# PATHOLOGY OF THE SKIN
# 2. Tumours of the skin

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- **Tumour (Neoplasia)**
  - ***Benign or malignant***
- **Malignant tumour**
  - ***Primary cutaneous tumour***
  - ***Metastatic tumour***

# Primary Cutaneous Malignant Skin Tumours

- **Epithelial (carcinomas)**

  **[Non melanoma skin cancer (NMSC): most common human cancer]**

  - ***basal cell carcinoma***
  - ***squamous cell carcinoma***
  - ***skin adnexal carcinomas (e.g. sebaceous carcinoma, Merkel cell carcinoma, microcystic adnexal carcinoma, adenoid cystic carcinoma, apocrine carcinoma)***

    **[Some adnexal tumours (benign and malignant) can be associated with visceral malignancy (e.g. sebaceous tumours – Muir Torre syndrome)]**

- **Melanocytic (melanoma)**
- **Lymphoid (lymphoma)**
  - **Mycosis fungoides (T cell lymphoma, long term course, clinically can mimic eczema or psoriasis)**
  - **Subcutaneous panniculitis-like T cell lymphoma**
- **Mesenchymal (sarcoma)**
  - **Dermatofibrosarcoma protuberans**
  - **Angiosarcoma (aetiologies: chronic sun-exposure and radiation)**
  - **[Kaposi sarcoma (associated with HHV8)]**

# SKIN CARCINOMA AETIOLOGIC FACTORS

- Ultraviolet (UV) light (sun / sunbeds)
  - Results in DNA damage: formation of pyrimidine dimers (UV signature mutations)
- Polycyclic hydrocarbons
- Ionizing radiation (*also implicated in angiosarcoma*)
- Chronic inflammation
  - Chronic sinus tracts
  - Chronic ulcers (Marjolin ulcer)
- Immunosupression (some tumours are HPV – related)
- Arsenicals

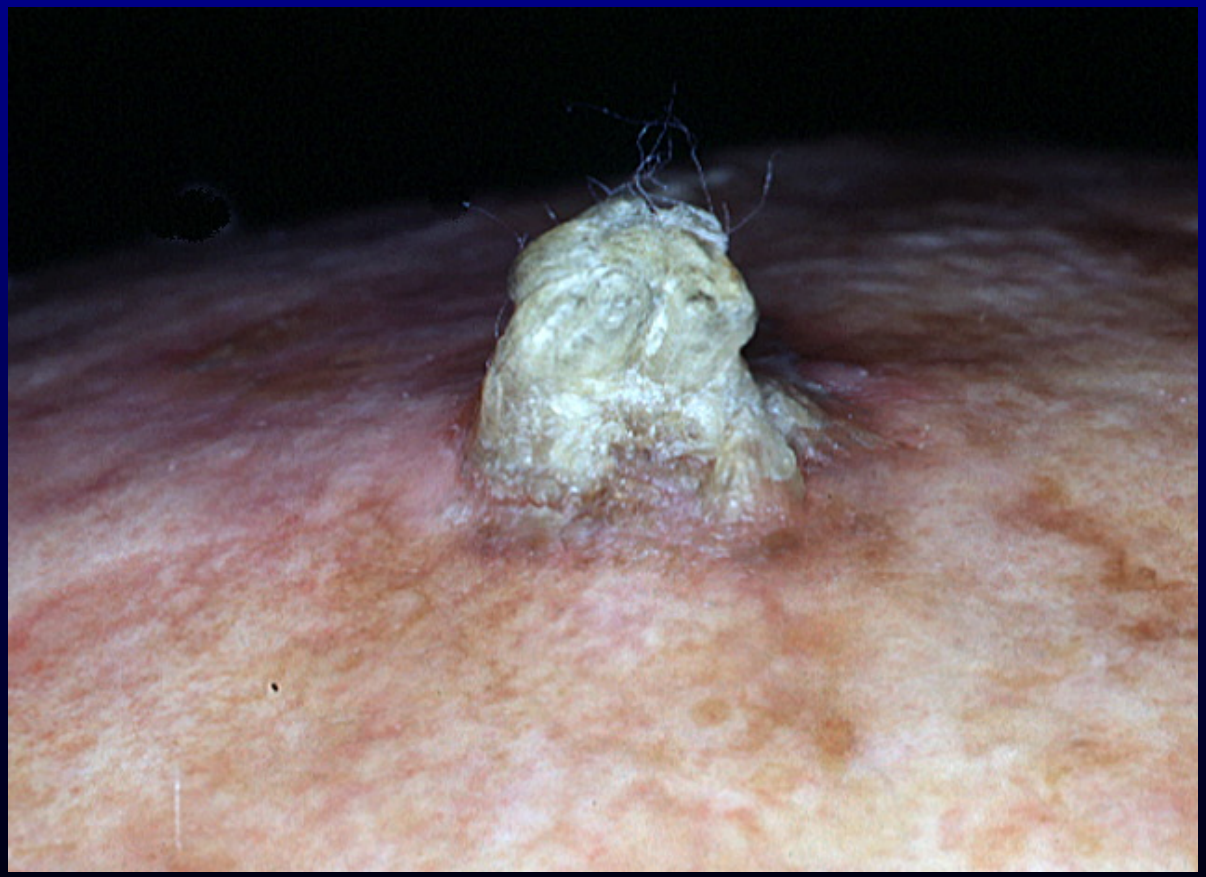
# Epithelial tumours

- Bowen’s disease
- Squamous cell carcinoma
- Basal cell carcinoma
- Sebaceous naevus (benign)
- Muir Torre syndrome tumours
- Merkel cell carcinoma (neuroendocrine tumour of skin)

# Bowen’s disease
# (squamous cell carcinoma in situ)

common on lower limbs in elderly females

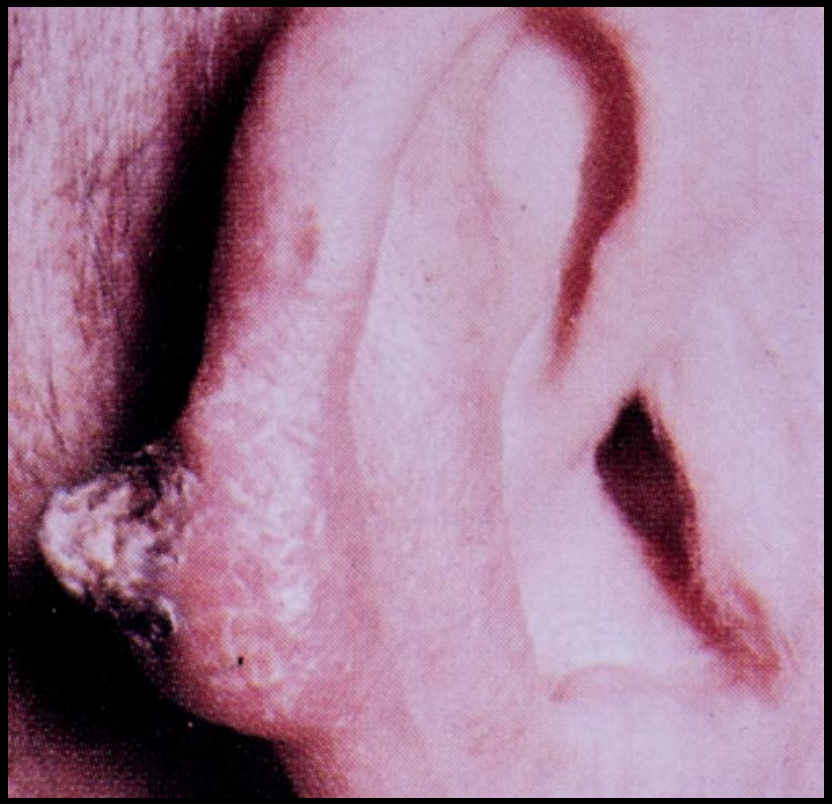
# Keratin horn
# This can overly actinic keratosis, SCC in situ or invasive SCC

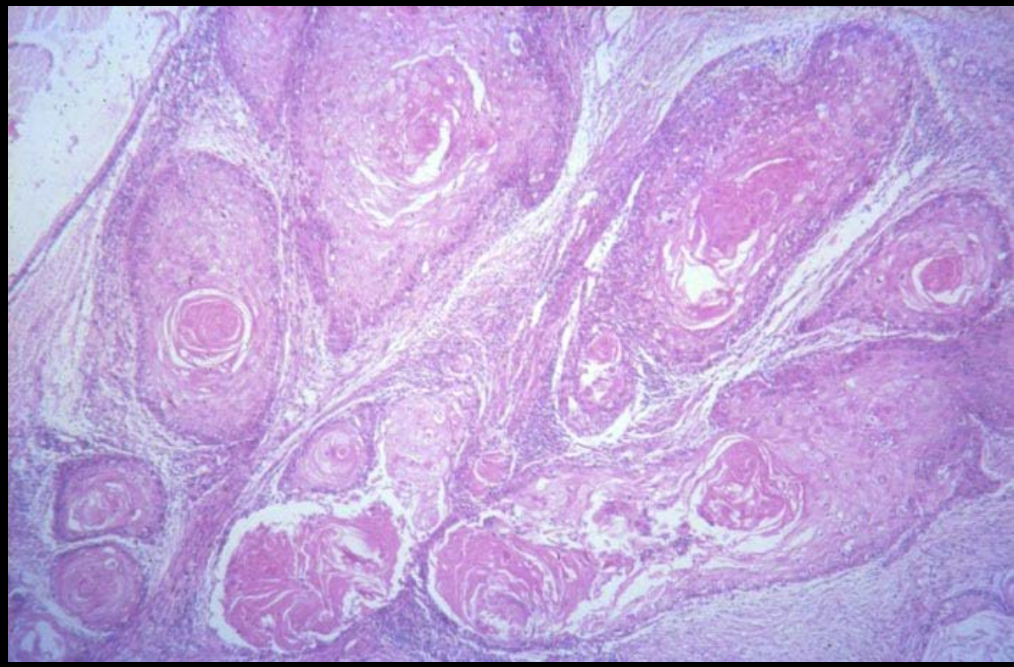


# Squamous cell carcinoma

- Most common on sun-exposed skin, especially head and neck
- Elderly patients M > F
- May arise at sites of chronic inflammation
  - osteomyelitic sinuses
  - varicose ulcers
- Frequent and multiple in following cohorts:
  - Immunosuppressed patients (renal transplantation) HPV-related
  - Xeroderma pigmentosum
  - Epidermolysis bullosa (dystrophic variant)

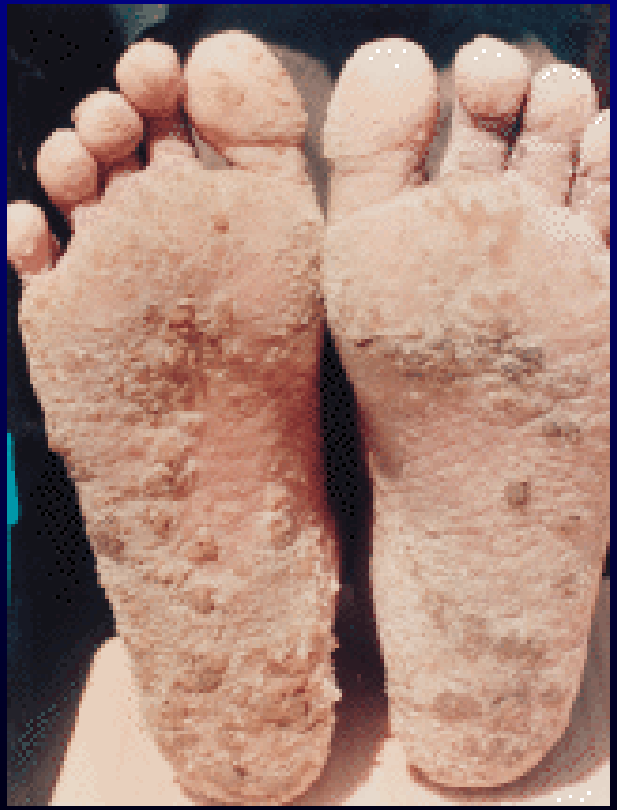
# Invasive squamous cell carcinoma of pinna of ear with overlying cutaneous horn



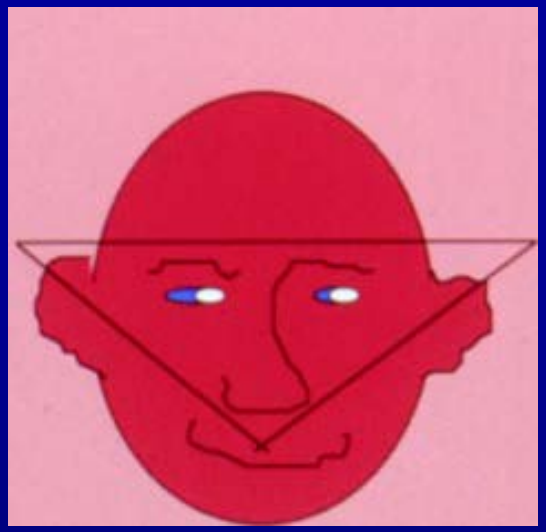


# Arsenical keratoses and squamous cell carcinoma

(contamination of irrigation water from ground table water as a result of forced irrigation due to green revolution GM products)



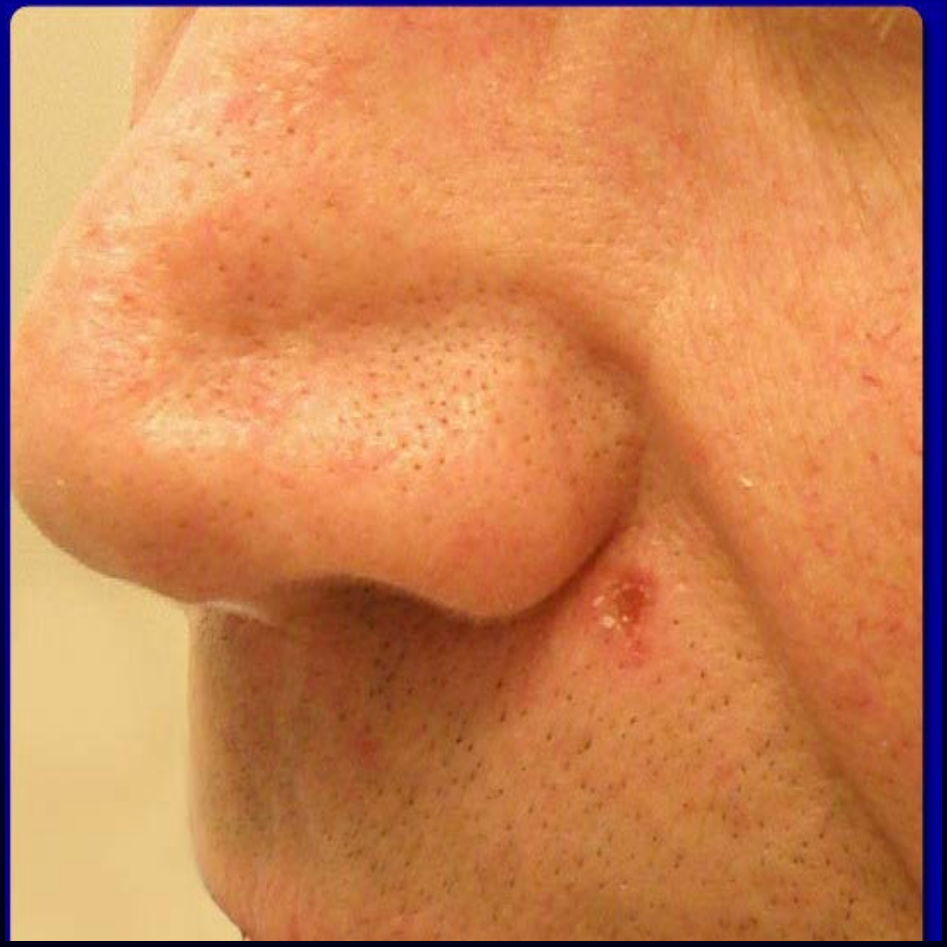
# Basal cell carcinoma

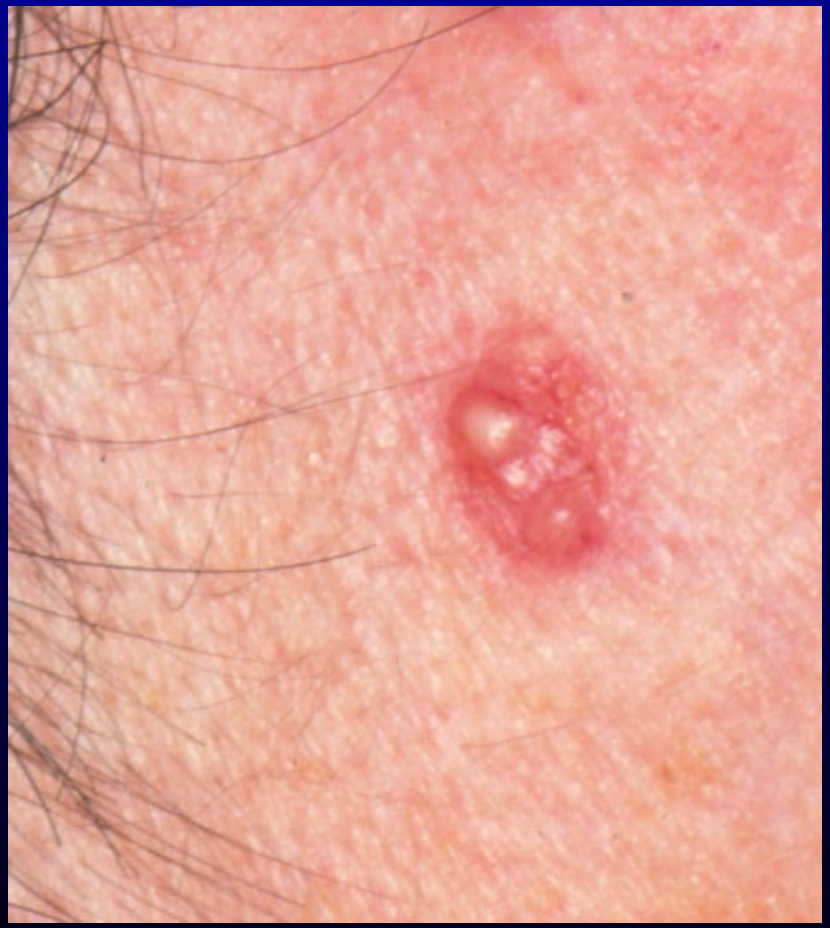


- Most common skin cancer (70%)
- Most common on sun-exposed skin
- Increased incidence with age
- In younger patients arises more commonly on trunk
- Frequently ulcerates centrally but invades very slowly
- Local recurrence risk if incompletely excised
- Rarely metastasizes < 1%
- UV- induced mutations in patched gene (PTCH)
- Gorlin syndrome (naevoid basal cell carcinoma syndrome)
  - multiple BCCs, keratocysts of jaw
  - Germline mutations in patched gene (PTCH) on chromosome 9q (component of the Sonic hedgehog signaling pathway)

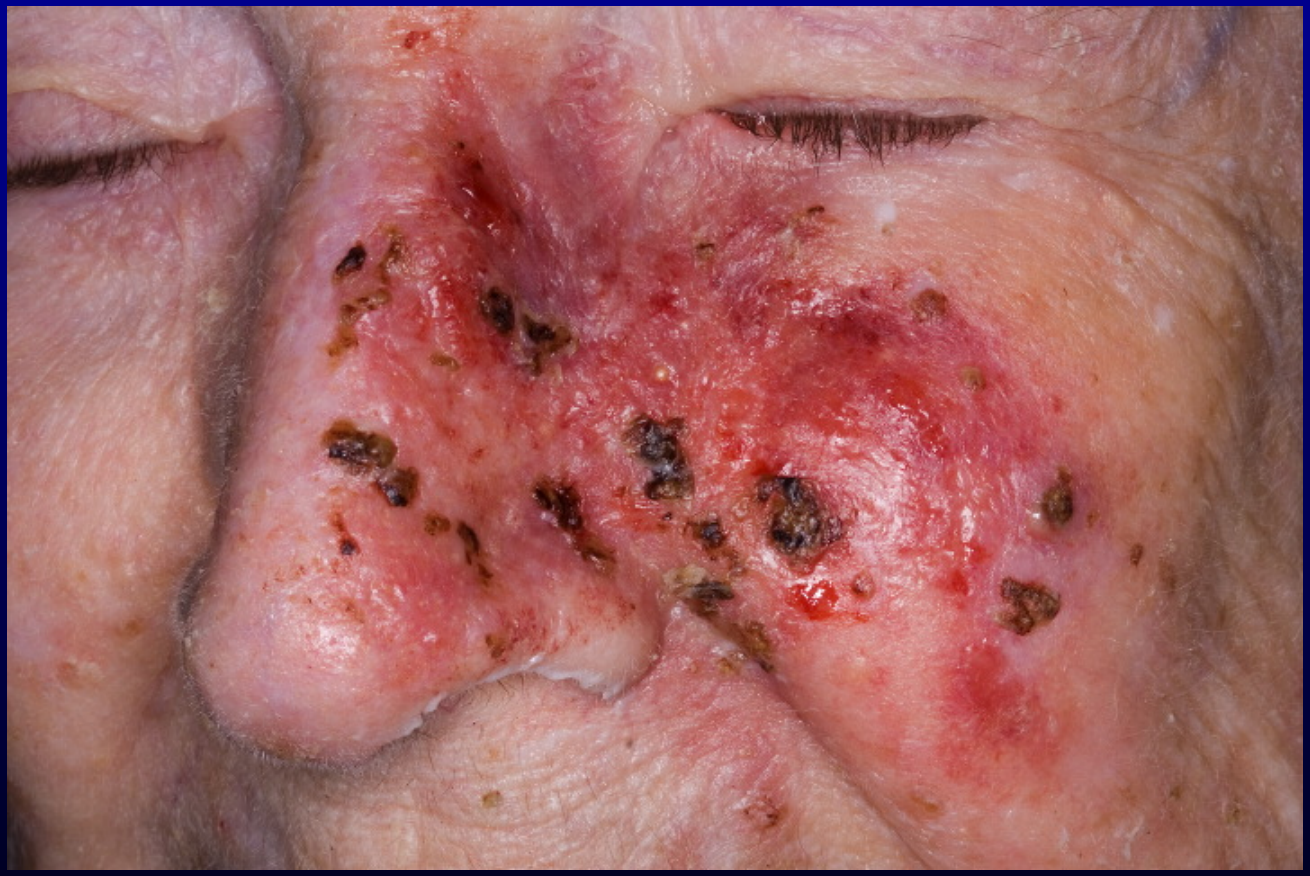
# Basal cell carcinoma

most commonly presents as small pearly papule or eroded plaque

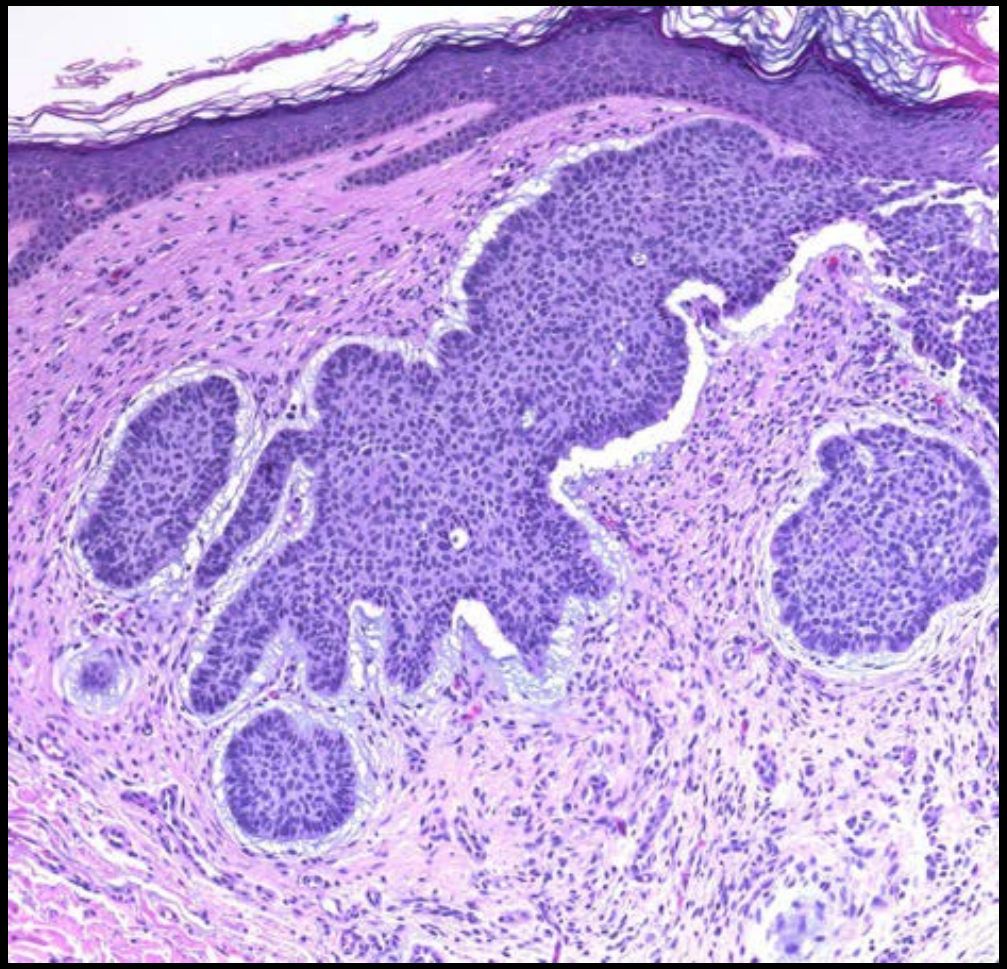




# BCC can be extensive and can be problematic when encroaches on eye (following topical treatment with imiquimod)



**Basal cell carcinoma: basaloid islands invade into dermis with connection to overlying epidermis**



# Basal cell carcinoma

## Molecular events

### Primary tumour

Activation of the Sonic hedgehog signaling pathway

- loss of patched gene (PTCH)
- activation of smoothened gene (SMO)

### Metastases are very rare

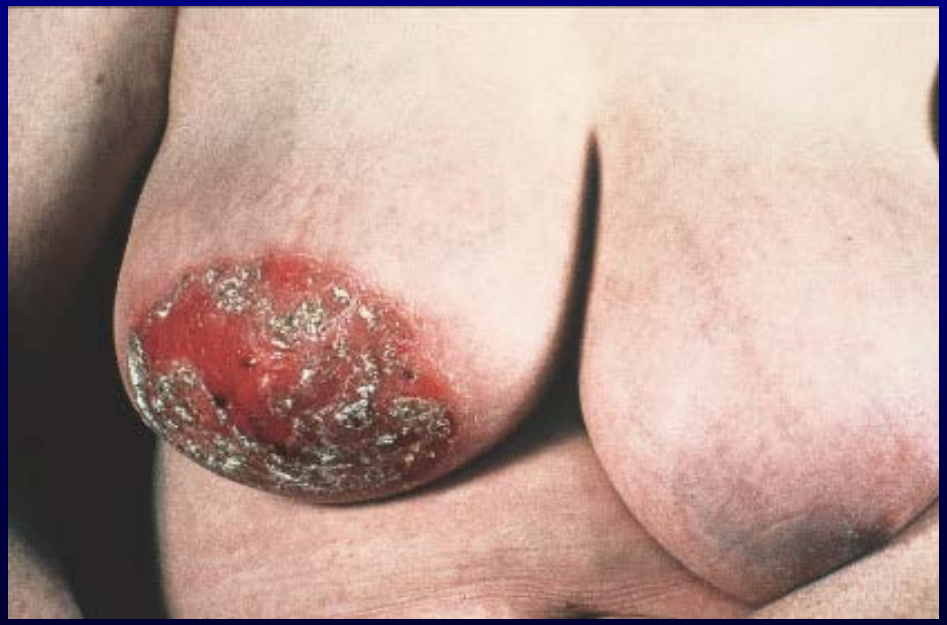
Accumulation of other genetic events e.g. trisomy 6

# Paget's disease of the breast

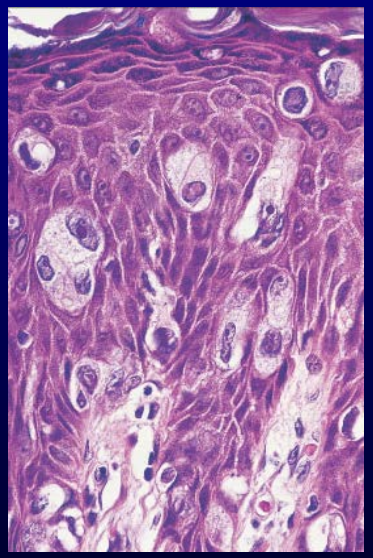
Mammary carcinoma in situ (DCIS) grows in epidermis of nipple

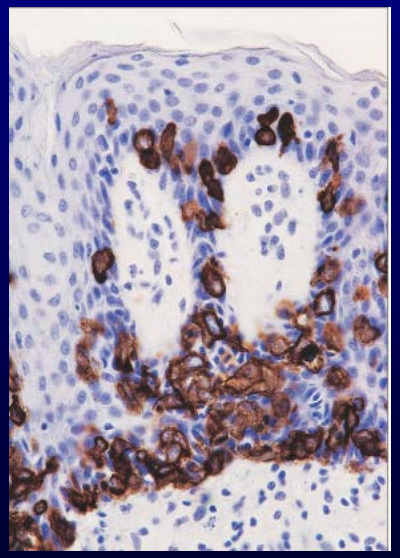
May be associated with underlying invasive mammary carcinoma

Also Paget's disease can occur in the genital area



**Cytokeratin**





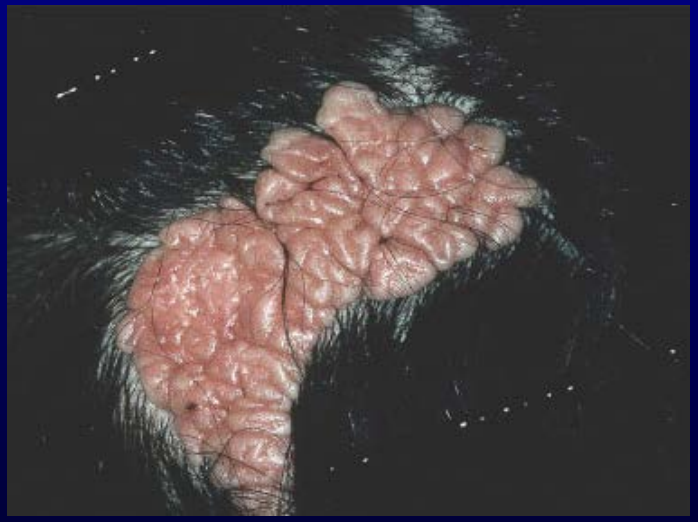
# Sebaceous naevus

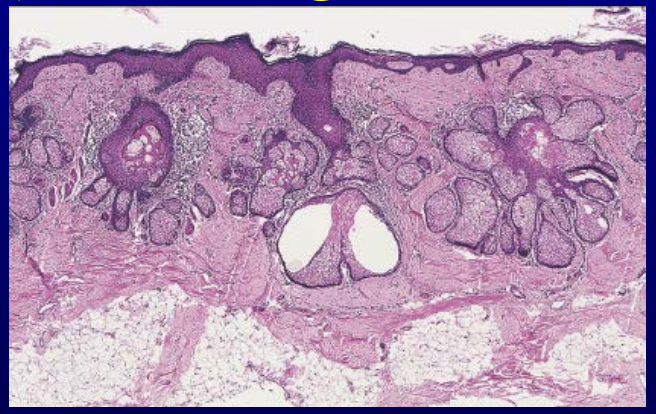
Common on scalp and head and neck

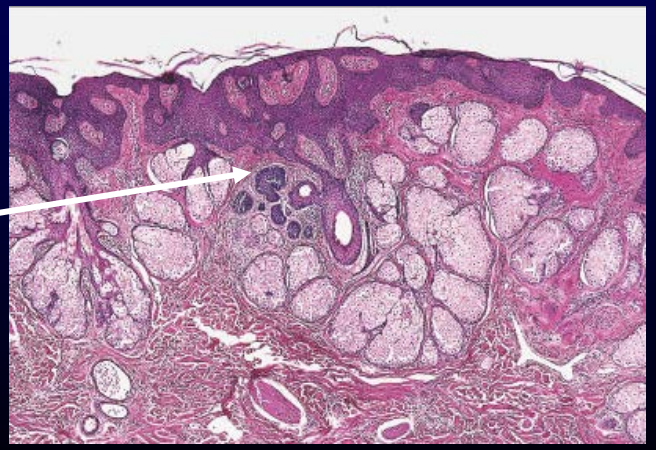
Congenital lesions

Composed of a proliferation of sebaceous glands, apocrine glands

Tumours can arise within them (both benign and malignant)







(Benign) trichoblastoma

Most common benign tumour to arise in sebaceous naevus

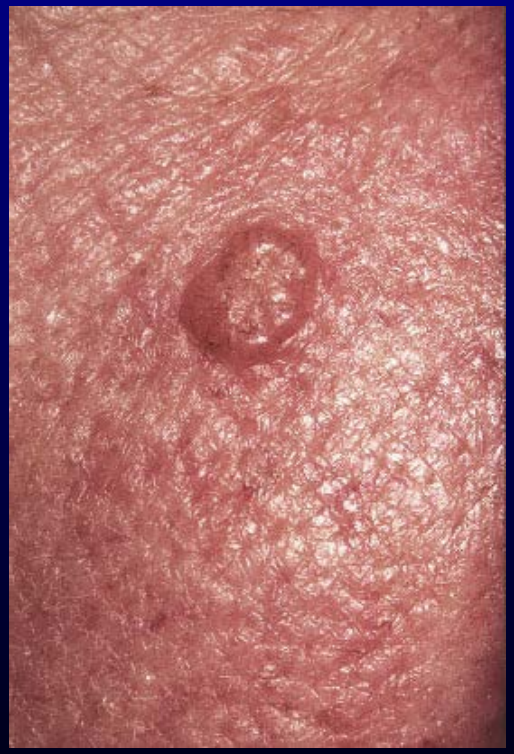
# Muir Torre syndrome

- Autosomal dominant condition
- Associated with visceral malignancy especially hereditary non polyposis colorectal carcinoma
- DNA missmatch repair gene mutations
- Sebaceomas, cystic sebaceous neoplasms

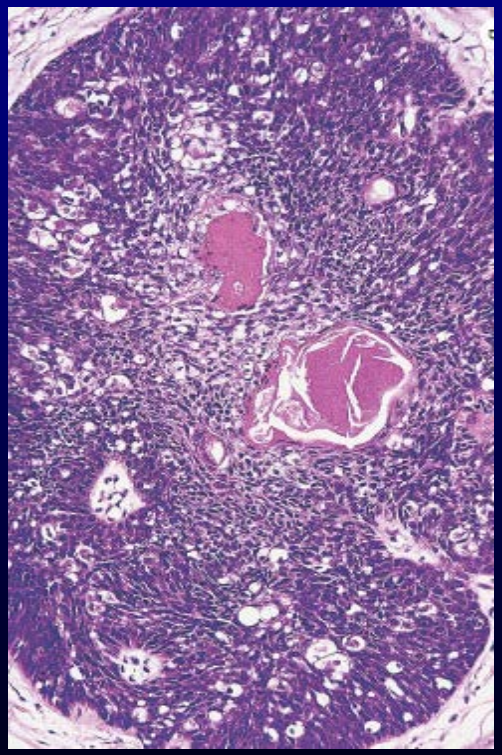
# Muir Torre syndrome

Most classic sebaceous neoplasm in this syndrome is the sebaceoma (majority of these are benign)

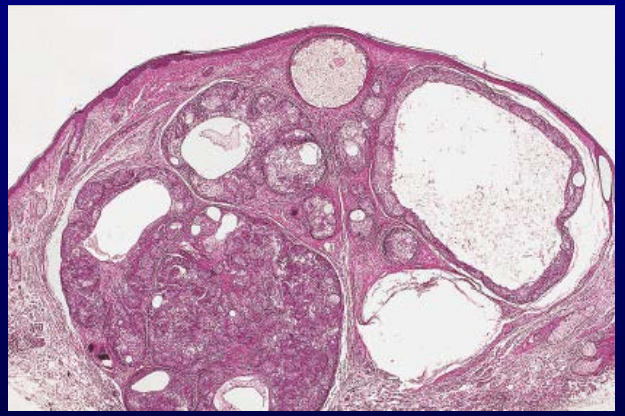
Sebaceoma



Basaloid solid variant with sebaceous differentiation



Cystic variant of sebaceoma



# Sebaceous carcinomas

- Most common around the eye
- Can be aggressive

# Merkel cell carcinoma (Primary cutaneous neuroendocrine cell carcinoma)

- Elderly patient
- Sun exposed areas
- Rapidly growing purplish nodules
- Aggressive behaviour
- Cytokeratin positive (dot-like)
- Neuroendocrine markers positive (chromogranin)

# Melanocytic naevi and melanoma

# Melanocytic naevus

- Benign melanocytic lesion
- Many variants
  - Most common variants
    - Junctional
    - Compound
    - Dermal
  - Congenital or acquired
    - Giant congenital naevus
  - Less common variants that can clinically mimic melanoma
    - Regressing / halo naevus
    - Spindle cell naevus of Reed
    - Spitz
    - Dysplastic

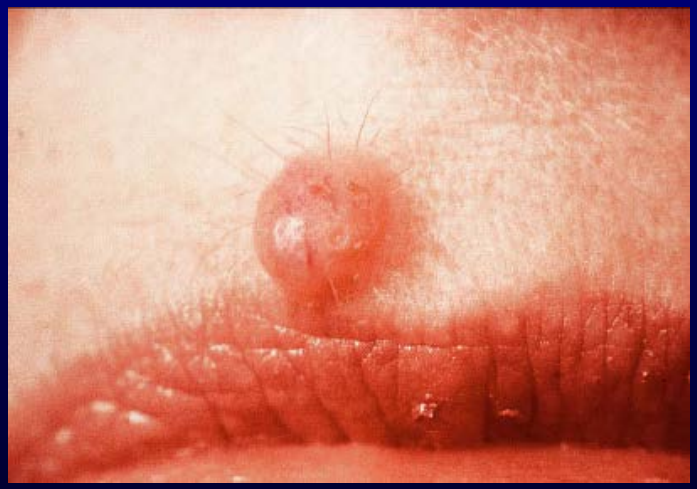
# Melanocytic naevi

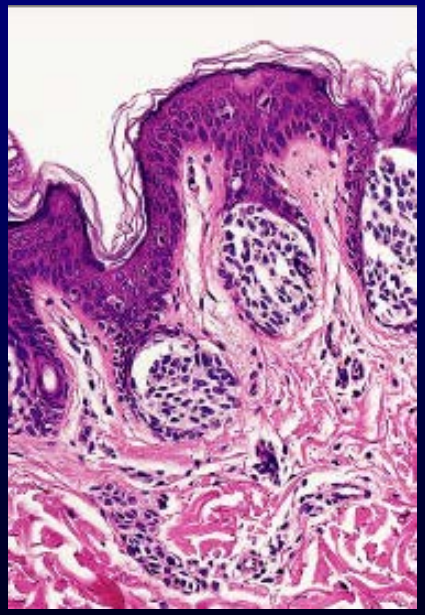
**Junctional naevus**

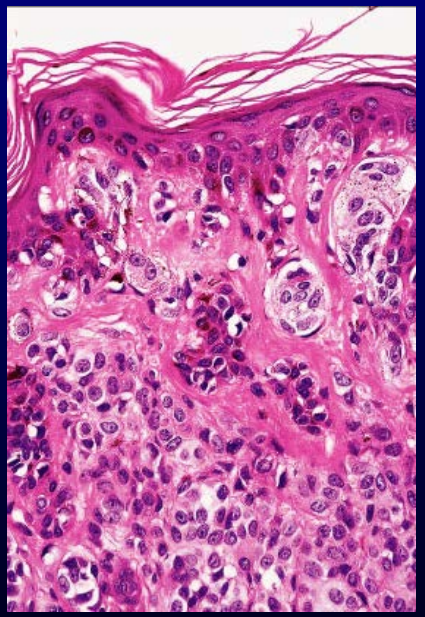
Melanocytes along dermoepidermal junction

**Compound naevus**

Melanocytes along junction and in dermis





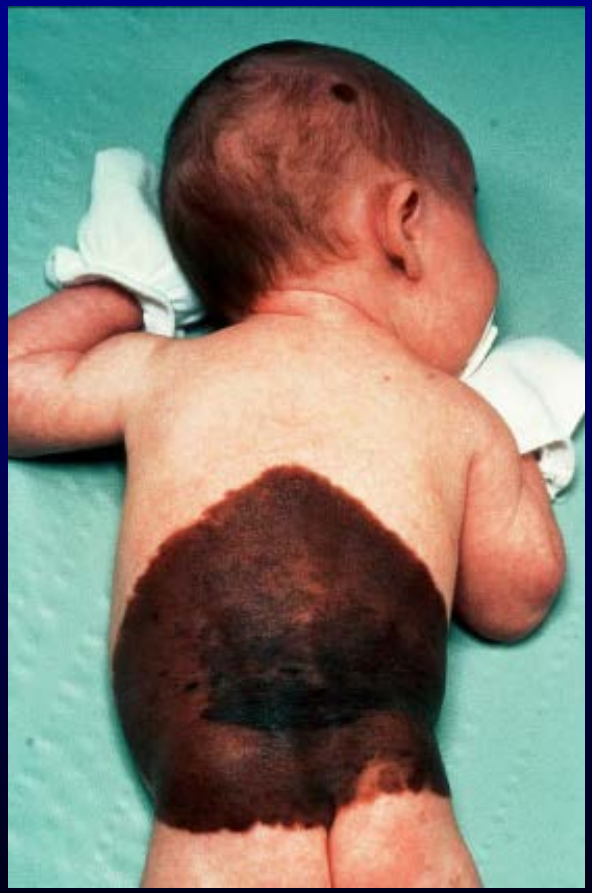


# Giant congenital naevus
# (Garment naevus)

1/20,000 infants

Risk of development of melanoma 6%

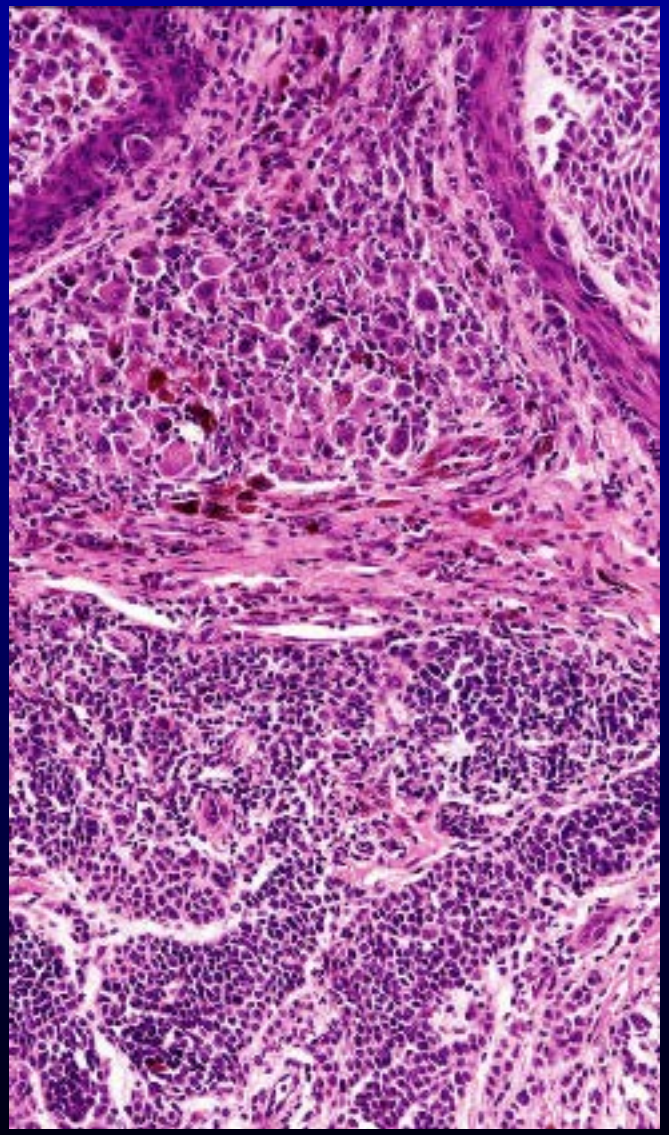
(2 peaks: <10 y and adult life)



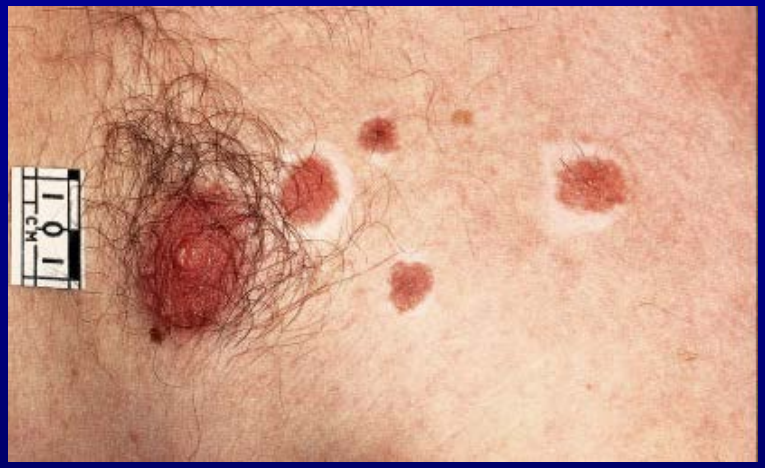
Melanoma arising in a congenital naevus: large melanoma cells (above) with background naevus cells (below)

Melanoma

Naevus

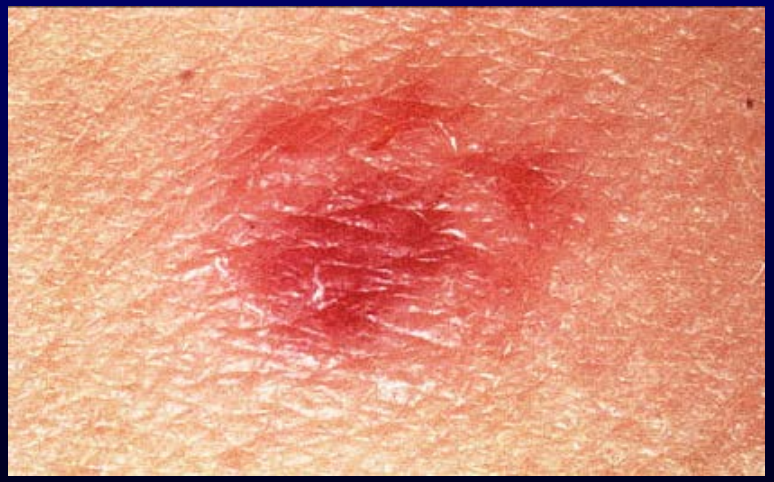


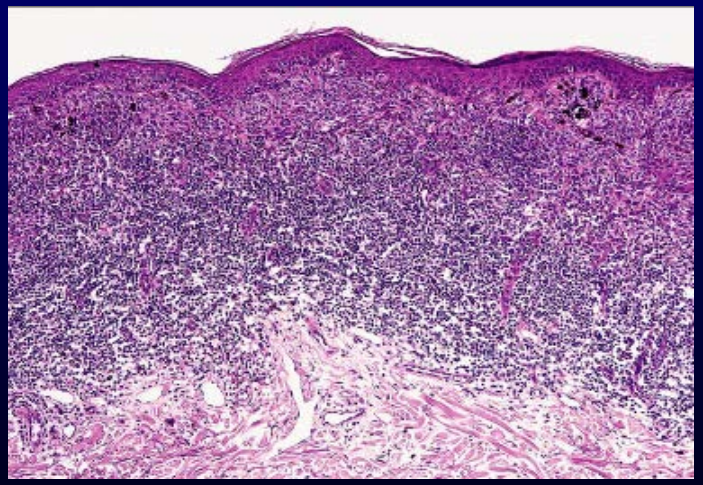
# Inflamed/halo naevi



Benign lymphocytic autoimmune response to naevus

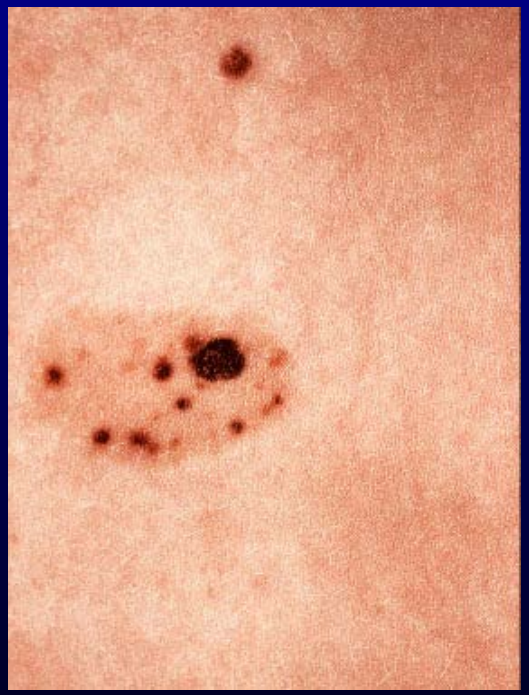
Naevus can regress entirely





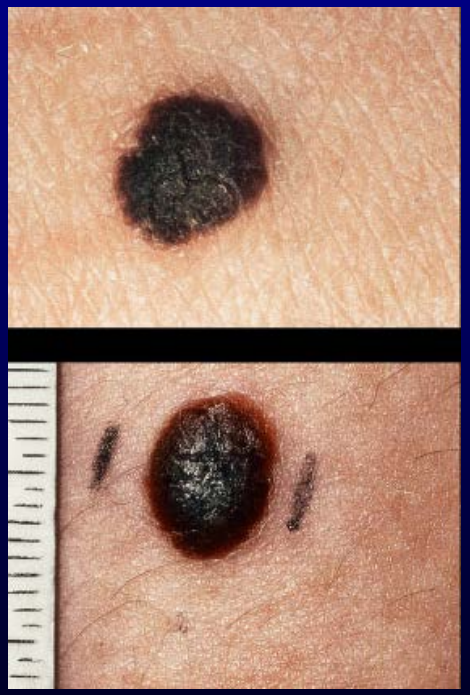
# Melanoma mimics

Naevus spilus (speckled naevus)
nodules of compound naevus within a junctional naevus



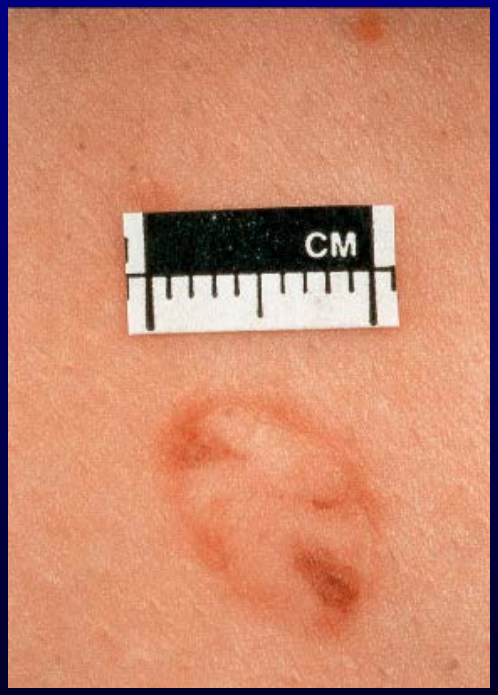
Spindle cell naevus (of Reed)

Most commonly occurs on thigh of young women



Recurrent naevus

(after incomplete excision some naevi recur)



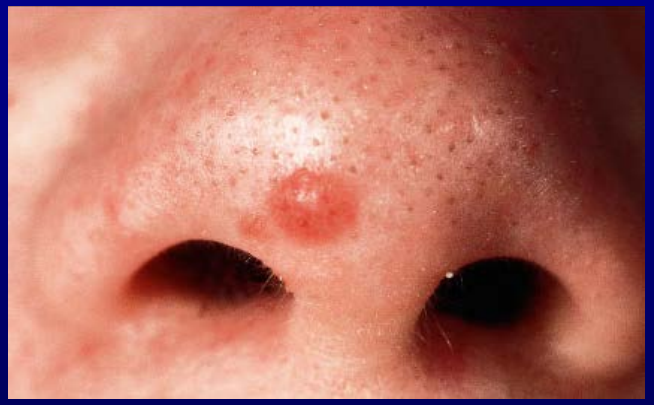
# Spitz naevus

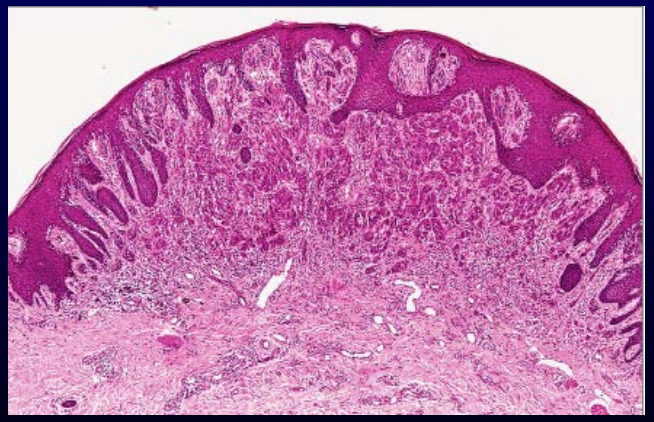
Most commonly occurs in children but can occur in adults

Usually amelanotic

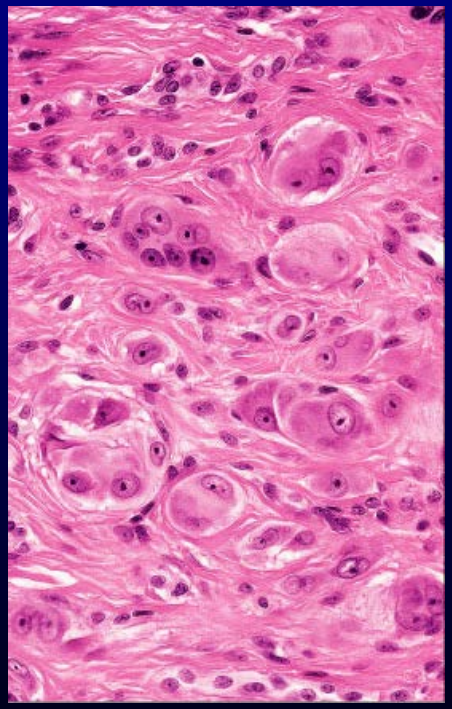
Composed of large plump cells or spindle cells

Can mimic melanoma

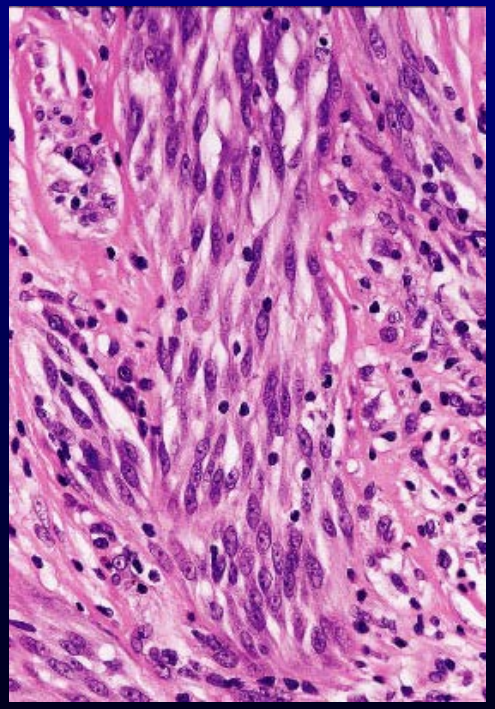




Epithelioid cell variant

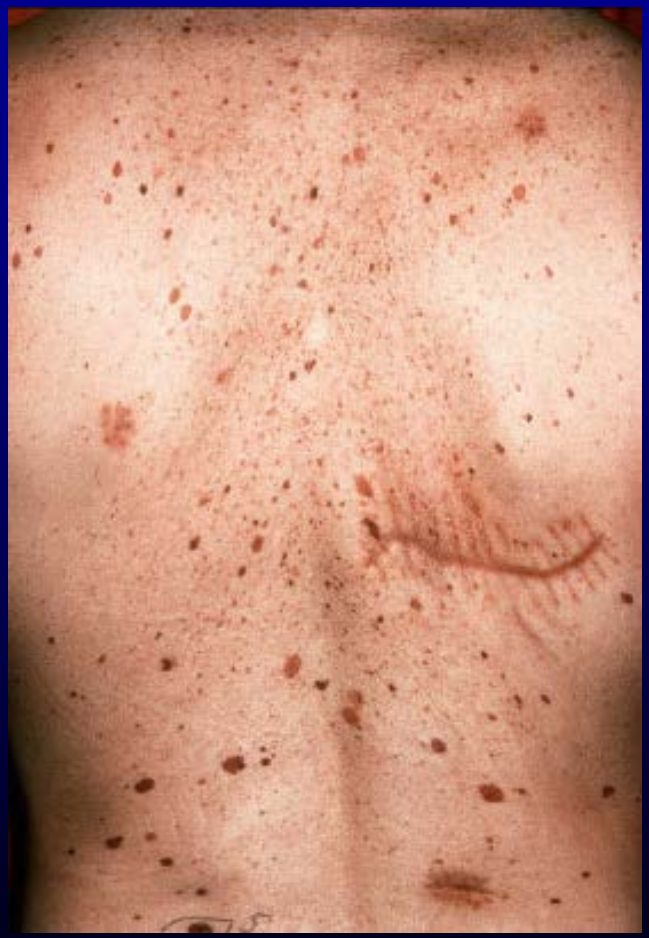


Spindle cell variant



# Dysplastic naevus syndrome

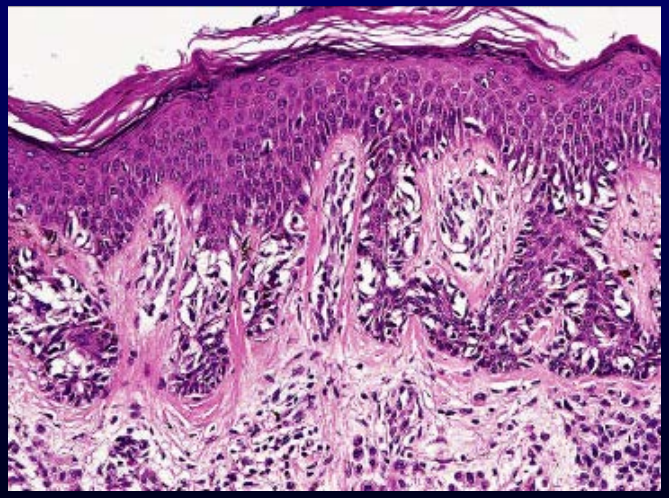
Clinically atypical large naevi

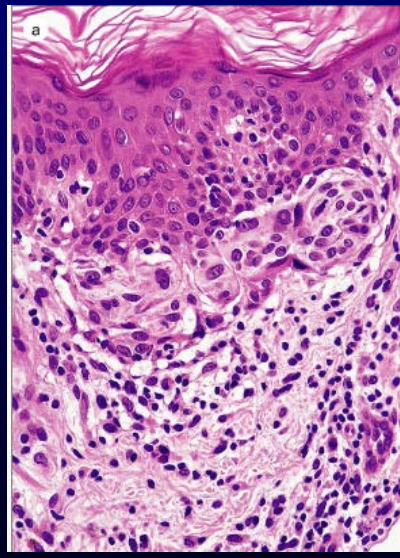


Histologically naevi show cytological and architectural atypia of melanocytes with dermal fibrosis and lymphocytic inflammation

Dysplastic naevi can mimic melanoma

Risk of melanoma





**Classification of dysplastic melanocytic nevi (DMN)**

1. ***Hereditary melanoma***
   a. Individuals with DMN phenotype* and at least one blood relative with melanoma ($D_1$)
   b. Individuals with DMN phenotype and at least two blood relatives with melanoma ($D_2$)
2. ***Familial DMN***
   Individual with blood relatives having DMN phenotype but not melanoma
3. ***Personal history of melanoma***
   Individuals with both DMN phenotype and personal history of melanoma
4. ***Sporadic DMN***
   Individuals with DMN phenotype but no personal or family history of melanoma or a family history of DMN

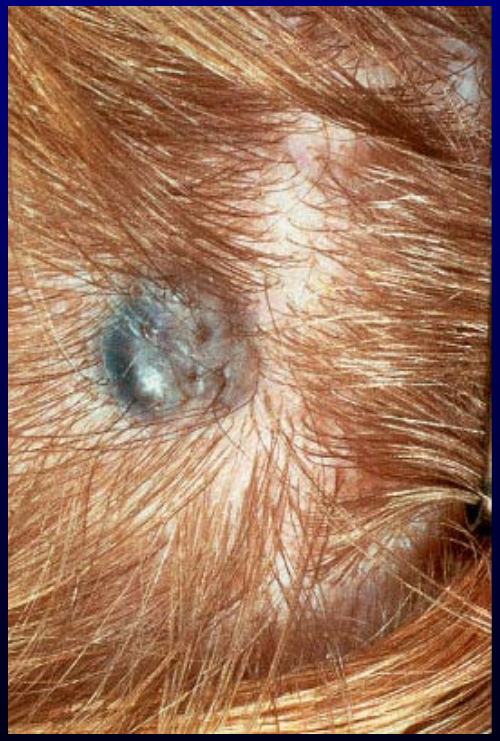
* The minimum criteria for this phenotype have not been quantified. The classic presentation is one of increased numbers of both typical and clinically atypical nevi.
Reproduced with permission from Elder, D.E. et al (1983) *American Journal of Dermatopathology*, **4**, 455–460.

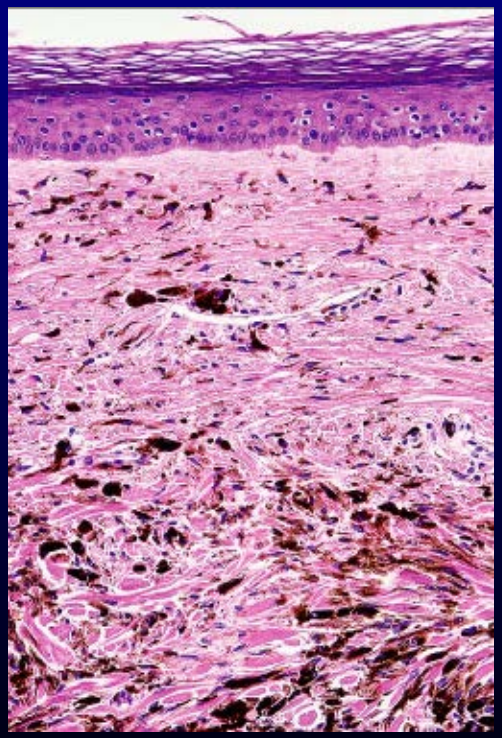
# Blue naevus

Scalp, face, neck and chest are common sites

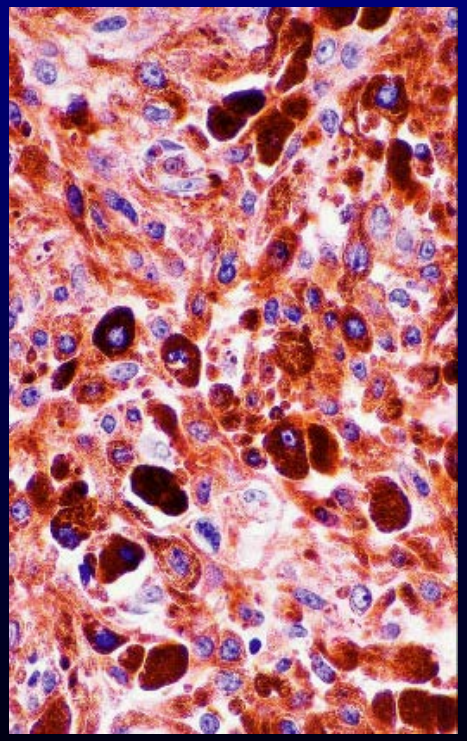
Melanotic dendritic spindled melanocytes

Epithelioid variant is associated with Carney complex (associated with cardiac myxomas and lentigines)





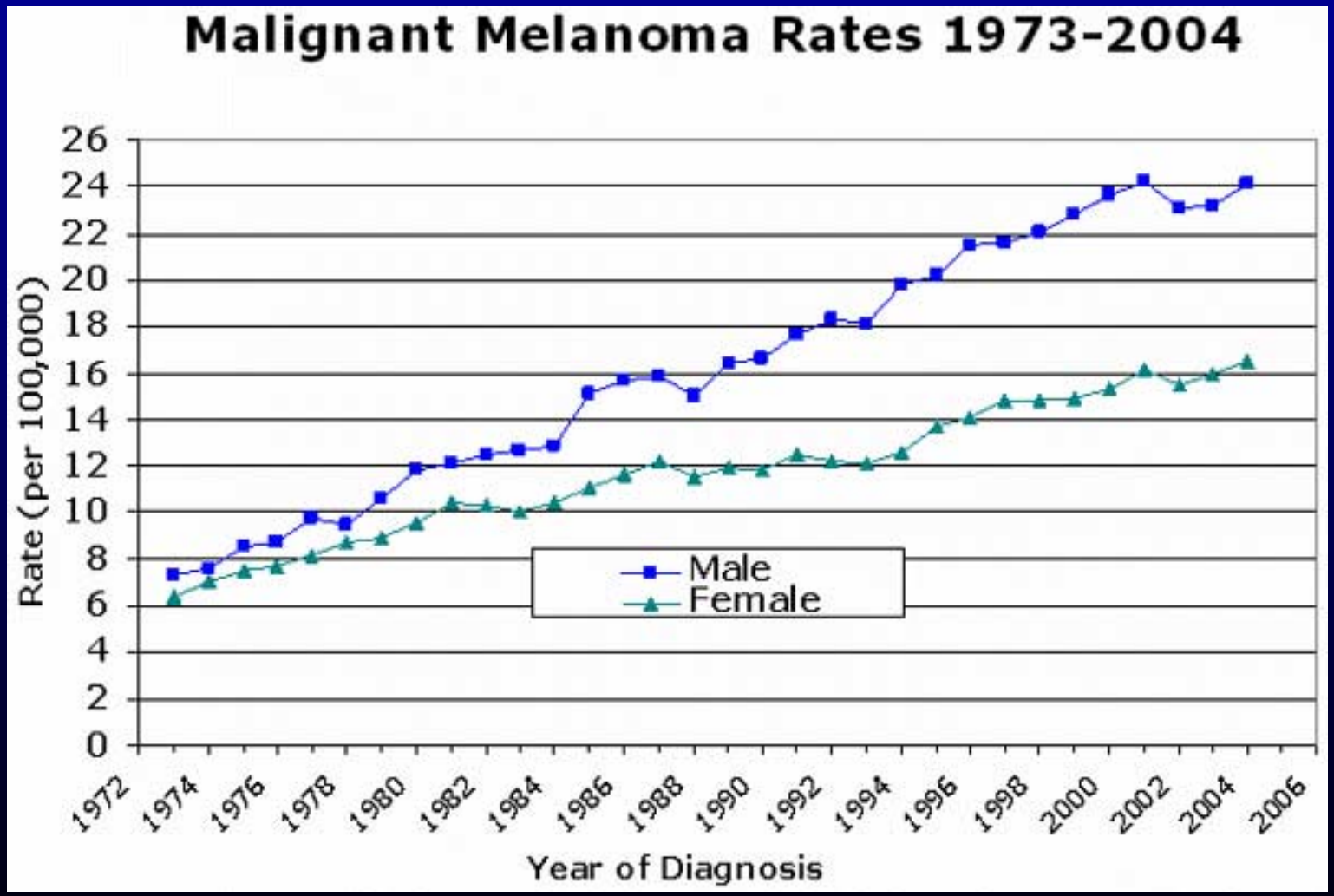
Epithelioid blue naevus



# Malignant melanoma

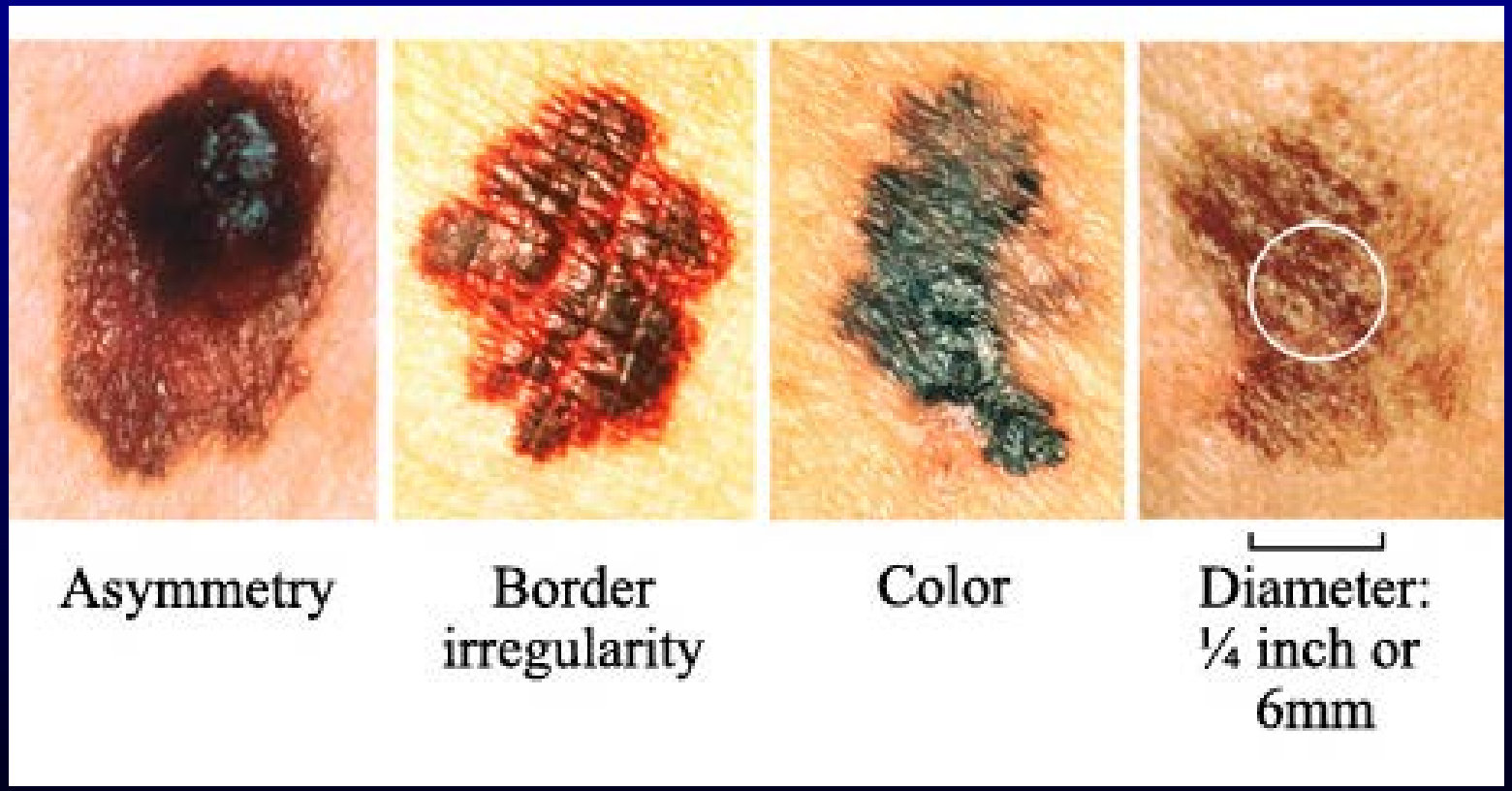
- Incidence is increasing, especially in Australia
  - changes in ozone layer
  - diagnostic criteria have changed and increased screening
- Incidence increases with age
- Prognosis related to stage at presentation, depth of invasion, level of invasion (Clark) and ulceration
  - Most important prognostic indicators in localized melanoma
    1. Tumour thickness (Breslow depth)
    2. Ulceration
- Most common on sun-exposed skin (intermittent exposure worse)
- Acral lentiginous melanoma relatively more common in dark skinned races
- Metastasis by both lymphatic route (lymph nodes) and haematogenous route (liver, lungs)
- Sentinel node mapping for melanomas >1<4 mm Breslow depth
  - 5 year survival 56% when + and 90% when negative
- Some variants (naevoid melanoma) are very difficult to diagnosis
- Primary lesion can regress completely - can present with metastases

# Melanoma is increasing in incidence, especially in higher socioeconomic groups



# Clinical diagnosis of melanoma ABCD rule

(not specific for melanoma as atypical naevi can share these features)



# Malignant melanoma

## Histologic types

Superficial spreading melanoma

Nodular melanoma

Lentigo maligna melanoma

Acral lentiginous melanoma

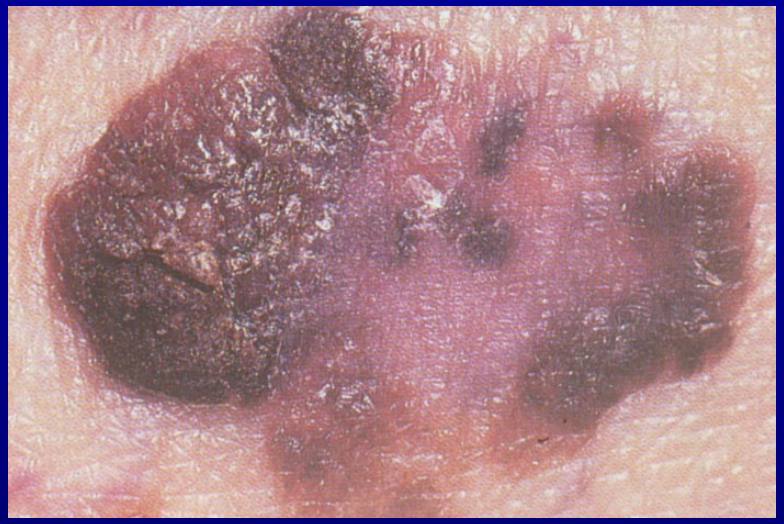
Naevoid melanoma

Small cell melanoma

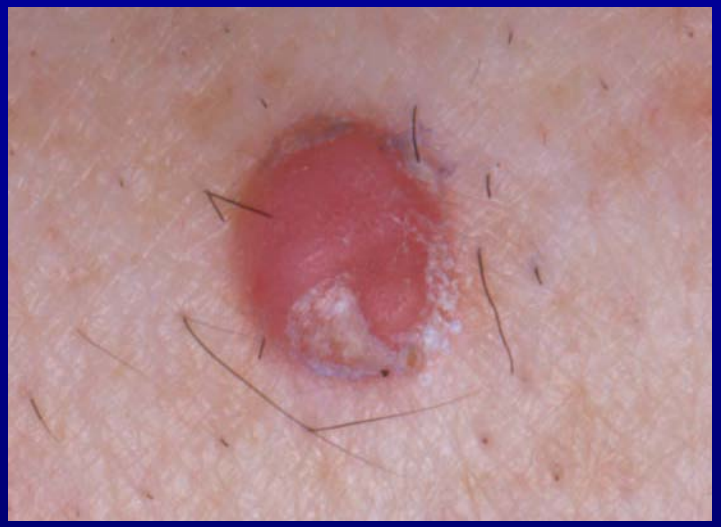
Desmoplastic

Mucosal sites – lentiginous melanoma

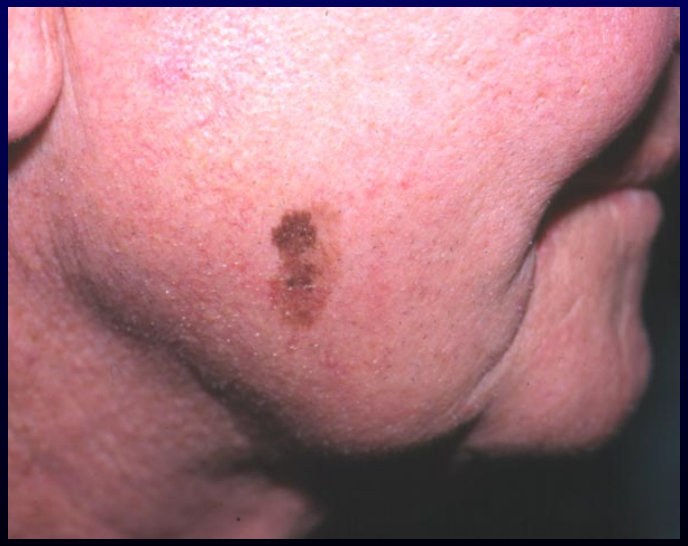
## Superficial spreading malignant melanoma



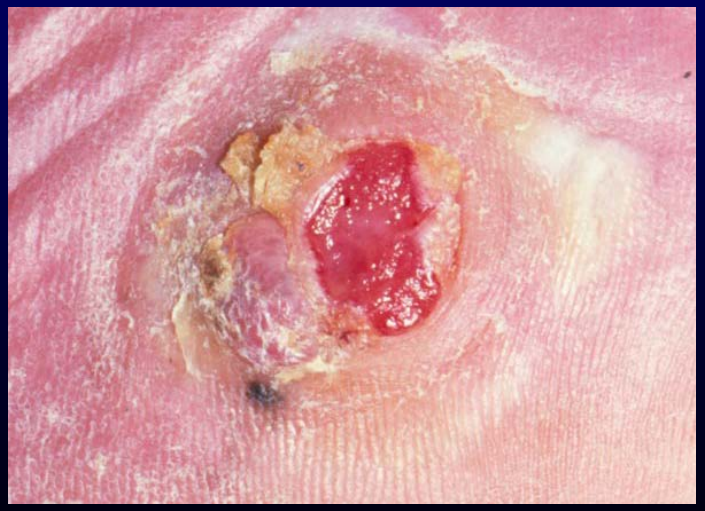
## Nodular melanoma (amelanotic case)



## Lentigo maligna melanoma

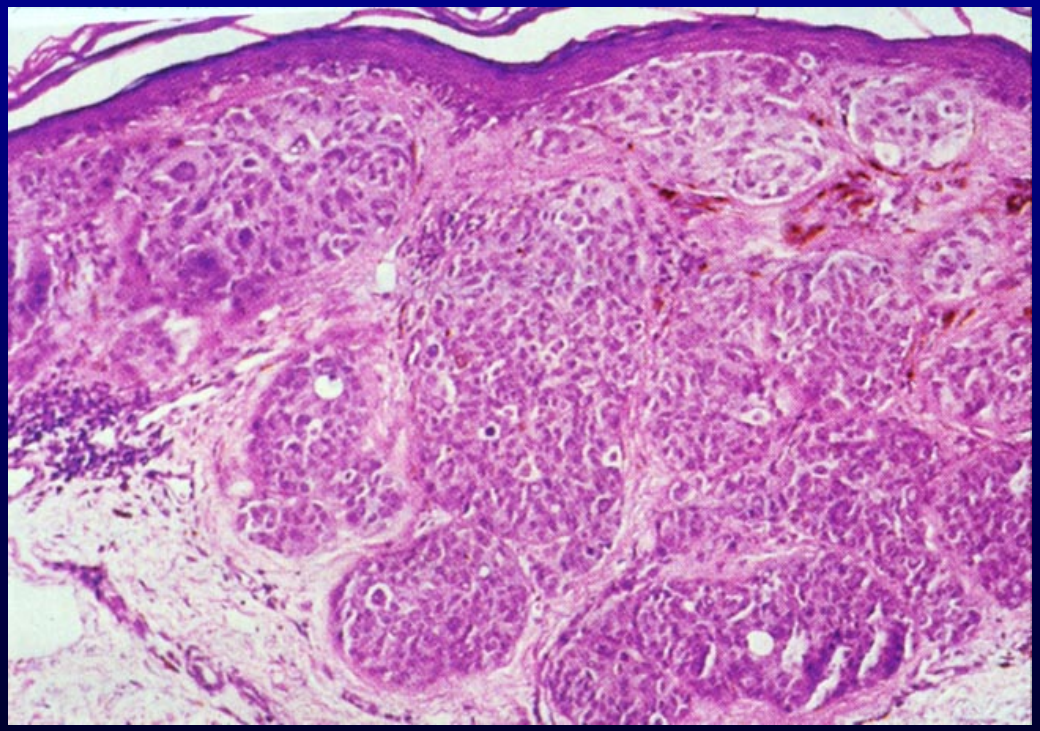


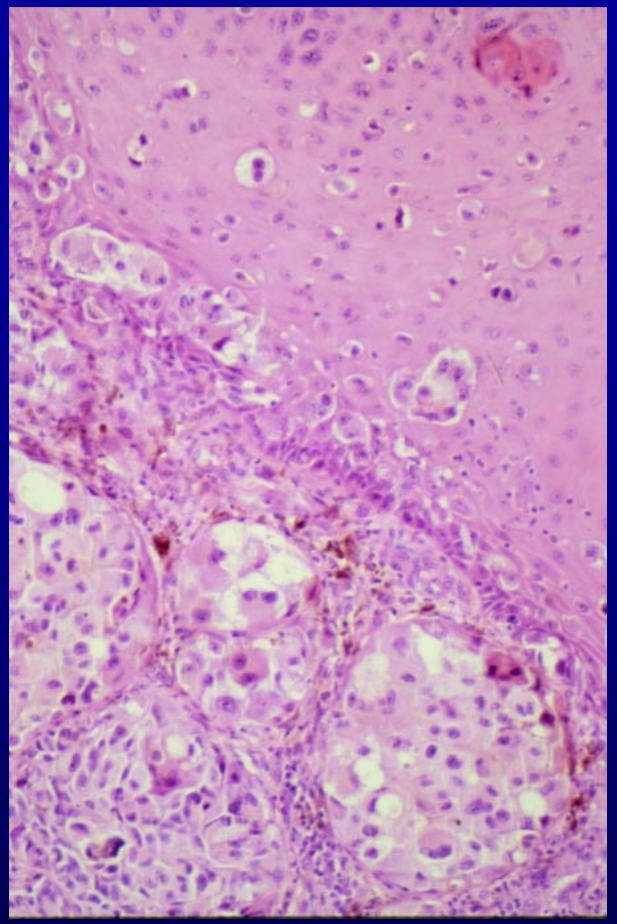
## Acral lentiginous melanoma

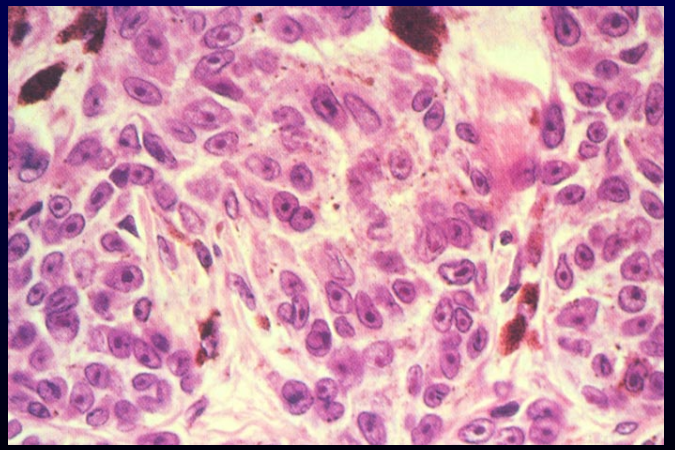


# HISTOLOGY OF MALIGNANT MELANOMA

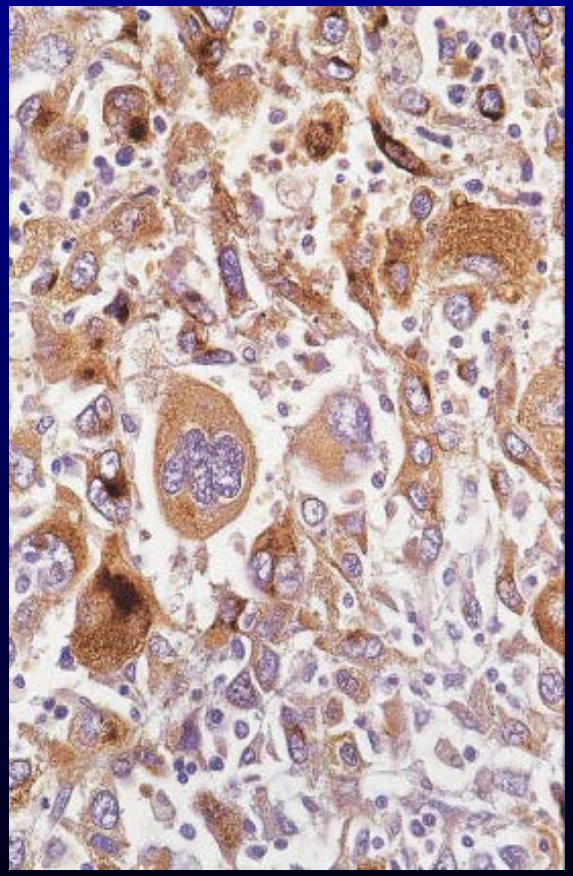
**Malignant epithelioid cells invade the epidermis and dermis**

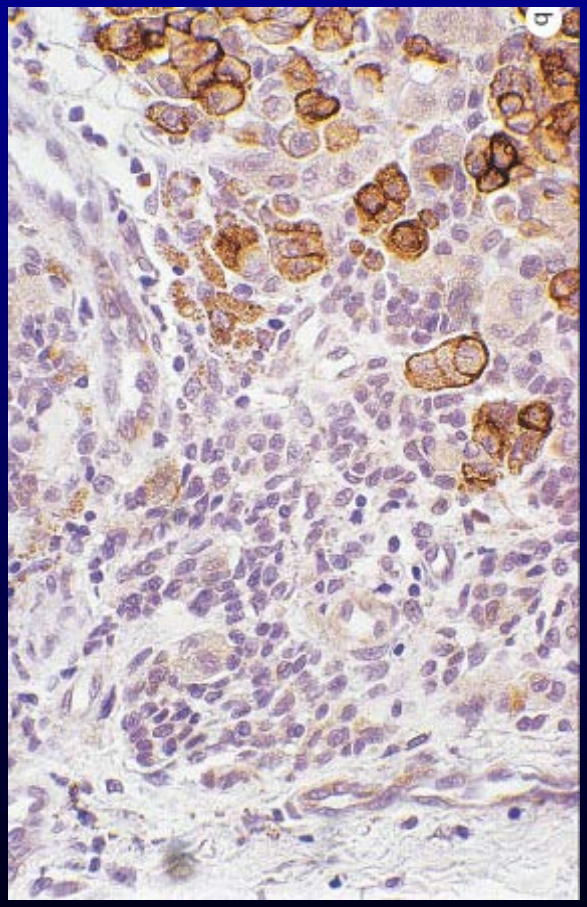






HMB-45 can be positive in melanoma
Other helpful immunostains are S100 protein and melan A

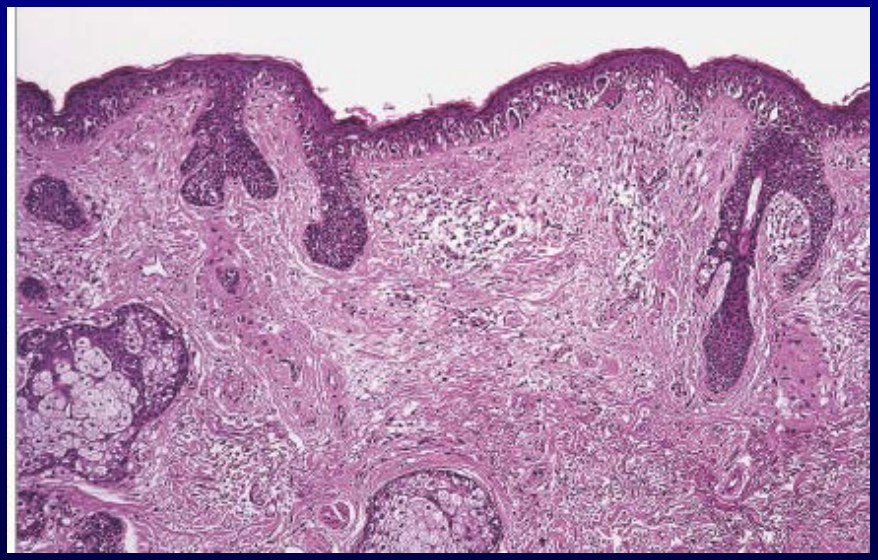


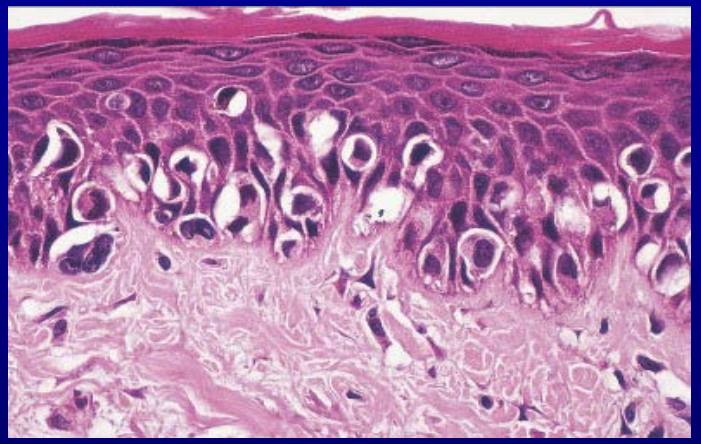


# Lentigo maligna

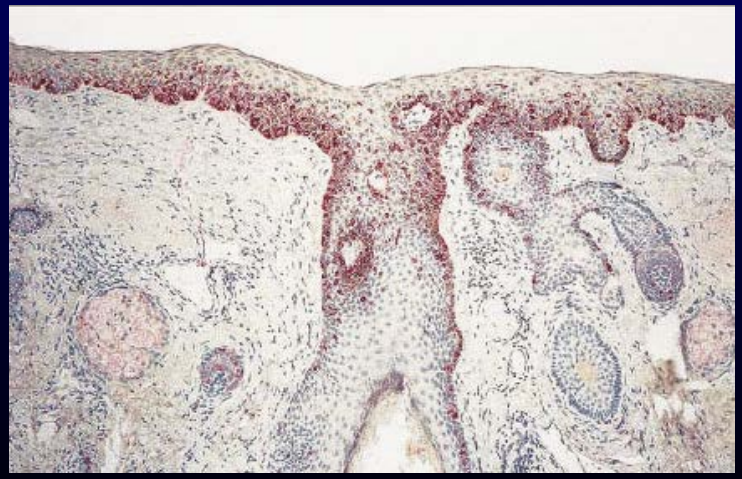
A form of melanoma in situ that occurs on chronically sun damaged skin

Generally grows in situ for years before invading dermis when it is termed lentigo maligna melanoma





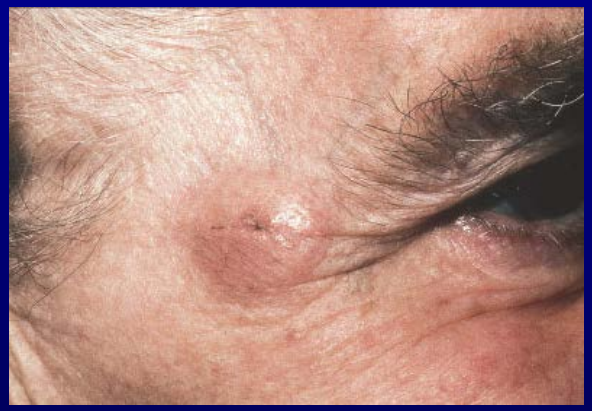
Melan A immunostain can highlight the lentigo maligna cells



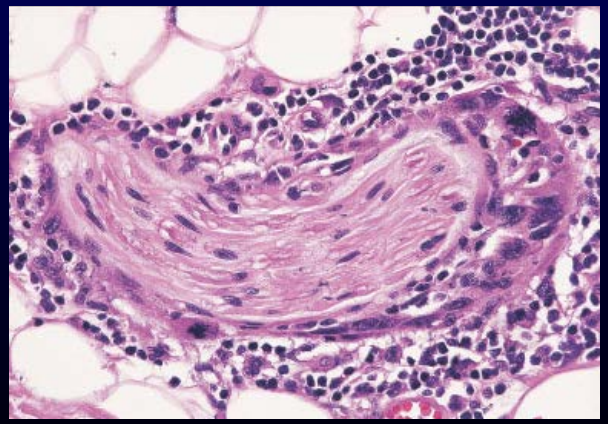
# Desmoplastic melanoma

## Can arise in setting of lentigo maligna

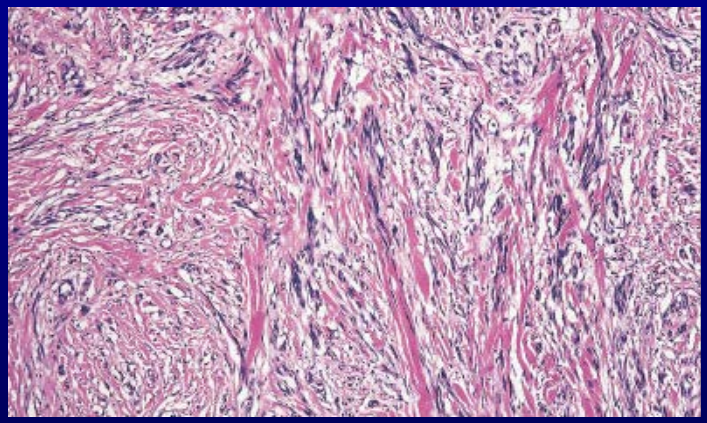
## Lesions usually clinically benign – can mimic scar



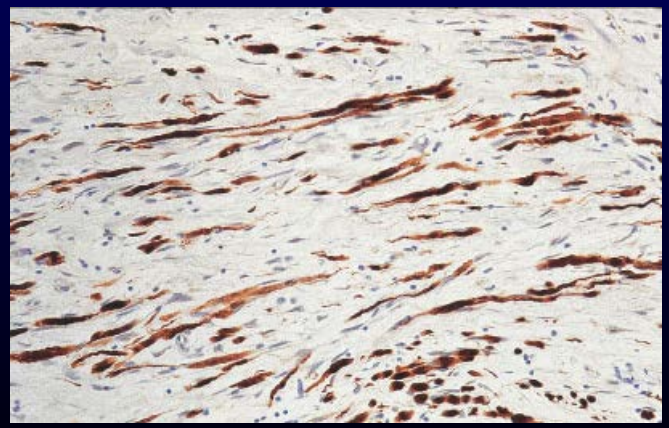
Perineural invasion is common; therefore high rate of local recurrence



Can mimic a scar



Melanoma cells stained with S100 protein



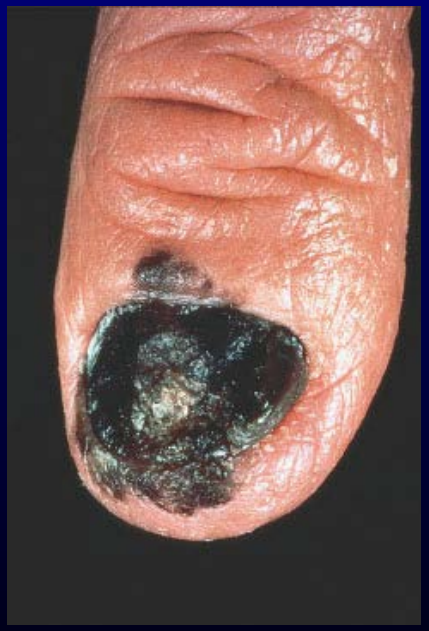
**Acral lentiginous melanoma**
**Subungual melanoma**

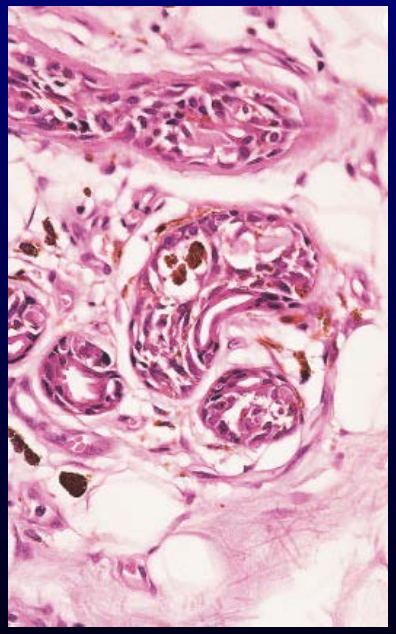
Hutchinson's sign can be seen in advanced cases – pigmentation extends onto nail fold

Extension down eccrine ducts typical of acral lentiginous melanoma

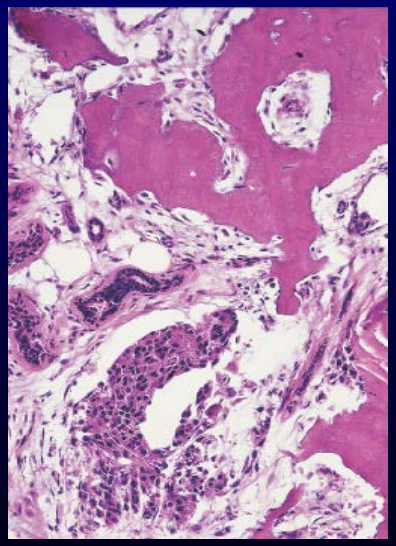
Heterologous osseous and cartiginous metaplasia can be seen

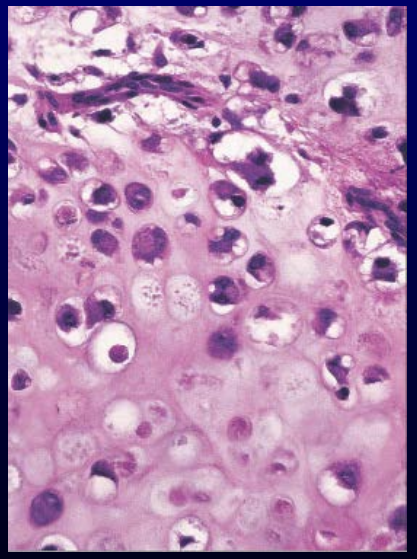
Melanoma involves eccrine ducts





Heterologous osseous and cartiginous metaplasia in acral lentiginous melanoma





# Malignant melanoma

## Poor prognostic indicators

### Primary tumour

Depth (Breslow) measured in mm
- 0-1 mm
- 1-2 mm
- 2-4 mm
- > 4 mm

Ulceration

Site

Male sex

Vascular invasion

Perineural invasion : increased local recurrence

### Lymph node metastases

Site of involvement

Number of involved lymph nodes

### Distant Metastases

Site
- Visceral mets:worst
- Lung mets: intermediate
- Skin mets: better

Elevated blood LDH (lactate dehydrogenase)

**AJCC 2002 revised melanoma staging**

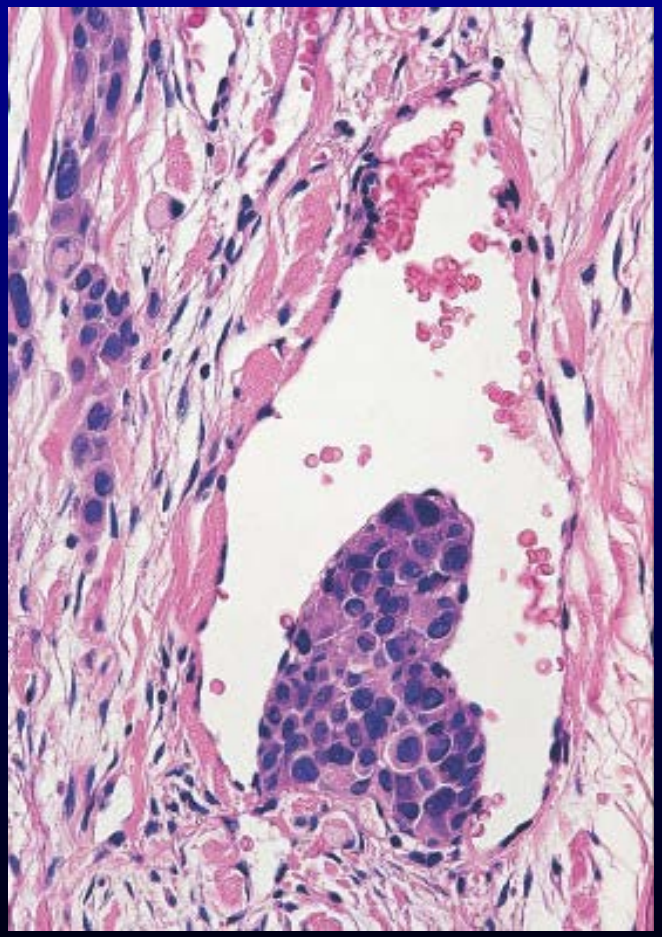
| Stage | Histological features/TNM classification | Overall survival | | |
|---|---|---|---|---|
| | | 1 year (%) | 5 years (%) | 10 years (%) |
| 0 | Intraepithelial/in situ melanoma (TisN0M0) | | 100 | 100 |
| IA | ≤ 1 mm without ulceration and Clark level II/III (T1aN0M0) | | 95 | 88 |
| IB | ≤ 1 mm with ulceration or level IV/V (T1bN0M0) | | 91 | 83 |
| | 1.01–2 mm without ulceration (T2aN0M0) | | 89 | 79 |
| IIA | 1.01–2 mm with ulceration (T2bN0M0) | | 77 | 64 |
| | 2.01–4 mm without ulceration (T3aN0M0) | | 79 | 51 |
| IIB | 2.01–4 mm with ulceration (T3bN0M0) | | 63 | 51 |
| | > 4 mm without ulceration (T4aN0M0) | | 67 | 54 |
| IIC | > 4 mm with ulceration (T4bN0M0) | | 45 | 32 |
| IIIA | Single regional nodal micrometastasis, non-ulcerated primary (T1–4aN1aM0) | | 69 | 63 |
| | 2–3 microscopic regional nodes, non-ulcerated primary (T1–4aN2aM0) | | 63 | 57 |
| IIIB | Single regional nodal micrometastasis, ulcerated primary (T1–4bN1aM0) | | 53 | 38 |
| | 2–3 microscopic regional nodes, ulcerated primary (T1–4bN2aM0) | | 50 | 36 |
| | Single regional nodal macrometastasis, non-ulcerated primary (T1–4aN1bM0) | | 59 | 48 |
| | 2–3 macroscopic regional nodes, non-ulcerated primary (T1–4aN2bM0) | | 46 | 39 |
| | In-transit met(s)/satellite lesion(s) *without* metastatic lymph nodes (T1–4a/bN2cM0) | | 30–50 | |
| IIIC | Single microscopic regional node, ulcerated primary (T1–4bN1bM0) | | 29 | 24 |
| | 2–3 macroscopic regional nodes, ulcerated primary (T1–4bN2bM0) | | 24 | 15 |
| | 4 or more metastatic nodes, matted nodes/gross extracapsular extension, or in-transit met(s)/satellite(s) *and* metastatic nodes (anyTN3M0) | | 27 | 18 |
| IV | Distant skin, subcutaneous, or nodal mets with normal LDH (anyTanyNM1a) | 59 | 19 | 16 |
| | Lung mets with normal LDH (anyTanyNM1b) | 57 | 7 | 3 |
| | All other visceral mets with normal LDH or any distant mets with increased LDH (anyTanyNM1c) | 41 | 9 | 6 |

Breslow thickness is defined as the thickness of the lesion using an ocular micrometer to measure the total vertical height of the melanoma from the granular layer to the area of deepest penetration. The Clark's level refers to levels of invasion according to depth of penetration of the dermis.
Adapted with permission from Balch, A.C. et al (2001) *Journal of Clinical Oncology* 19:3635–3648. Lippincott Williams & Wilkins.©

# Adverse prognostic indicators in melanoma

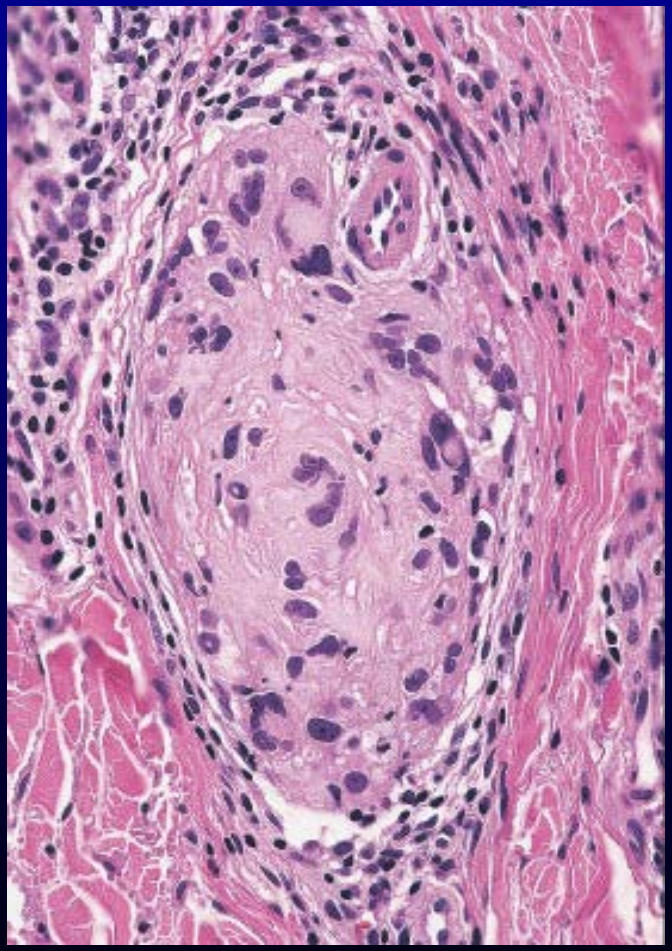
Lymphovascular invasion

Confers increased risk of metastasis

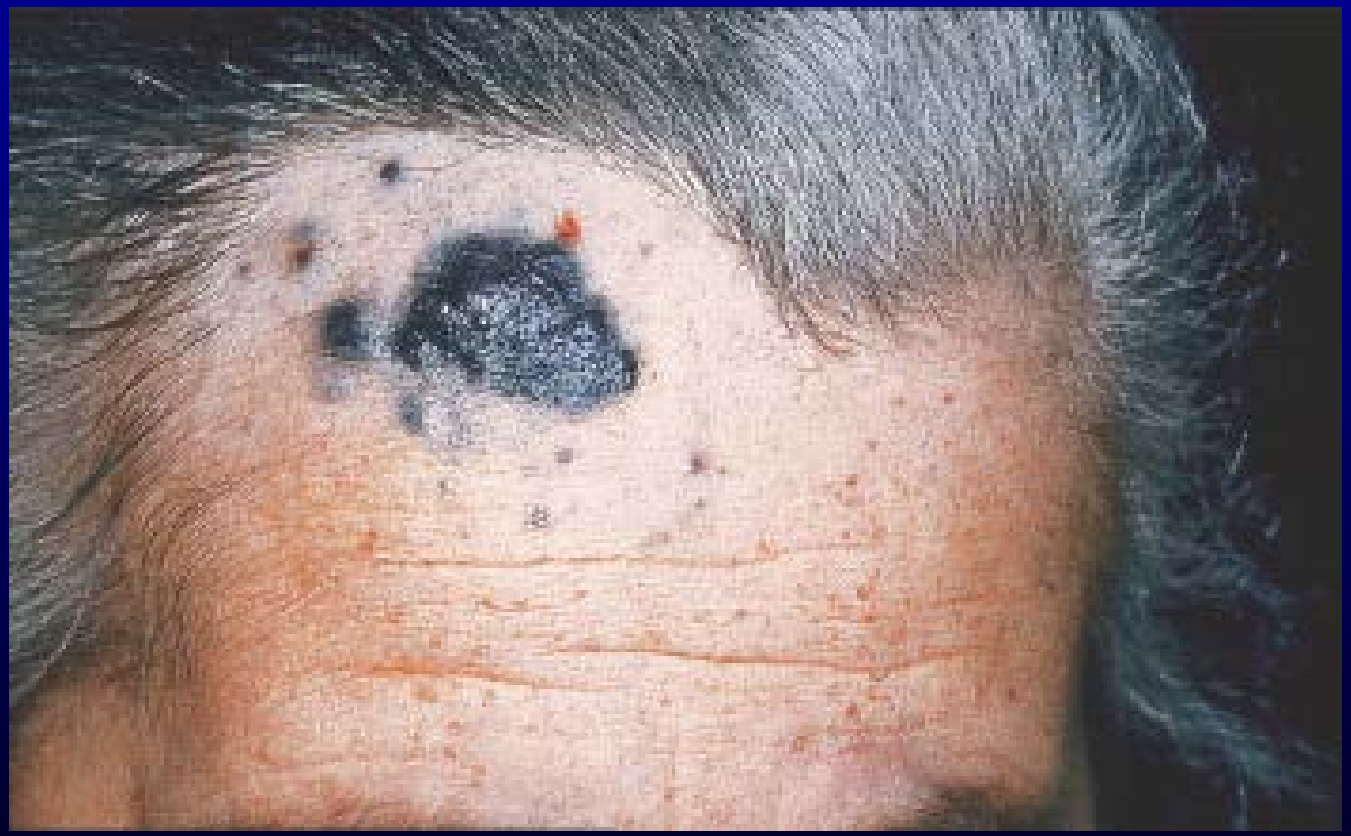


Peri / intraneural invasion

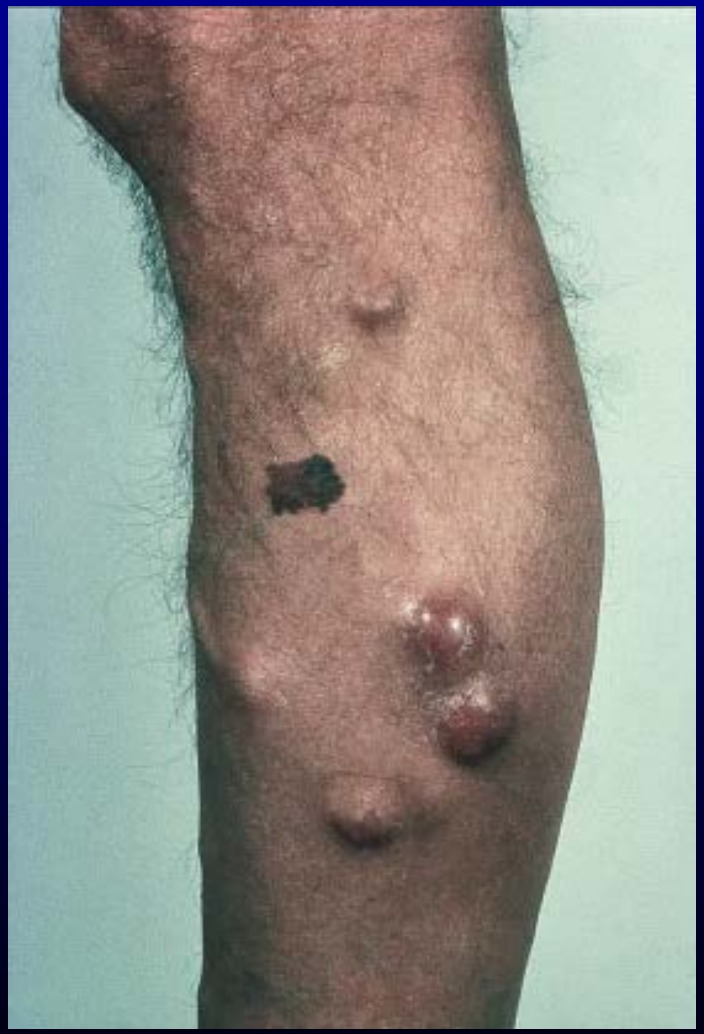
Confers increased risk of local recurrence



# Adverse prognostic factor
# Microsatellite deposits



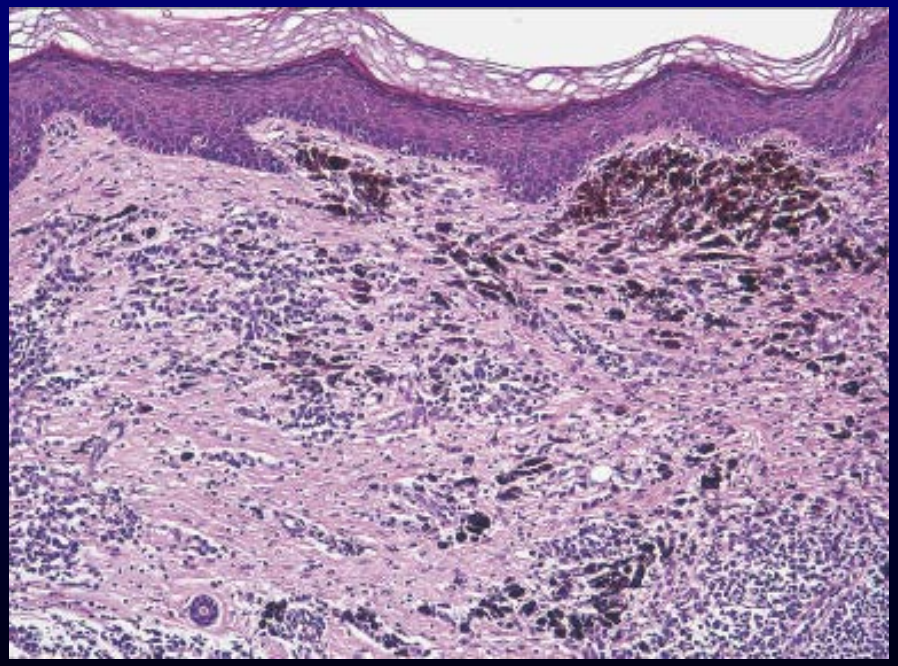
# Metastatic melanoma

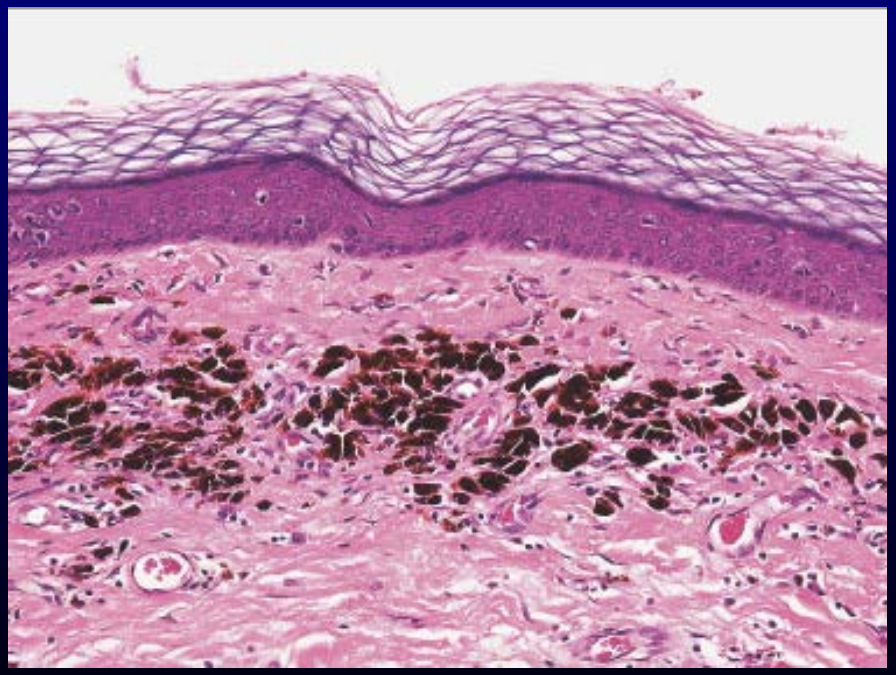


## Regression

Melanoma undergoes apoptosis and scarring, melanophages, lymphocytic inflammation and a proliferation of blood vessels is seen in its place

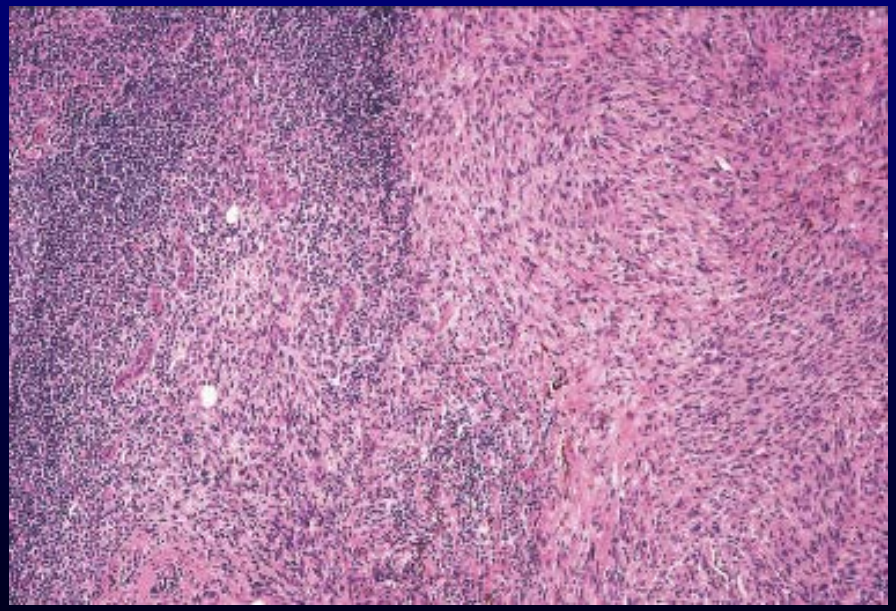
Melanoma can disappear entirely





# Sentinel lymph node examination

Performed in cases of melanomas of Breslow depth 1-4mm
Lymph node draining the area of melanoma is detected using radioactive tracer and blue dye
Lymph node is excised and examined thoroughly by pathologist
If metastasis present completion lymphadenectomy is performed
Sentinel lymph node examination adds prognostic information but the technique has not reliably been shown to improve survival and there are some controversies regarding this procedure



# Malignant melanoma

## Molecular events

### Primary tumour

*Genes implicated*

- **p16 (CDKN2A)**
- **CDK 4**
- **MC1R (melanocortin 1 receptor)**
- **B-RAF**
- **N-RAS**
- **p53**
- **cyclin D1**
- **cKIT**

### Nodal metastases

Accumulation of other genetic events including frequent chromosomal aberrations

**Melanoma families:**

**Mutations in**

**p16 (CNKN2A)**

**CDK4**

# FUTURE FOR MELANOMA DIAGNOSIS

- Cytogenetics/genetics in ambiguous melanocytic lesions /prognosis?

  FISH probes are in development

  – distinguish between melanoma and Spitz naevi
    - melanoma: multiple chromosomal aberrations

      -9, -10, -6q, 8p +7, +8q, +6p, +1q, +17, +20
    - naevi: none / rare aberrations

      Spitz naevi 50% normal, 50% +11p

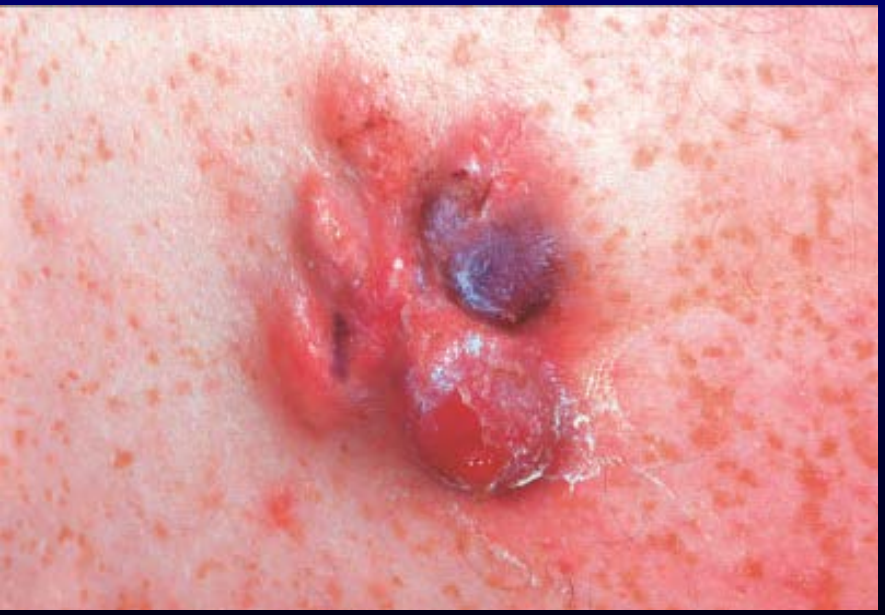
- Currently no effective therapy for locally advanced melanoma: need to identify targets for molecular targeted therapy?

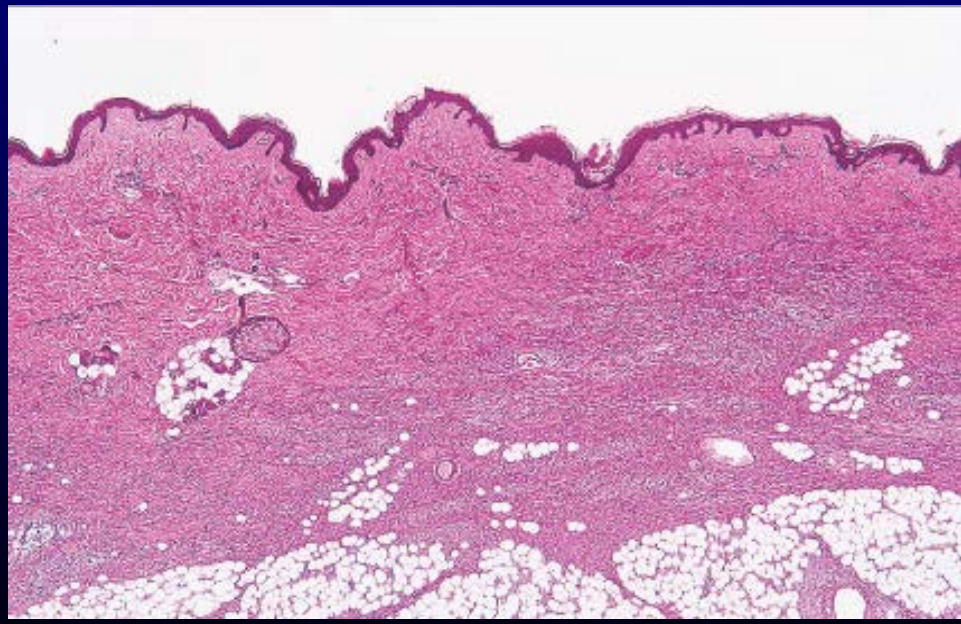
# Selected mesenchymal tumours

- Dermatofibrosarcoma protuberans
- Kaposi sarcoma
- Cutaneous angiosarcoma
- Atypical fibroxanthoma

# Dermatofibrosarcoma protuberans

Spindle cell sarcoma
Initially grows in dermis as a plaque, then invades subcutis and becomes a tumour
High local recurrence
Potential for metastasis when dedifferentiates into higher grade sarcoma (fibrosarcomatous change)



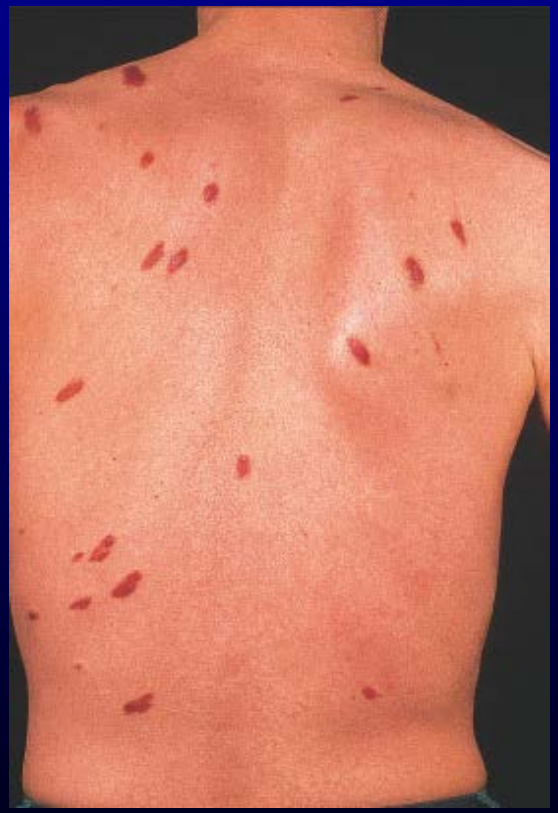


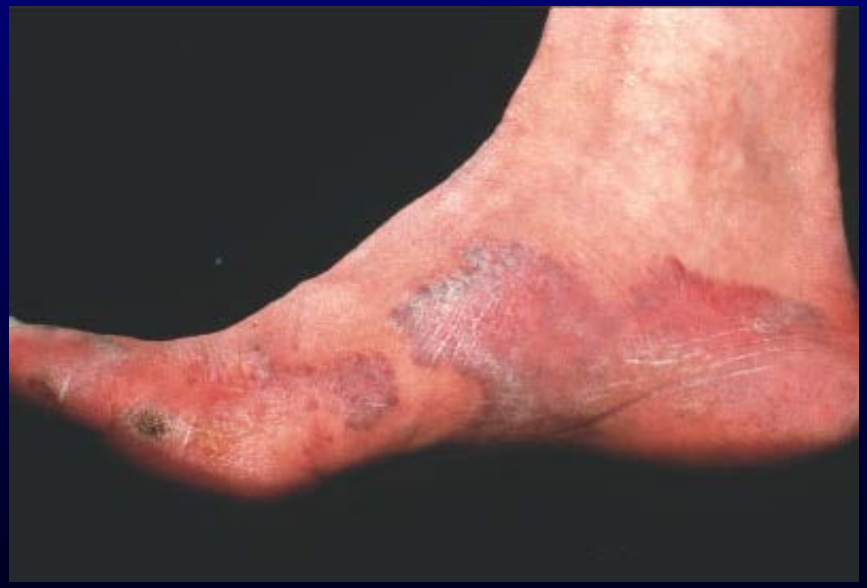
# Kaposi sarcoma

Vascular tumour (v reactive vascular proliferation ?)

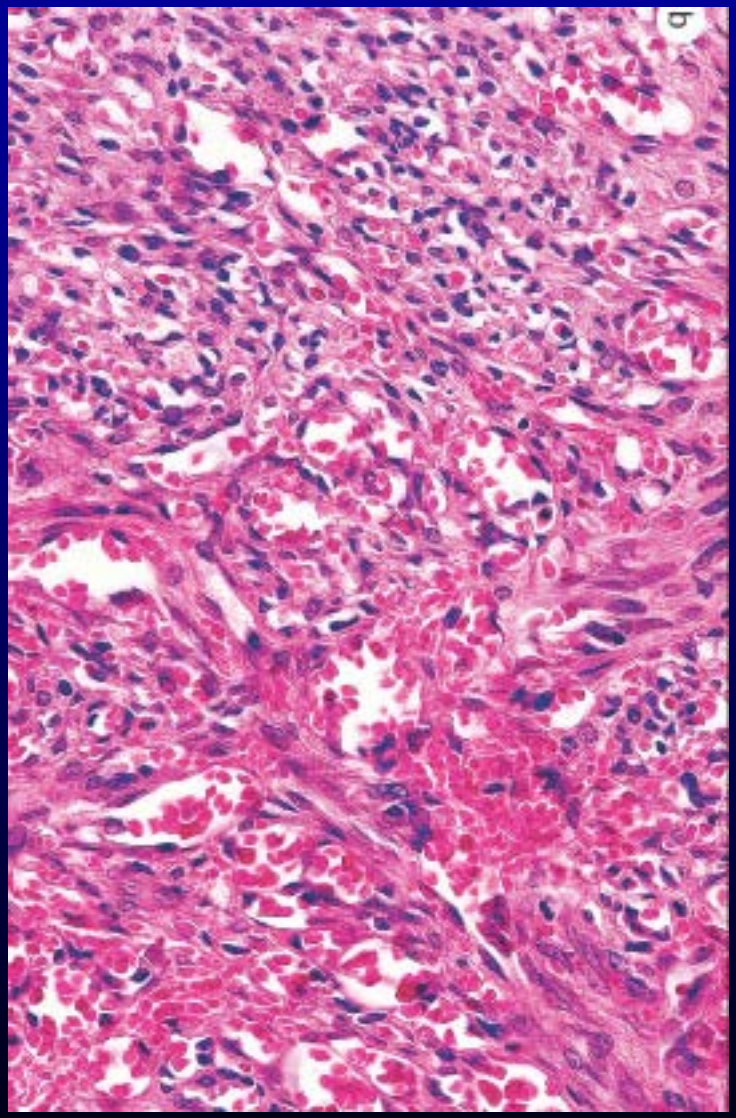
HHV8 (Kaposi sarcoma virus)

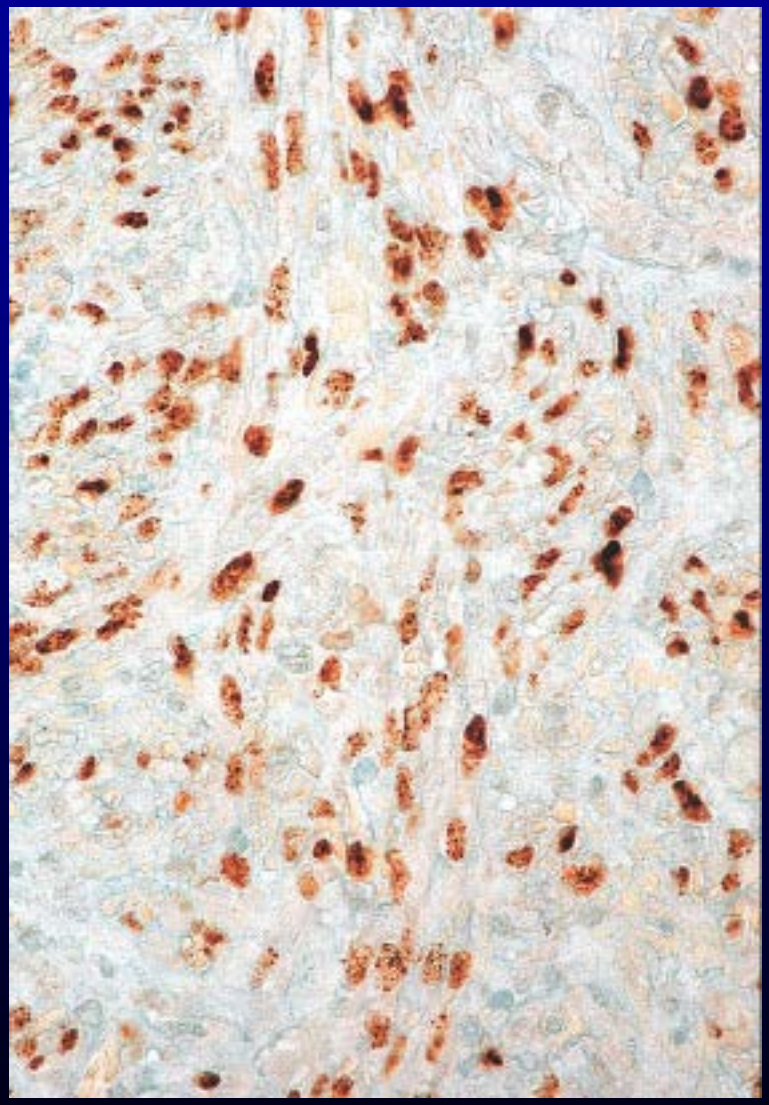
Different subtypes: endemic, HIV, renal transplant associated





# Kaposi sarcoma: spindle cell vascular proliferation
# HHV8 immunostain is positive





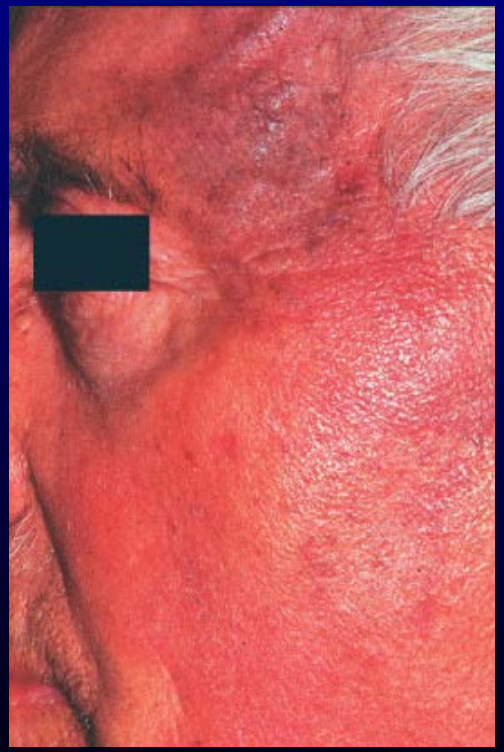
# Cutaneous angiosarcoma

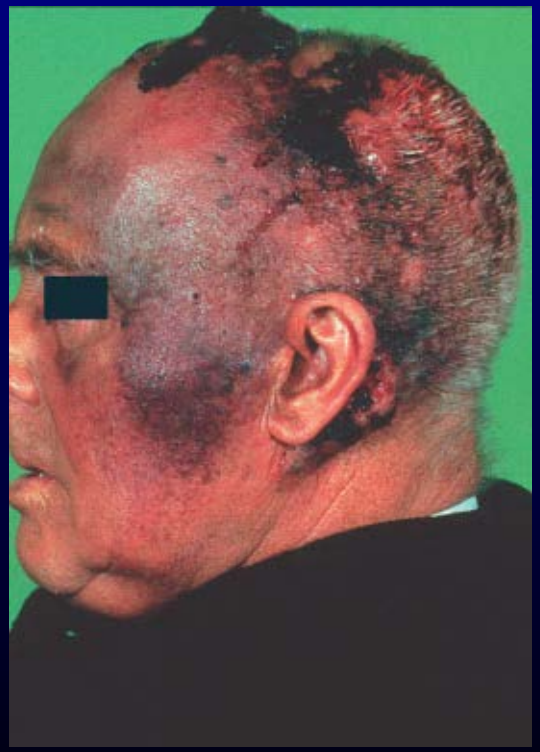
Arises on sun damaged skin of head and neck

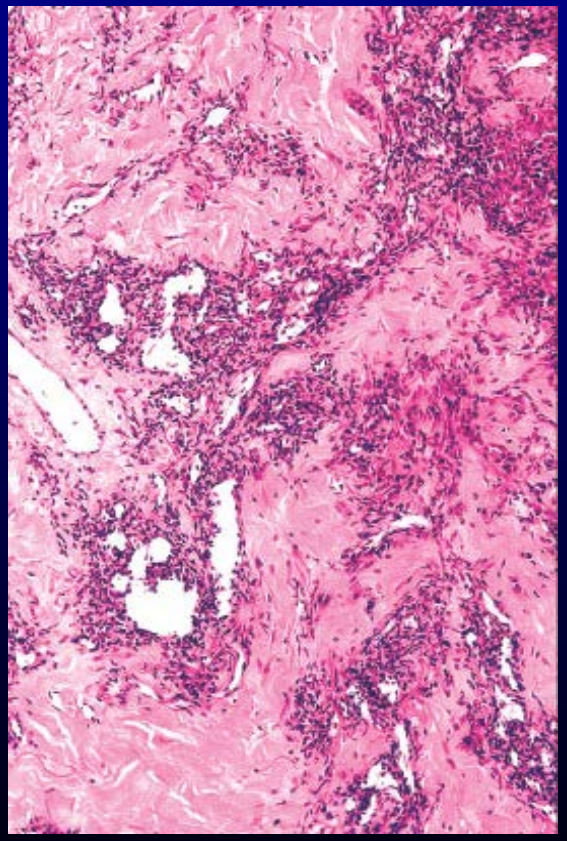
Location at other sites (e.g. breast) can be associated with prior radiotherapy or lymphoedema

Can present as subtle bruise in early stage

Poor prognosis, no effective therapy – high recurrence rate following excision



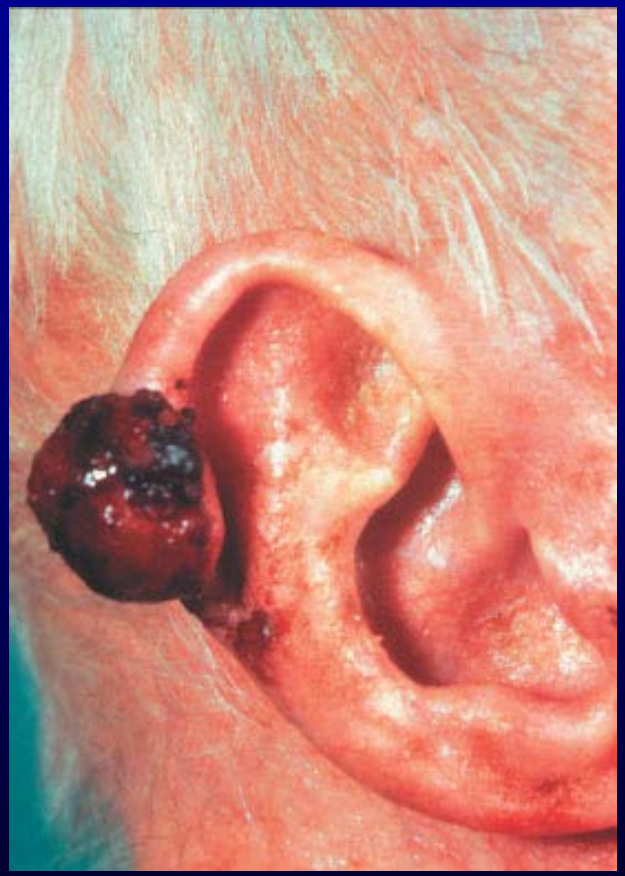


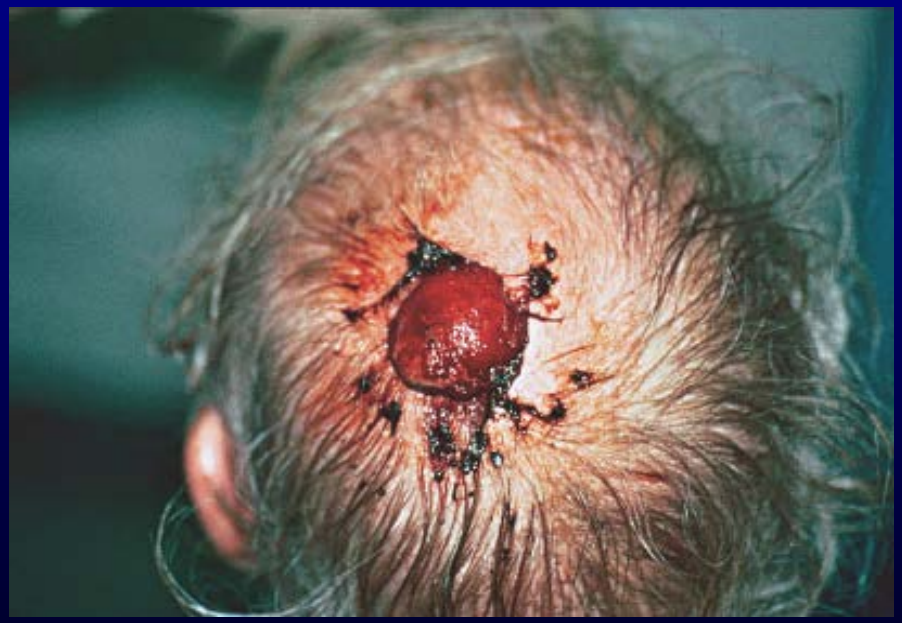


# Atypical fibroxanthoma

- Rapidly growing fleshy or ulcerated nodules on sun exposed skin , generally on bald scalps
- Sun induced malignant mesenchymal proliferations but they have a good prognosis and essentially do not metastasize
- Bizarre pleomorphic tumour cells with giant cells and spindle cells
- Have to exclude diagnosis of carcinoma by cytokeratin immunostain and melanoma by S100 protein and other melanocytic markers (HMB-45 and melan A)

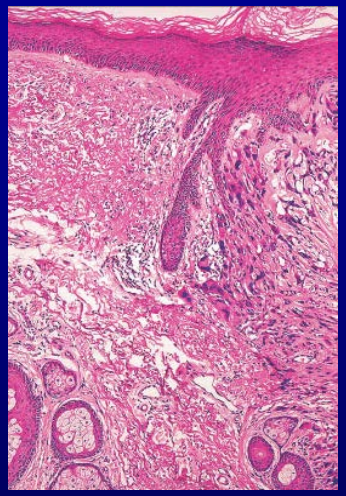
# Atypical fibroxanthoma

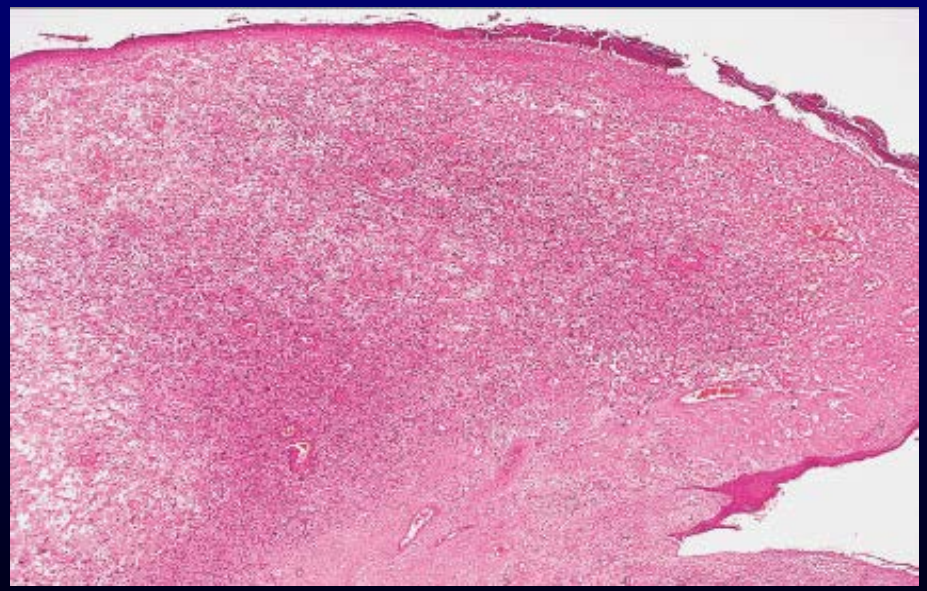


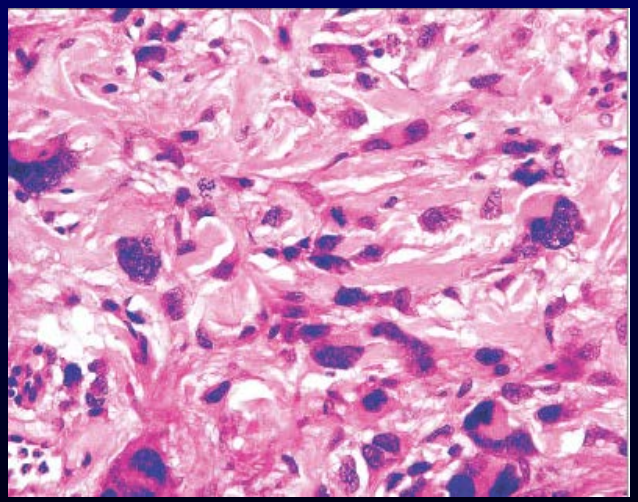


# Atypical fibroxanthoma (AFX)

**Polyoid tumour composed of bizarre pleomorphic cells with tumour giant cells and many mitoses**







# Lymphoma

- Many different types of cutaneous lymphoma, both T and B cell lymphomas
- Mycosis fungoides (T cell lymphoma with epidermotropism) that has a chronic course
- CD30 positive cutaneous lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Anaplastic large cell lymphoma
- Subcutaneous panniculitis-like T cell lymphoma

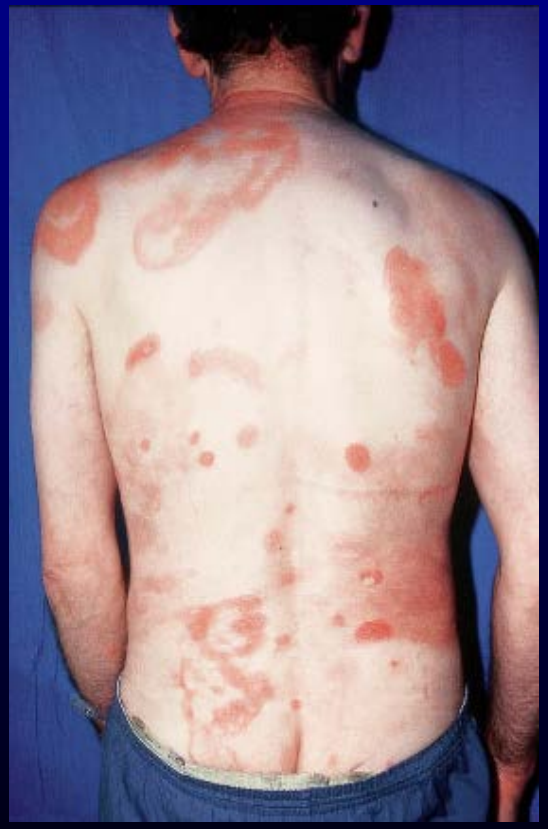
  CD8 positive and can mimic panniculitis of lupus erythematosus

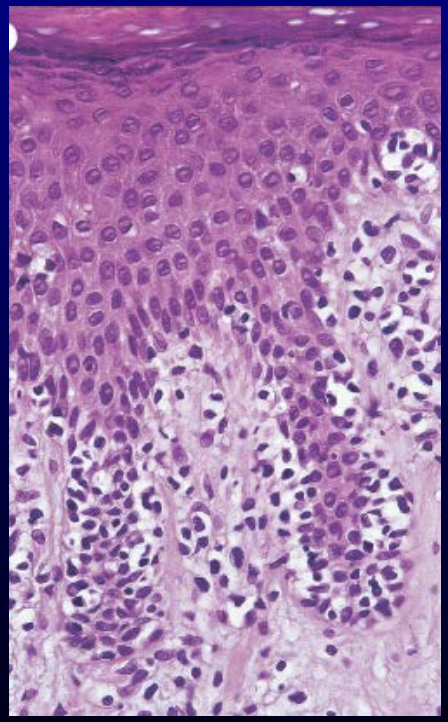
# Mycosis fungoides

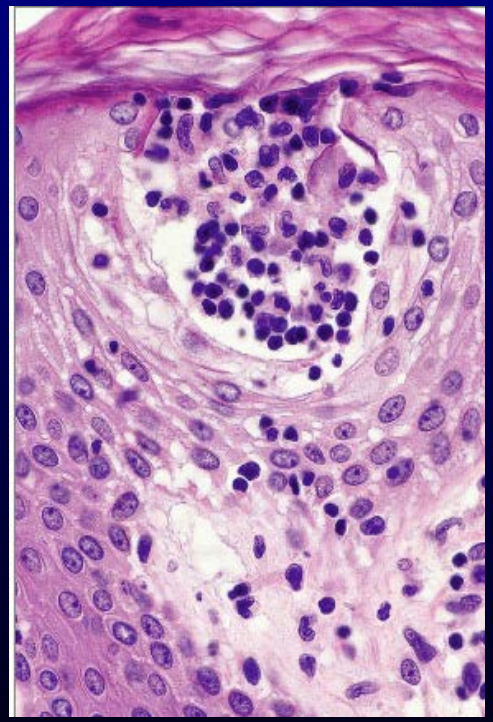
Commonest cutaneous lymphoma, chronic course, clinically can mimic eczema

T cell lymphoma with epidermotropism and late dissemination to lymph nodes

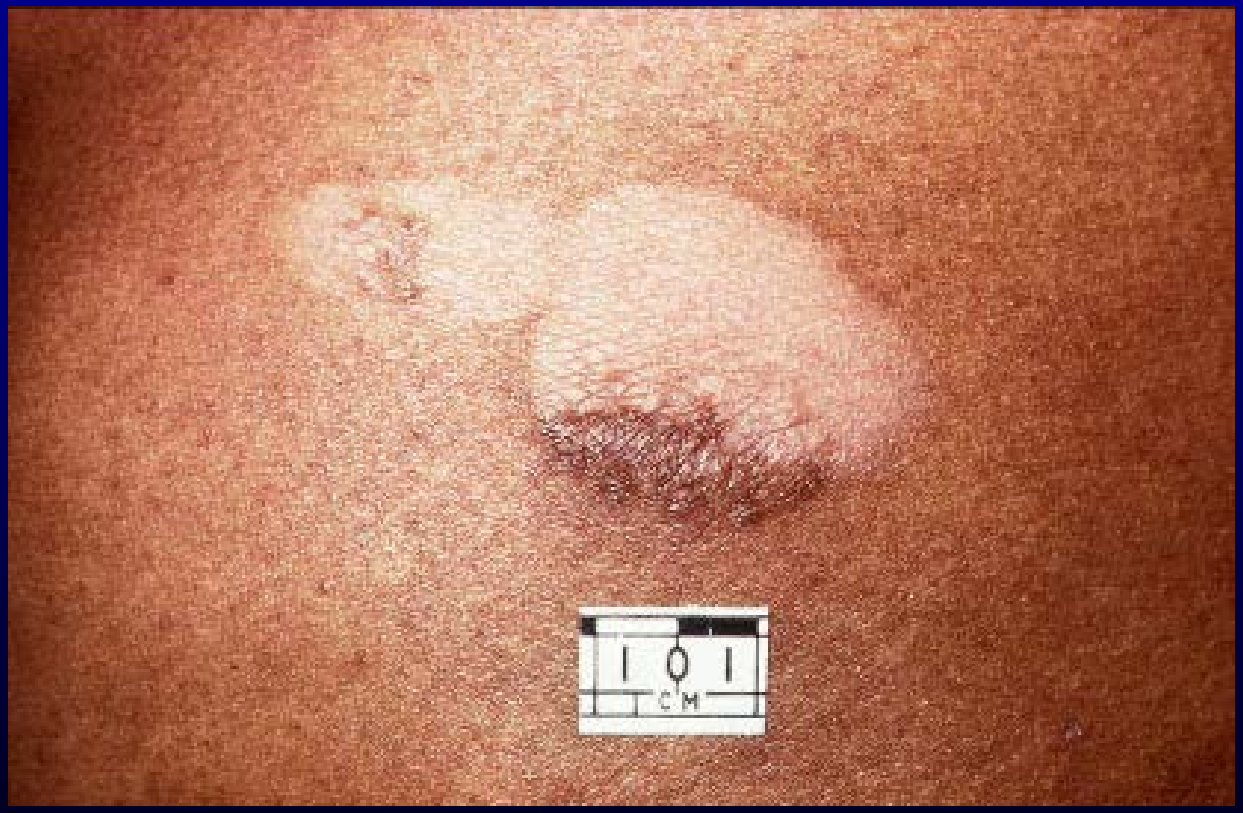
Malignant T lymphocytes present in epidermis



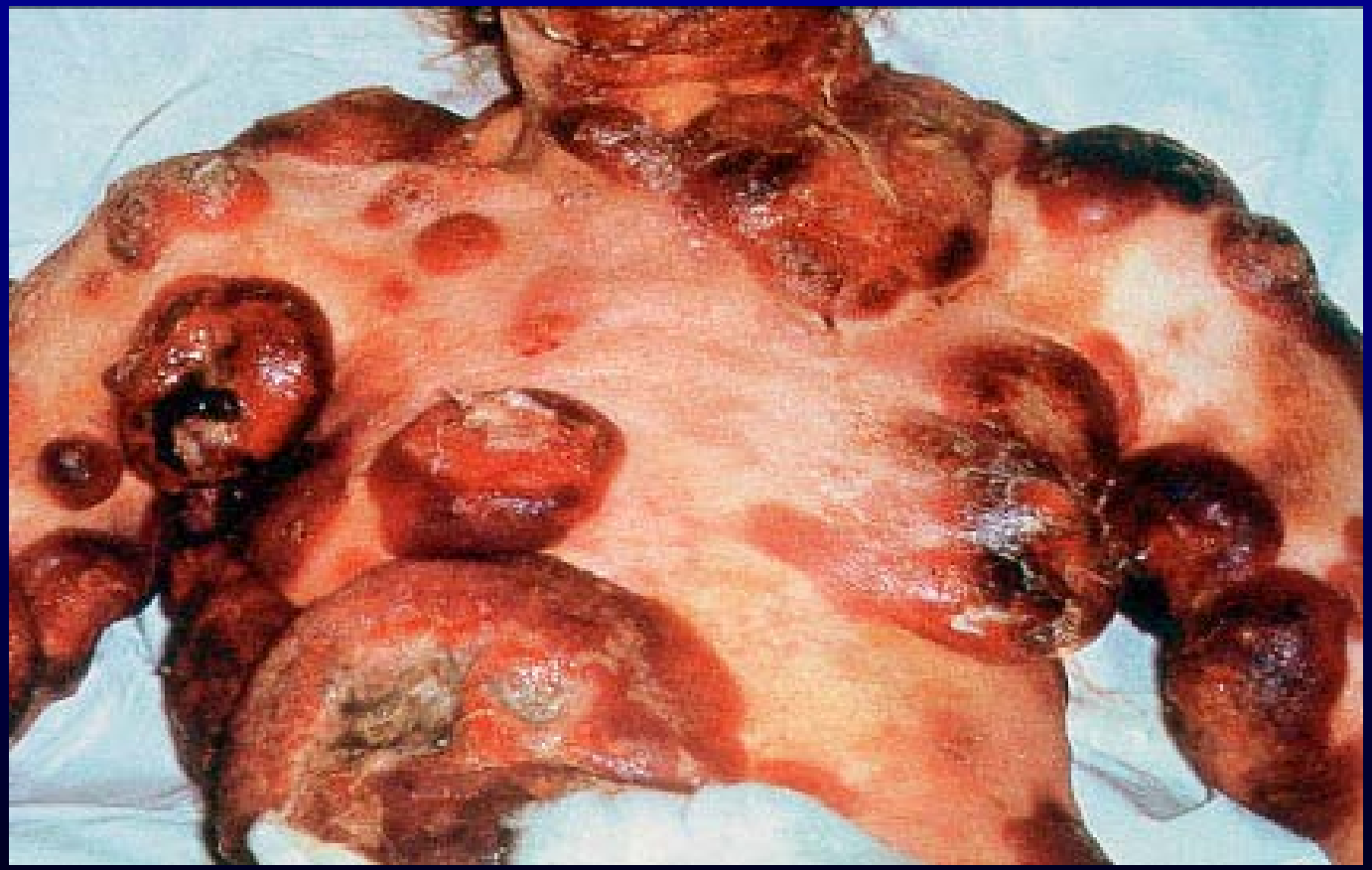




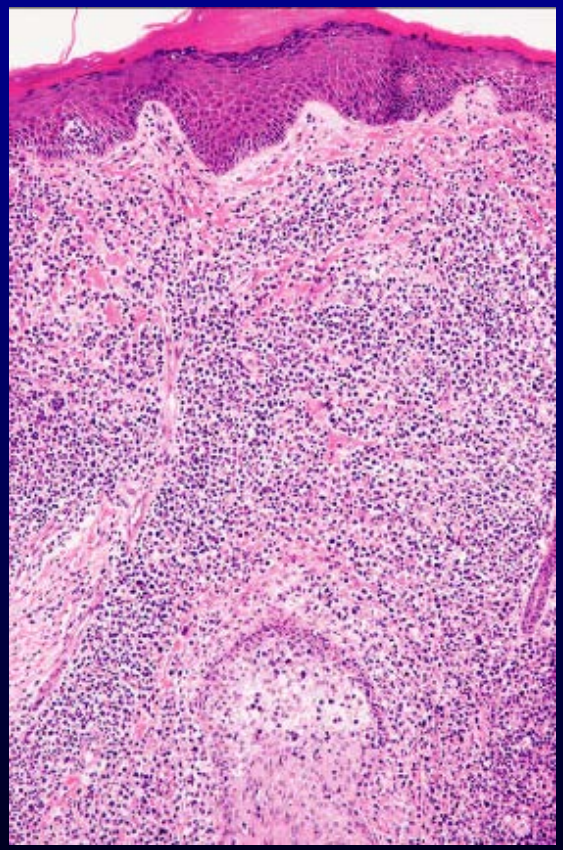
Hypopigmented variant of mycosis fungoides
Can mimic fungal infection
More common in black patients

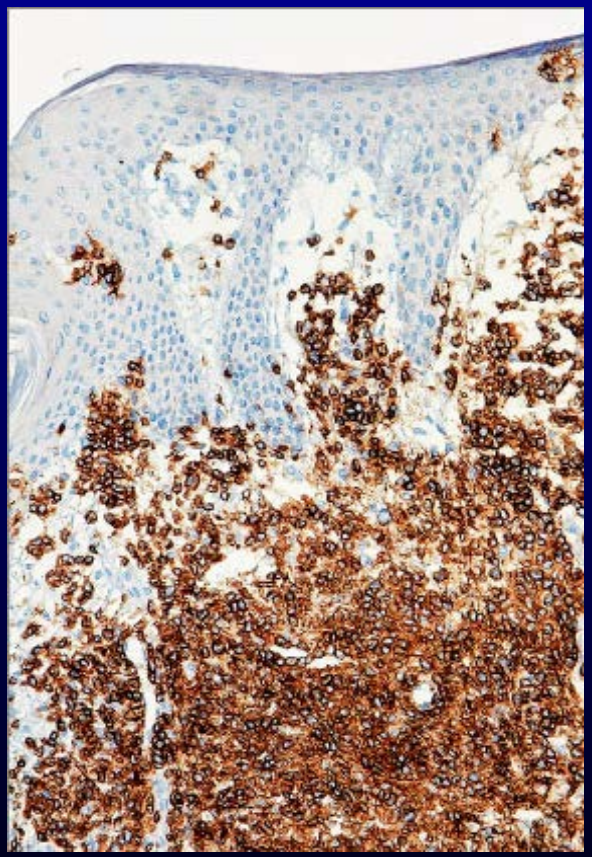


# Late tumour stage mycosis fungoides

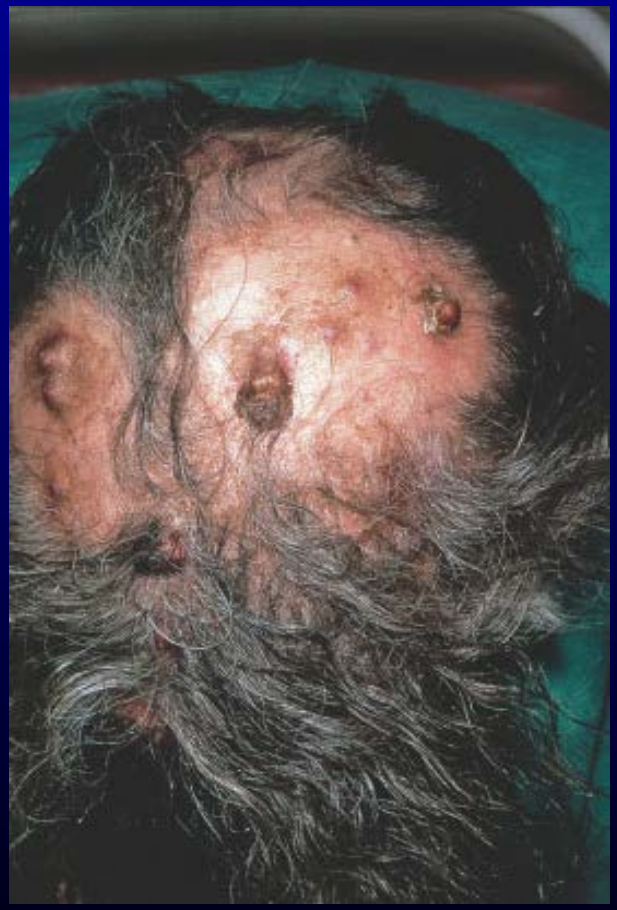


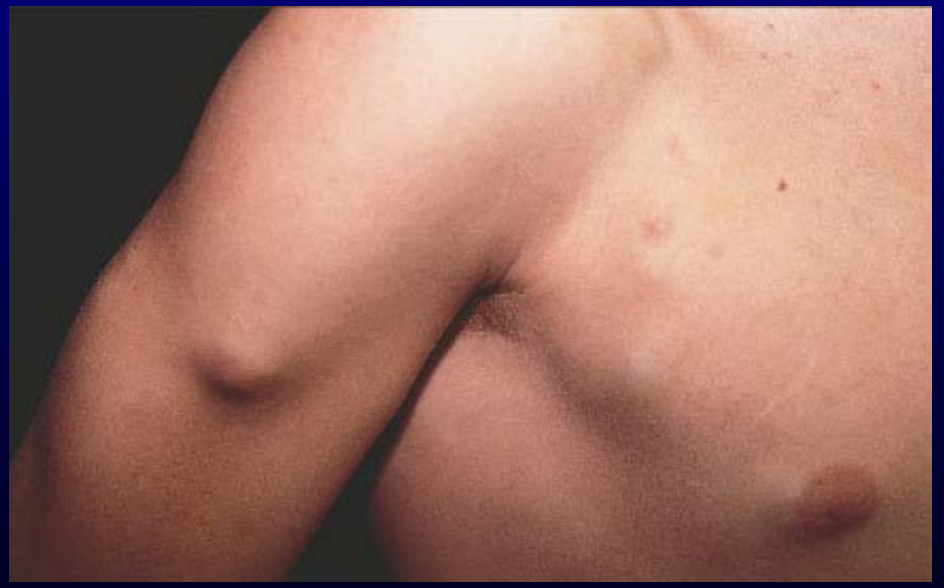
# Tumour stage mycosis fungoides Dermal proliferation of malignant T lymphocytes (CD4 positive)



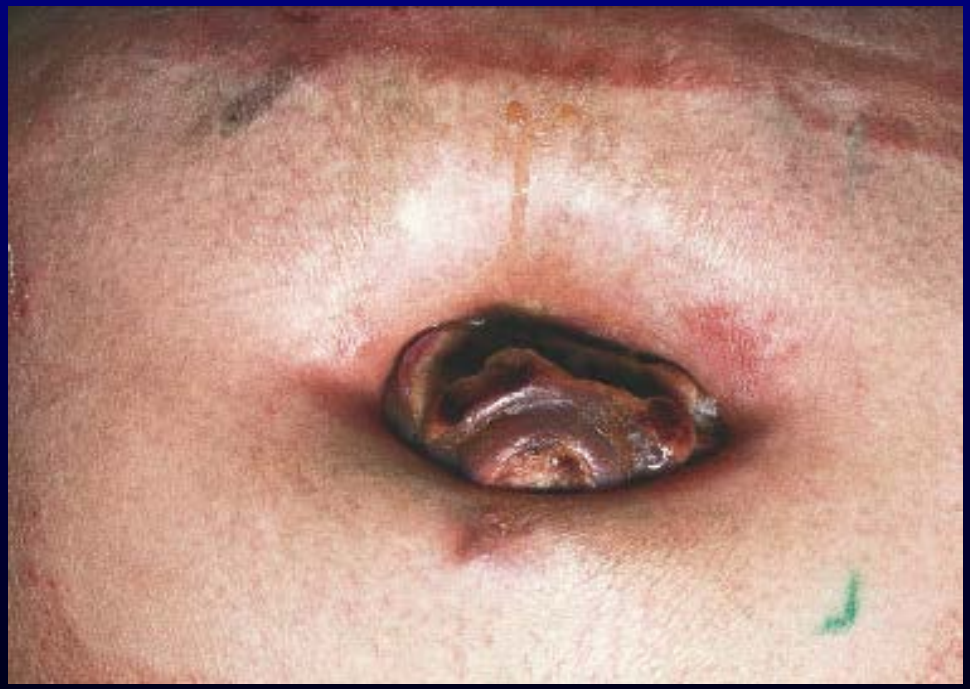


# Metastases to skin (secondary cancer) Predilection for location of metastases on scalp and head and neck

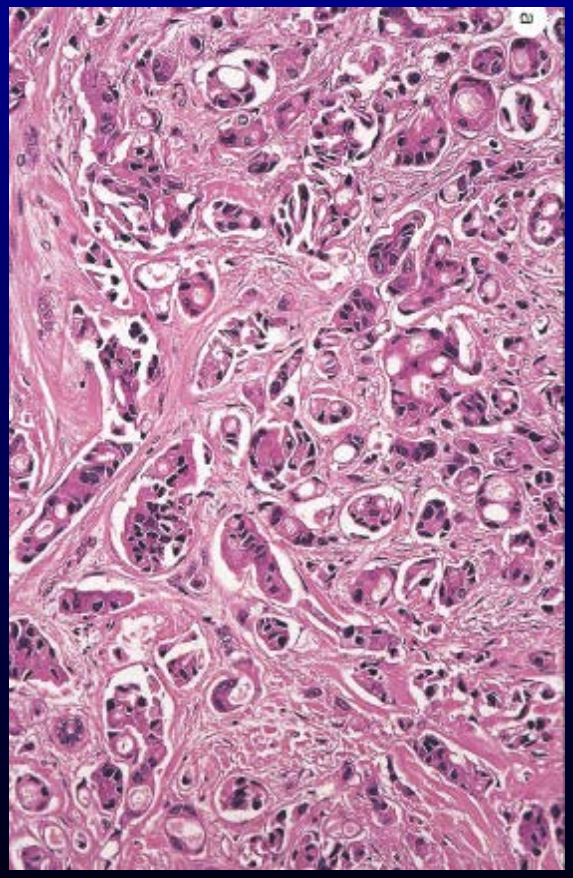




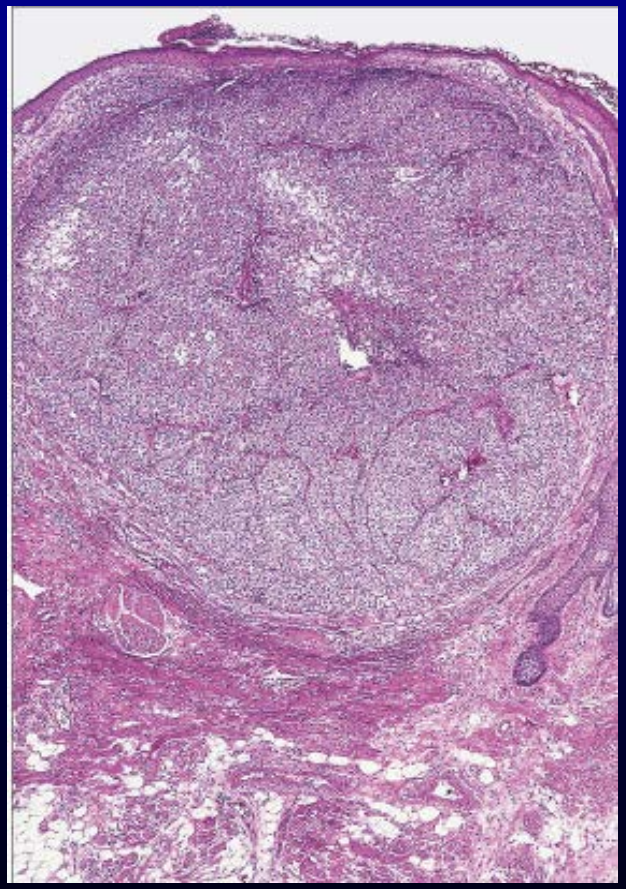
# Sister Mary Joseph nodule
# Umbilical deposit of metastatic colon carcinoma

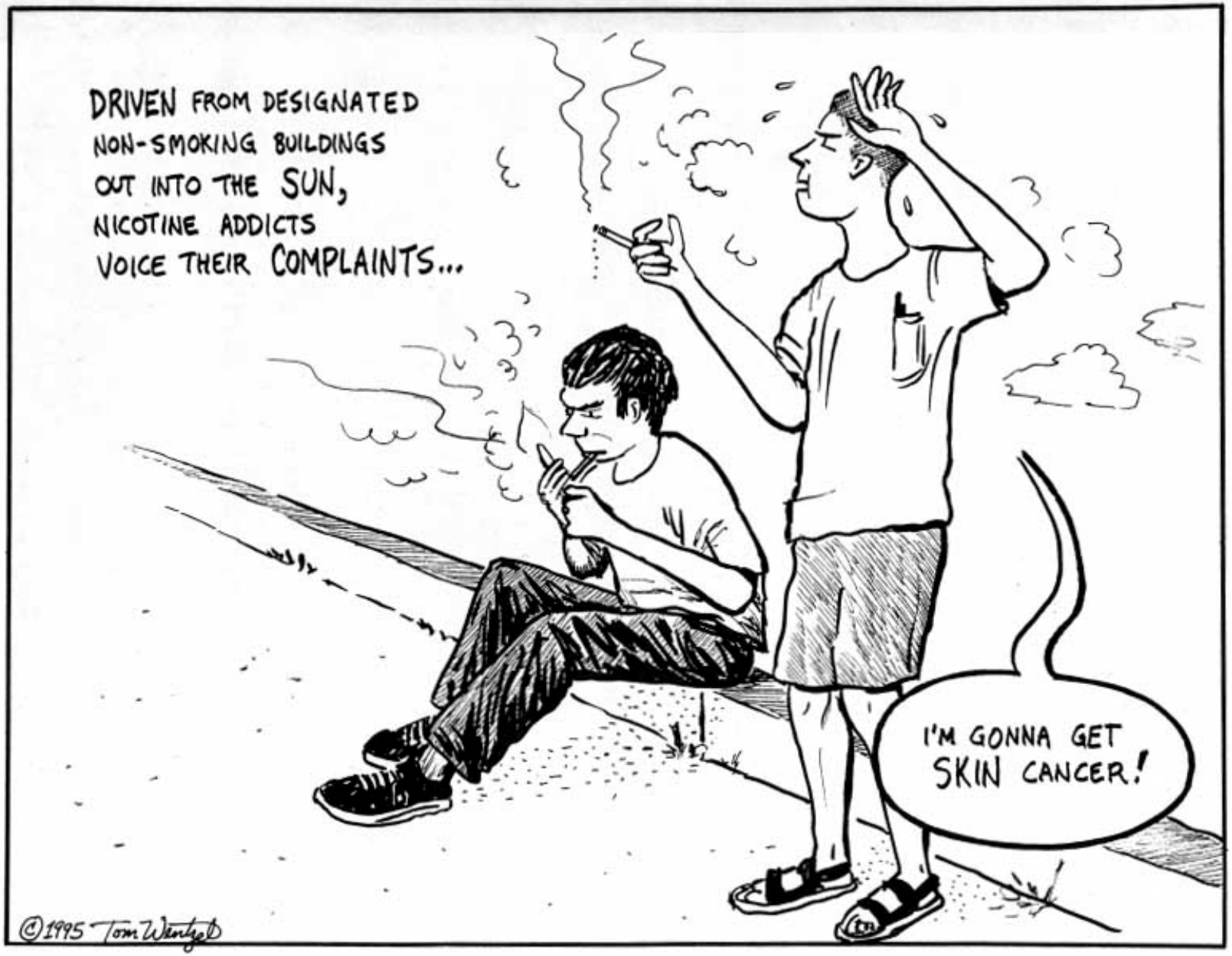


Metastatic breast adenocarcinoma



Metastatic renal cell carcinoma




DRIVEN FROM DESIGNATED NON-SMOKING BUILDINGS OUT INTO THE SUN, NICOTINE ADDICTS VOICE THEIR COMPLAINTS...
I'M GONNA GET SKIN CANCER!
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