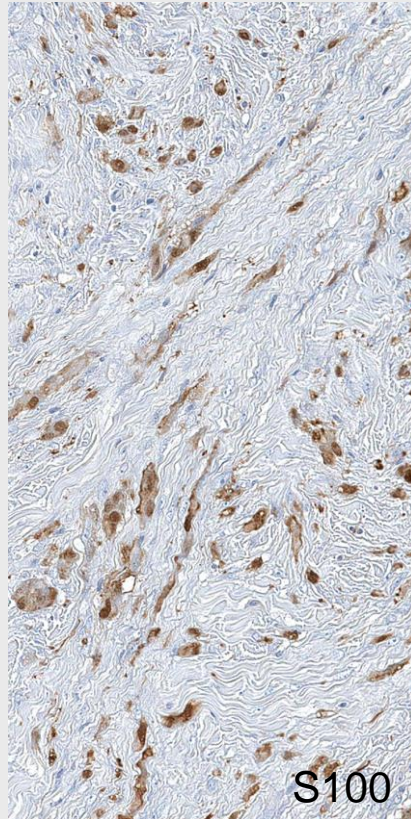
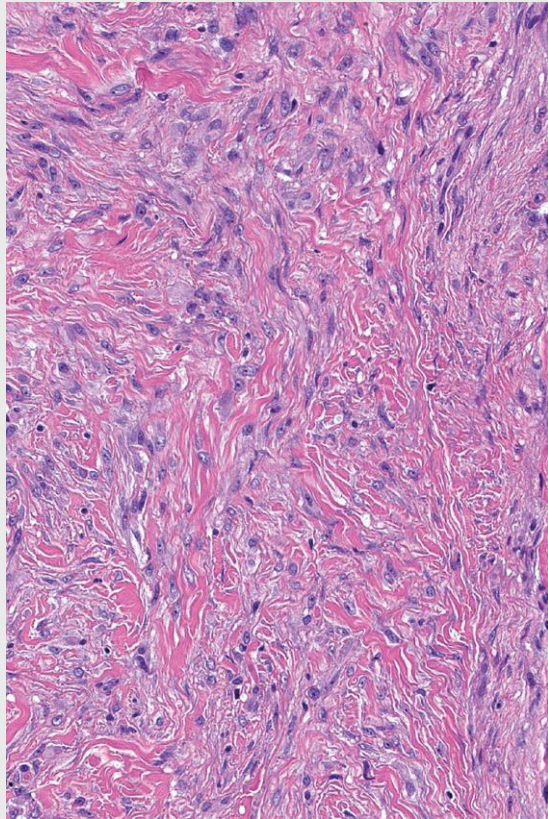


Epithelioid tumour cells infiltrating the basal layer of squamous epithelium as single cells and the subepithelial tissue as nests. Melanin is noted.



RGP melanoma, with atypical pigmented melanocytes in the basal layer spreading laterally and with vertical pagetoid spread, as well as invasive melanocytes in the stroma.

Desmoplastic Melanoma



Extension of desmoplastic melanoma into the nasal or oral mucosa from contiguous epidermis can be a diagnostic challenge, mimicking spindle cell squamous cell carcinoma. A wide panel of immunomarkers is necessary, including S100, because melanocytic markers may be negative.

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Mucosal Melanomas of the Head and Neck Histopathology Reporting Guide

Family/Last name: Date of birth:

Given name(s):

Patient identifiers: Date of request: Accession/Laboratory number:

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE. **SCOPE OF THIS DATASET**

OPERATIVE PROCEDURE (select all that apply)

☐ Not specified

☒ Biopsy (excisional, incisional), *specify*

☒ Resection, *specify (e.g. maxillectomy, hemiglossectomy, partial laryngectomy, etc.)*

☒ Neck (lymph node) dissection*, *specify*

☒ Other, *specify*

* If a *neck dissection* is submitted, then a separate dataset is used to record the information.

SPECIMENS SUBMITTED (Note 1)

☐ Not specified

☒ Anatomic site, *specify (may be multiple separate sites, but excluding lymph node dissection as that is a separate form)*

TUMOUR SITE (select all that apply) (Note 2)

☐ Cannot be assessed

☒ Sinonasal, *specify subsite(s)*

☐ Left ☐ Right

☐ Midline ☐ Laterality not specified

Subsite(s):

☒ Oral cavity, *specify subsite(s)*

☐ Left ☐ Right

☐ Midline ☐ Laterality not specified

Subsite(s):

☒ Larynx, *specify subsite(s)*

☐ Left ☐ Right

☐ Midline ☐ Laterality not specified

Subsite(s):

☒ Nasopharynx, *specify subsites(s)*

☐ Left ☐ Right

☐ Midline ☐ Laterality not specified

Subsite(s):

☒ Other, *specify site/subsite(s)*

☐ Left ☐ Right

☐ Midline ☐ Laterality not specified

Site/subsite(s):

TUMOUR FOCALITY

☐ Unifocal

☒ Multifocal, *specify number of tumours in specimen*

☒ Cannot be assessed, *specify*

TUMOUR DIMENSIONS (Note 3)

Maximum tumour dimension (largest focus in a single specimen)

Additional dimensions (largest tumour)
 x

☒ Cannot be assessed, *specify*

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 4)
(Value list from the World Health Organization Classification of Head and Neck Tumours (2017))

☐ Mucosal melanoma

☒ Melanoma (uncertain origin), *specify/comment*

☐ Cannot be assessed, *specify*

Histologic subtypes

☐ Balloon cell melanoma

☐ Mixed epithelioid and spindle cell melanoma

☐ Epithelioid cell melanoma

☐ Spindle cell melanoma

☐ Amelanotic melanoma

☐ Undifferentiated melanoma

☒ Other, *specify*

MARGIN STATUS (Note 5)

☒ Cannot be assessed, *specify*

Invasive melanoma

☒ Involved

Specify margin(s), if possible

☒ Not involved

Distance of invasive melanoma from closest margin

☐ Distance not assessable

Specify closest margin, if possible

Melanoma in situ

☒ Involved

Specify margin(s), if possible

☒ Not involved

Distance of melanoma in situ from closest margin

☐ Distance not assessable

Specify closest margin, if possible

COEXISTENT PATHOLOGY (select all that apply) (Note 6)

☐ None identified

☐ Melanoma in situ/pagetoid spread

☐ Melanosis

☒ Other, *specify*

ANCILLARY STUDIES (Note 7)

☐ Not performed

☒ Performed, *specify*

PATHOLOGICAL STAGING (UICC TNM 8th edition) (Note 8)**

TNM Descriptors (only if applicable) (select all that apply)

☐ m - multiple primary tumours

☐ r - recurrent

☐ y - post-therapy

Primary tumour (pT)**

☐ TX Primary tumour cannot be assessed

☐ T3 Tumour limited to the epithelium and/or submucosa (mucosal disease)

☐ T4a Moderately advanced disease
Tumour invades deep soft tissue, cartilage, bone, or overlying skin

☐ T4b Very advanced disease
Tumour invades any of the following: brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

** Note that the results of *lymph node/neck dissection* are derived from a separate dataset.

** Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2017, Publisher Wiley-Blackwell.

Genital Melanocytic Lesions

- WHO Classification (FGT5)
- Naevi
 - Acquired melanocytic naevus
 - Congenital melanocytic naevus
 - Blue naevus
 - Atypical melanocytic naevus of genital type
 - Dysplastic melanocytic naevus
- Melanoma
 - Mucosal melanoma

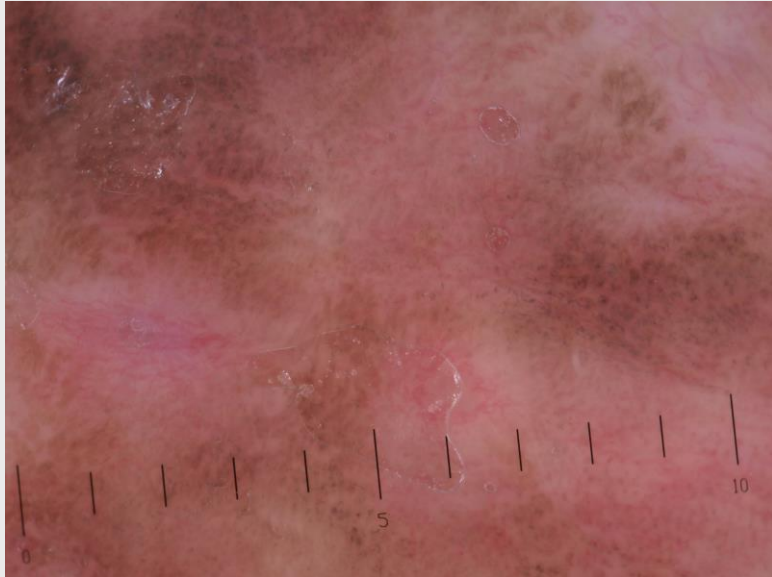
Genital Melanocytic Lesions

- WHO Classification (SKIN5)
- Mucosal and genital naevi
 - Melanosis
 - Genital naevus
- Mucosal melanomas
 - Mucosal melanomas

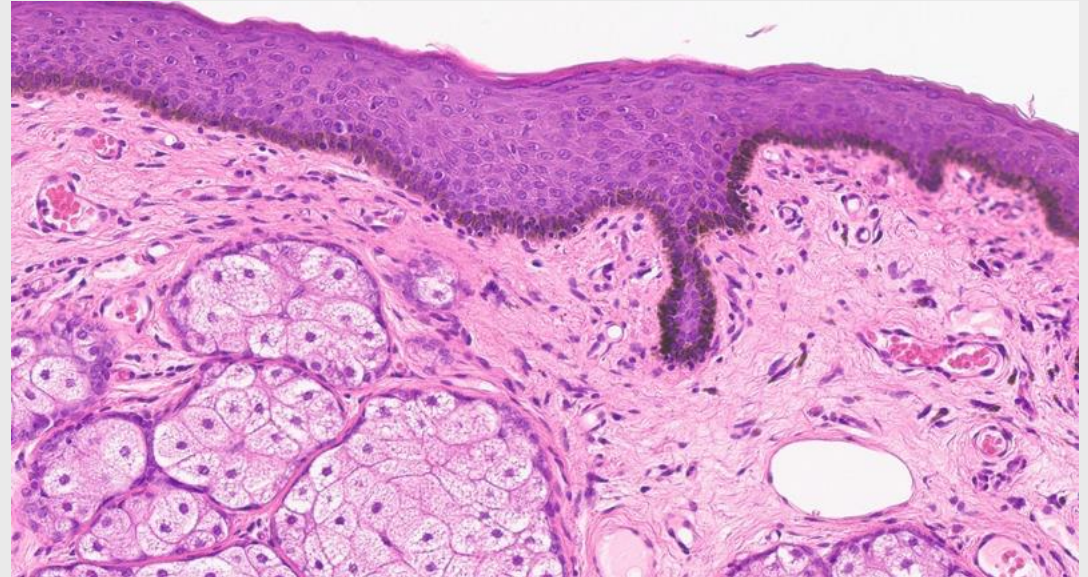
Genital Melanosis

- Benign flat pigmented lesions, which arise on mucous membranes and are characterized by an increased production of melanin pigment deposited in adjacent epithelial cells, occasionally associated with a slight increased number of epithelial melanocytes without significant proliferation.
- **Related terminology**
- Acceptable: lentiginosis; lentigo; melanotic macule; constitutional melanosis; complexion-related melanosis
- Not recommended: non-proliferative melanocytic pigmentary patch; ephelis; freckle

Genital Melanocytic Lesions



Dermoscopically, irregular diffuse pigmentation characterized by the presence of shades of brown and black colours in the absence of other dermoscopic parameters.

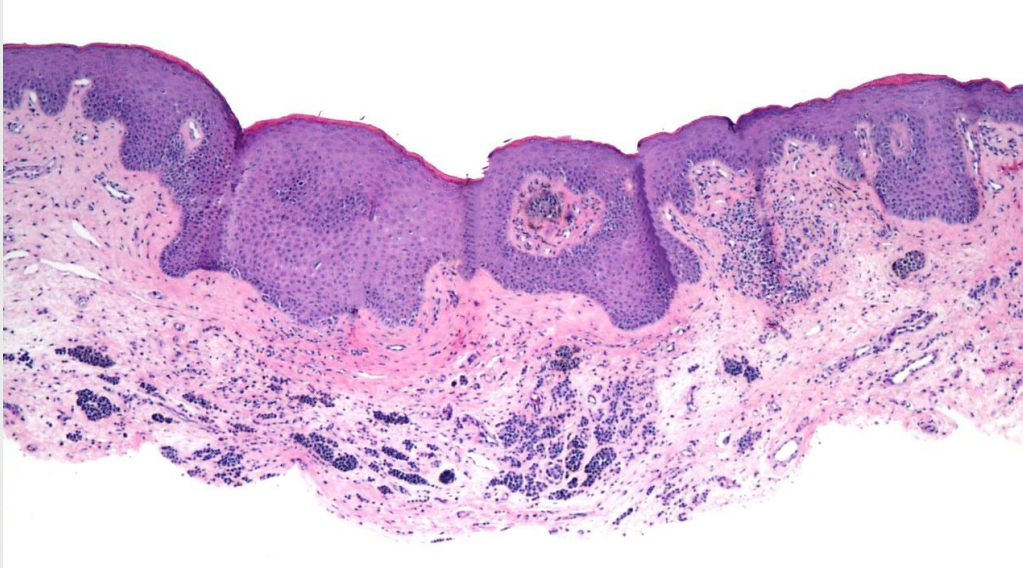


Melanocytes are inconspicuous and rare melanophages are present in the superficial dermis.

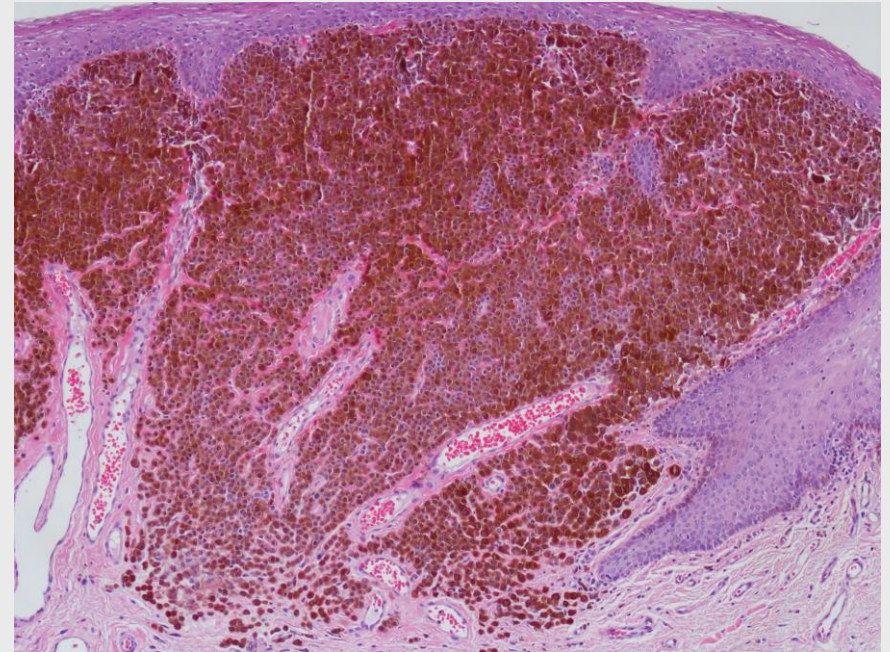
Genital Naevus

- Genital naevus is a benign melanocytic neoplasm located in the genital region.
- About 20% of all women have pigmented lesions in the genital region (including non-melanotic lesions), but < 5% of such lesions are melanocytic naevi
- Unlike mucosal melanomas which have mutually exclusive *KIT* and *TP53* mutations, most common and atypical genital naevi contain BRAF p.V600E mutations.
- Although all melanocytic lesions occurring in this anatomical location are by definition genital, the term 'genital naevus' is usually reserved for lesions with a junctional component of single cells and round or fusiform nests, with focal retraction artefact and dyscohesion.

Genital Naevus

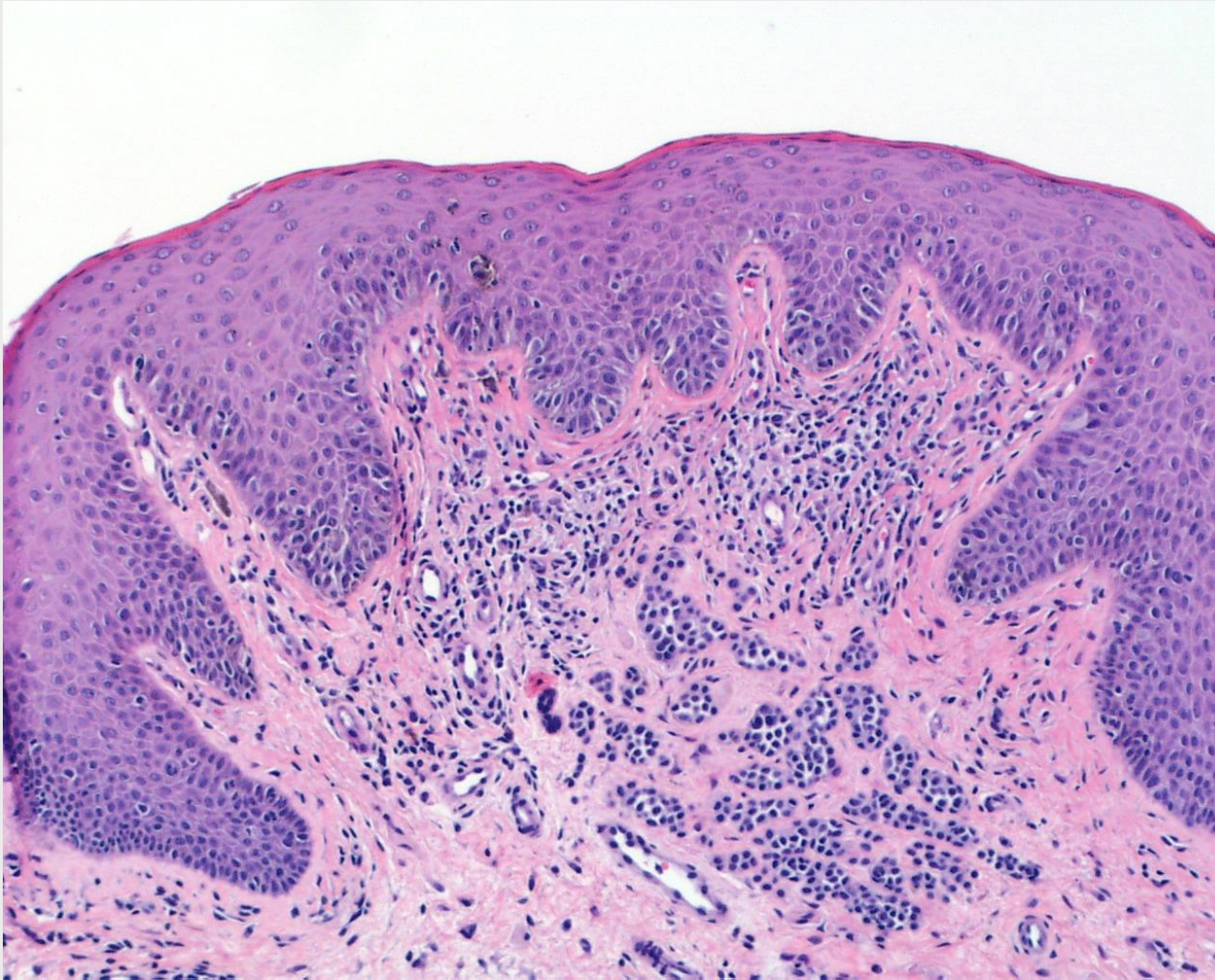


The lesion mostly involves the lamina propria under the epithelium. Small nests with delicate intervening stroma are observed.



Deeply pigmented cells extending deeply into the underlying stroma with evidence of cellular maturation.

Genital Naevus



There is a junctional component of single cells and small nests. The cells of the dermal component display mild atypia.

Genital Naevus

- **Essential and desirable diagnostic criteria**

- Essential:

- Pigmented genital lesion
- Benign melanocytic proliferation

- Desirable:

- Mild atypia, and superficial mitosis in the dermis, if any

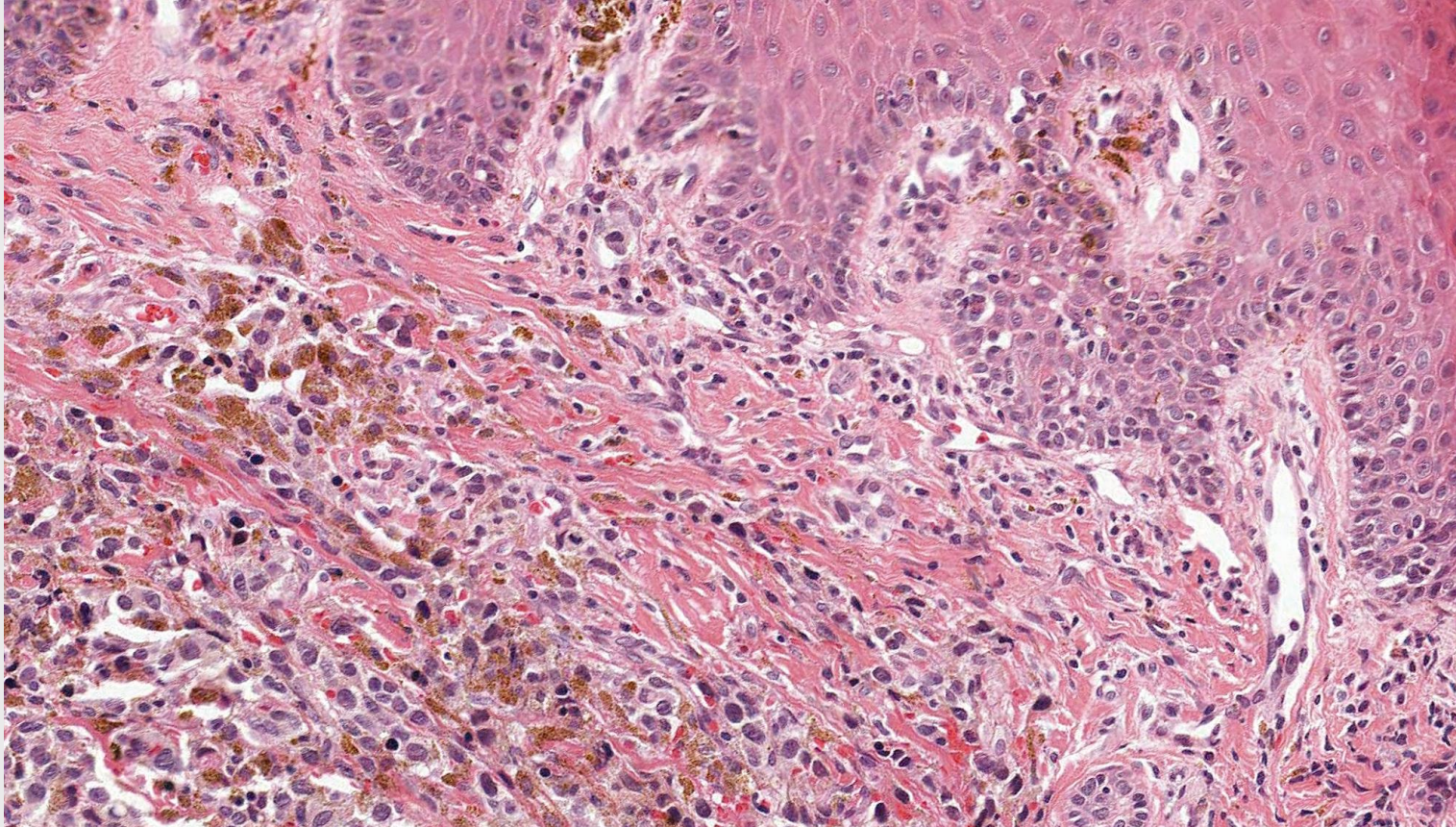
- **Differential diagnosis**

- Genital melanomas are much more common in elder individuals (postmenopausal women).
- Melanomas have a higher degree of cytological atypia, lack maturation, and have more dermal mitotic figures, some of them with atypical shapes.
- In melanomas, HMB45 is usually patchy, and Ki-67 highlights proliferating cells throughout the lesion.
- Dysplastic naevi share many features with genital naevi, in particular the architectural disorder (bridging and lamellar fibrosis).

Mucosal Melanoma

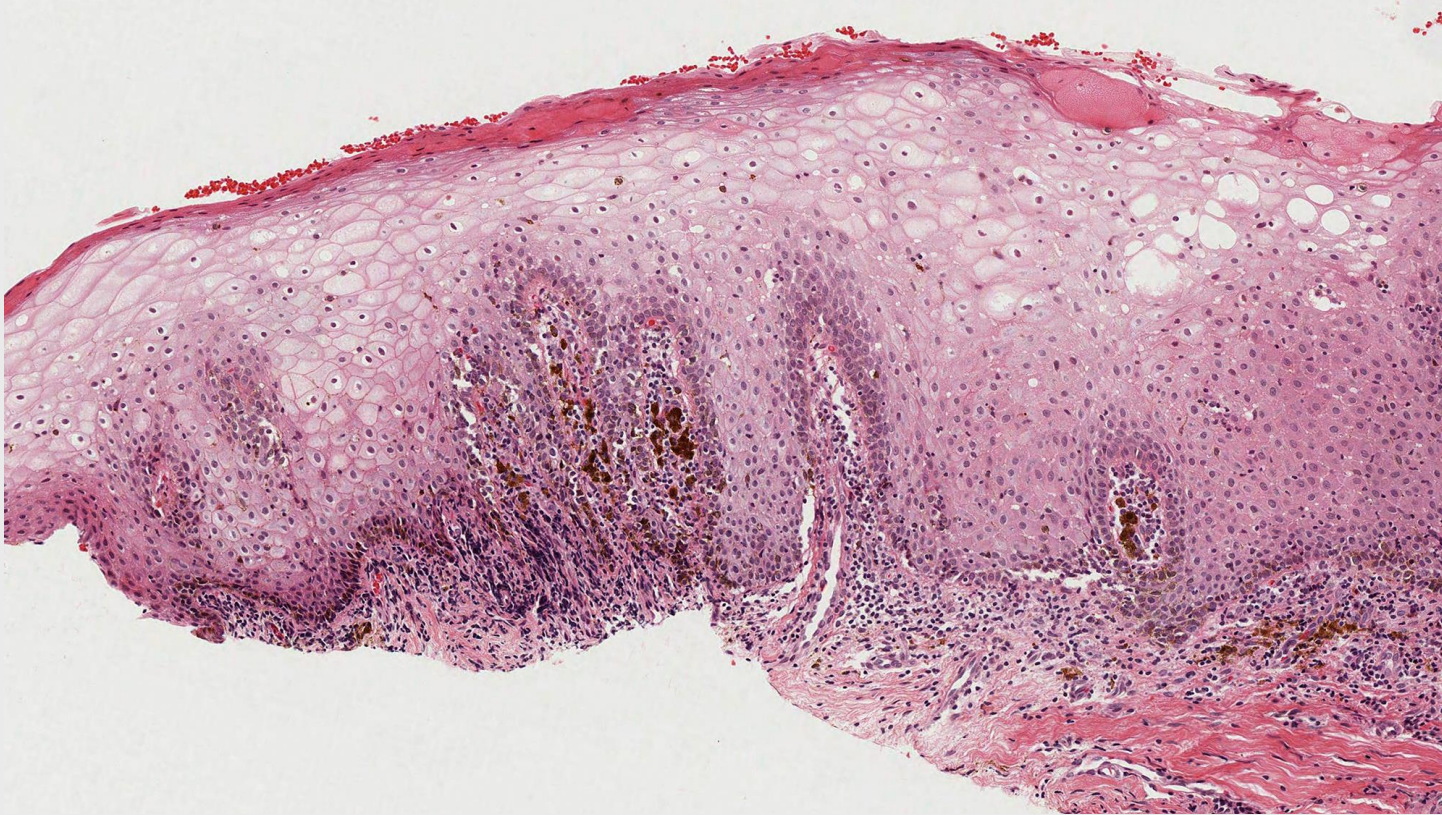
- Mucosal melanomas are melanomas arising in mucosal sites, including anogenital, oral, and sinonasal mucosa.
- Subtypes: Desmoplastic mucosal melanoma; Nodular mucosal melanoma; Mucosal lentiginous melanoma
- The most common sites are the head and neck mucosa (sinonasal and oral), followed by anorectal mucosa and female genital tract.
- No UV genetic signature.
- The most common somatic mutations affect *BRAF*, *NRAS*, *KIT*, *NF1*, *SPRED1*, *SF3B1*, *CDKN2A*, *PTEN*, *ATRX*, *TP53* with frequent amplifications of *CCND1*, *PAK1*, *GAB2*, *TERT*, *CDK4*, *MDM2*, *YAP1* and *CRKL* and deletions of *CDKN2A*, *PTEN*, *NF1*, and *SPRED1*
- *BRAF* and *KIT* mutation testing may assist choice of treatment.

Mucosal Melanoma



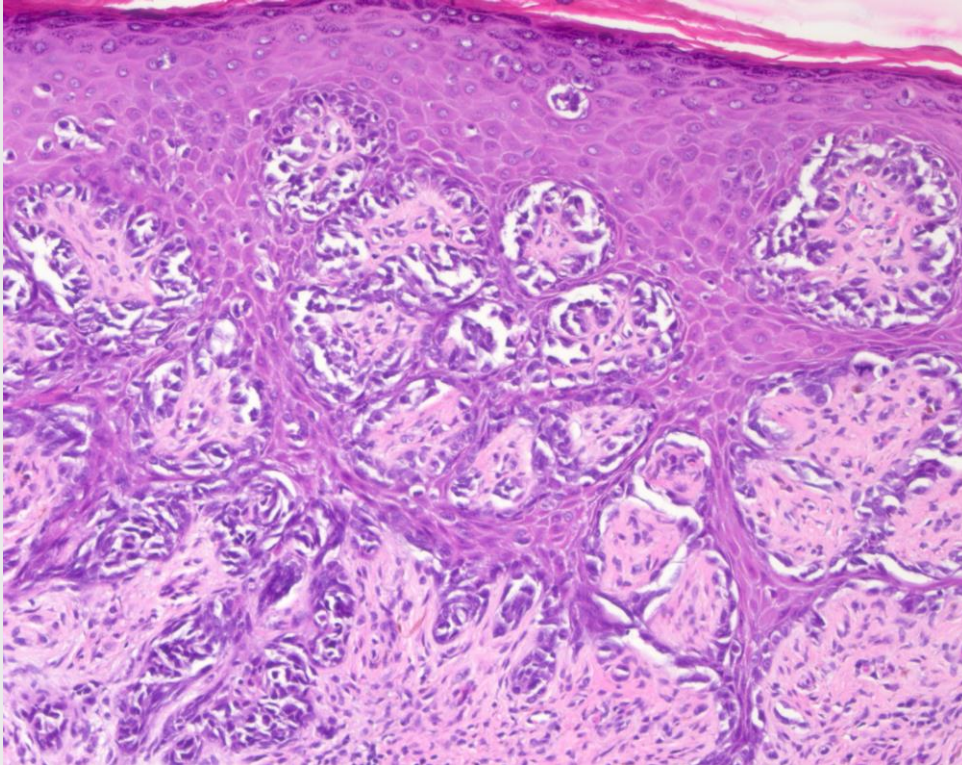
The invasive tumour is composed of uniformly atypical epithelioid cells (bottom left), admixed in this case with numerous melanophages. There is involvement of the overlying epithelium by atypical melanocytes, mostly basal in this field.

Mucosal melanoma



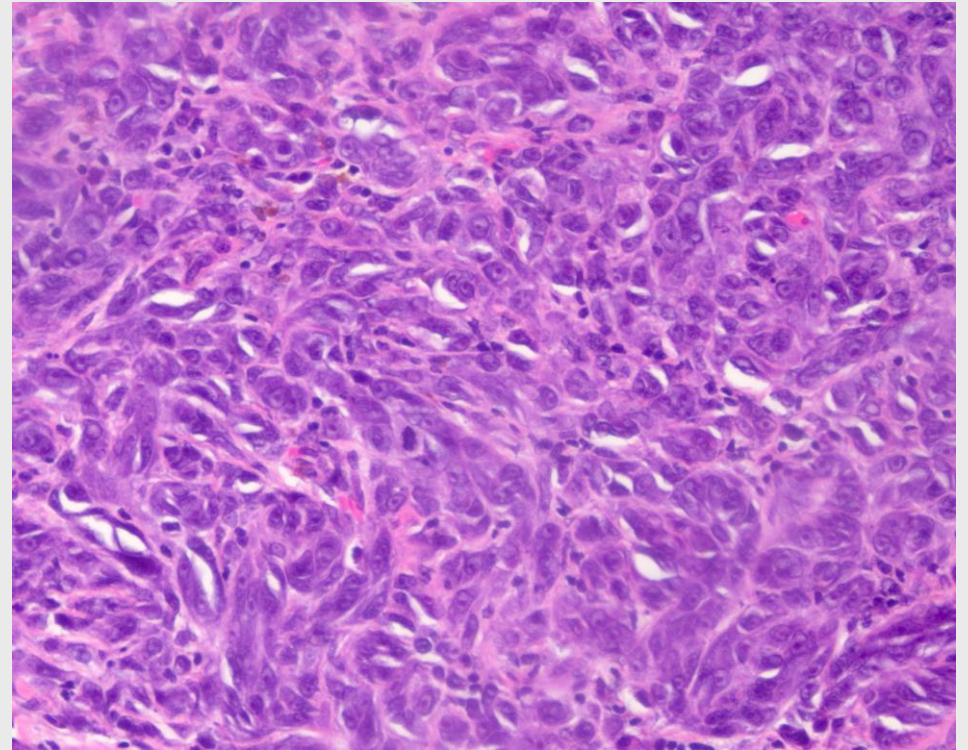
In the adjacent squamous epithelium, there is a basal (lentiginous) proliferation of atypical melanocytes (relatively subtle, as is often the case), with melanophages and lymphocytes in the subepithelial stroma.

Vulval melanoma



In situ melanoma showing a confluent nested and lentiginous proliferation of atypical melanocytes involving the basal epidermis. An occasional cell shows pagetoid spread.

(Richard Scolyer)



Invasive component: the large and pleomorphic invasive melanoma cells are epithelioid and spindle in shape. An occasional mitosis is present, and there is a small amount of melanin pigment.

Mucosal melanoma

- **Essential and desirable diagnostic criteria**
- Essential:
 - Melanocytic tumour with malignant features from a mucosal site
 - The diagnosis of primary mucosal melanoma, especially in the gastro-intestinal tract, requires consideration of a visceral metastasis originating from a melanoma elsewhere, including cutaneous melanomas that underwent complete regression
- Desirable:
 - Reactivity for melanocytic markers (if needed)
- **Other considerations**
 - Vulvar melanoma often shows an intraepidermal component with confluent nested and lentiginous growth pattern and with pagetoid spread
 - In contrast, vaginal melanoma is typically characterized by a lentiginous growth of single atypical melanocytes in the basal epithelial layer, sometimes with nests or confluent growth.
 - A subepithelial lymphocytic infiltrate is common.
 - A desmoplastic component may be present and such lesions lack the high tumour mutation burden of desmoplastic melanomas in sun-damaged skin.

Conclusion

- Melanocytic naevi do occur at mucosal sites, with most subtypes recognised.
- However, genital naevus is a benign melanocytic neoplasm located in the genital region with distinctive features.
- Mucosal melanomas in the oral cavity may be recognised early and diagnosis may be challenging, particularly in small or crushed biopsies.
- In less accessible sites, including the genital tract, late presentation with large lesions
- The use of ICCR datasets is helpful, where these exist.