SKIN CANCER

Mircea Betiu

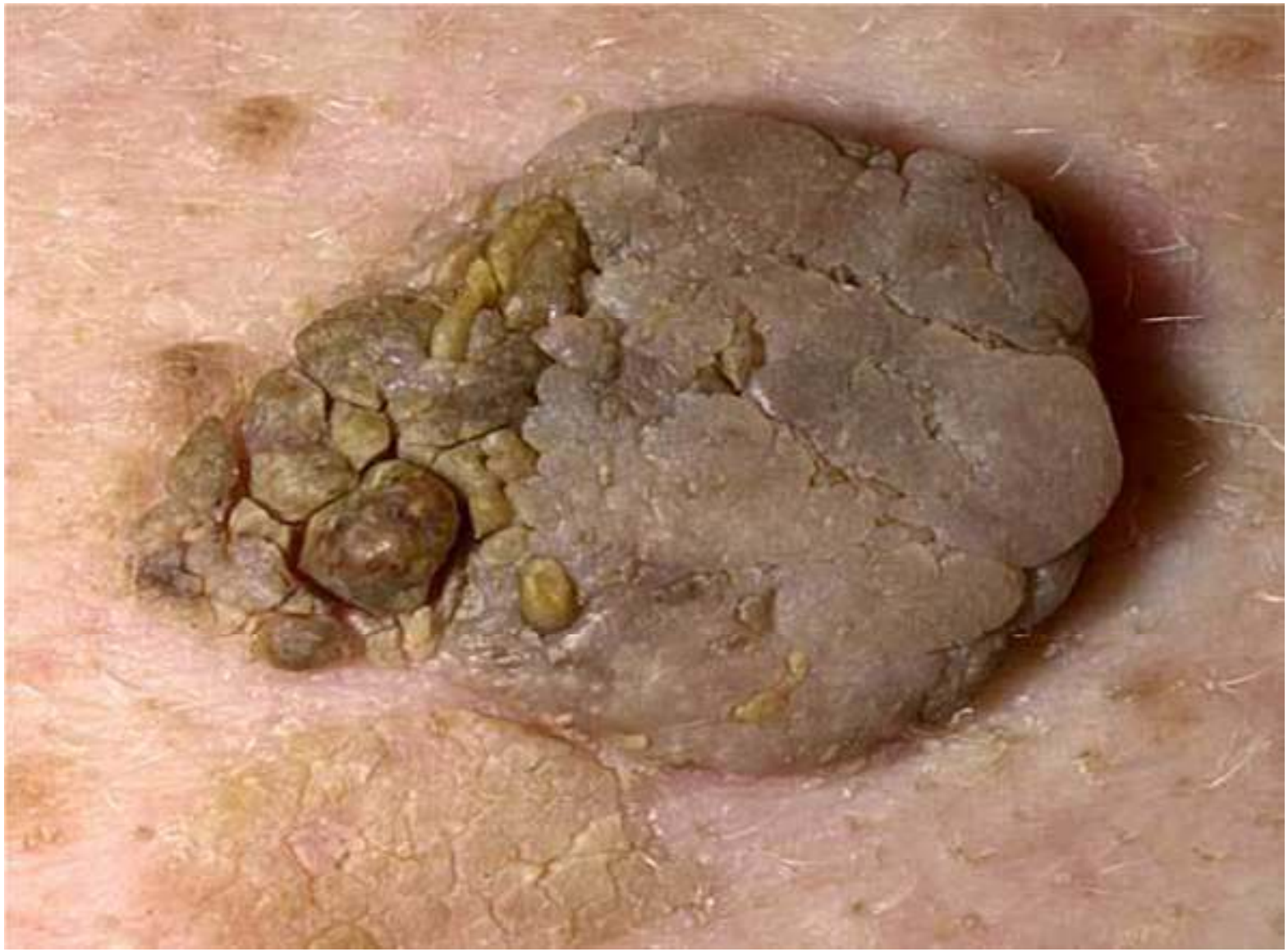
Cutaneous neoplasias

A. Benign cutaneous tumors;
B. Malign cutaneous tumors;
C. Cutaneous precancers;
D. Cutaneous paraneoplasias.

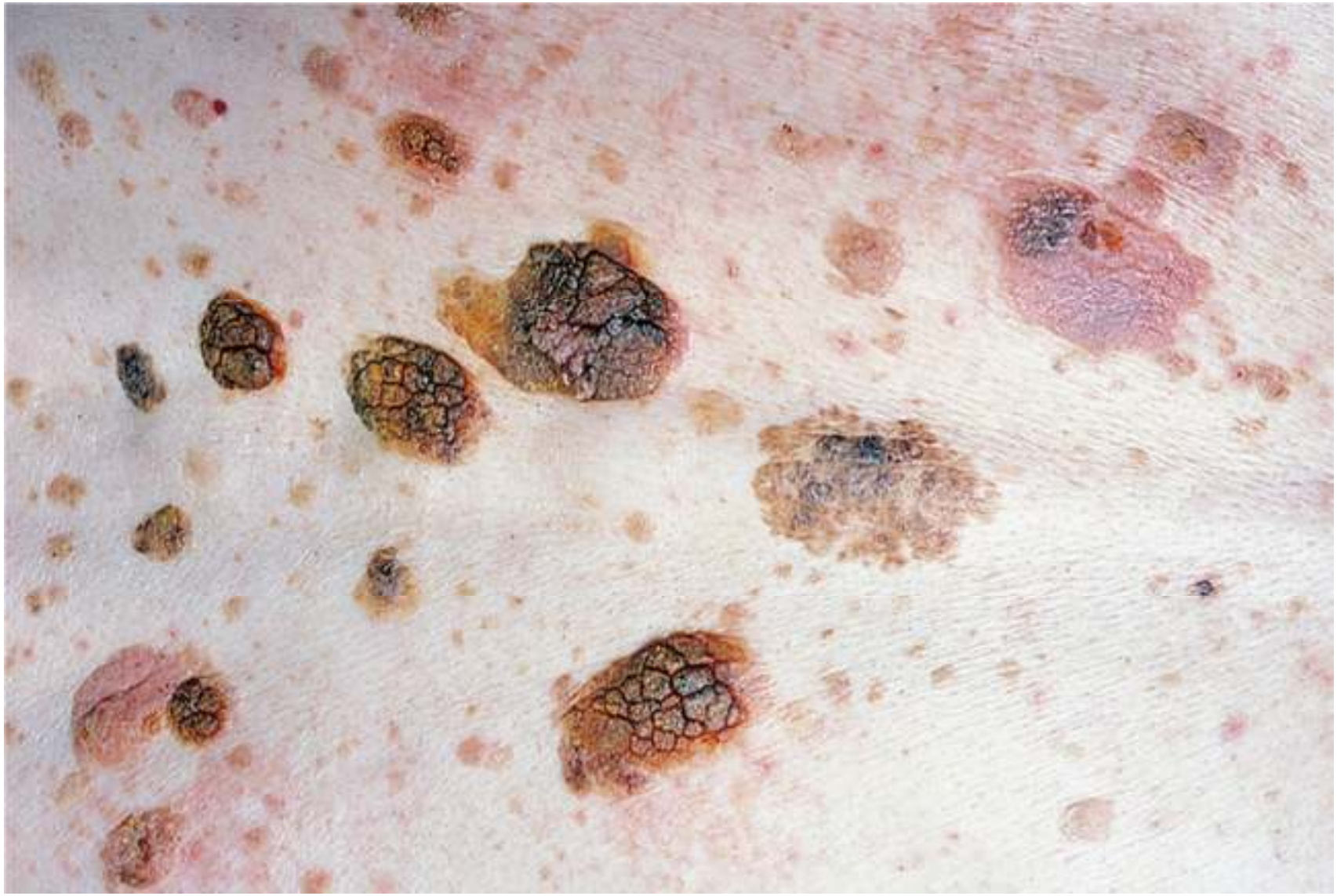
Benign tumors of the skin

- **1. Epithelial origin:**
  - **Seborrheic keratosis (wart);**
  - **Acanthoma;**
  - **Keratoacanthoma;**
  - **Trichoepitelioma;**
  - **ILVEN, etc.**

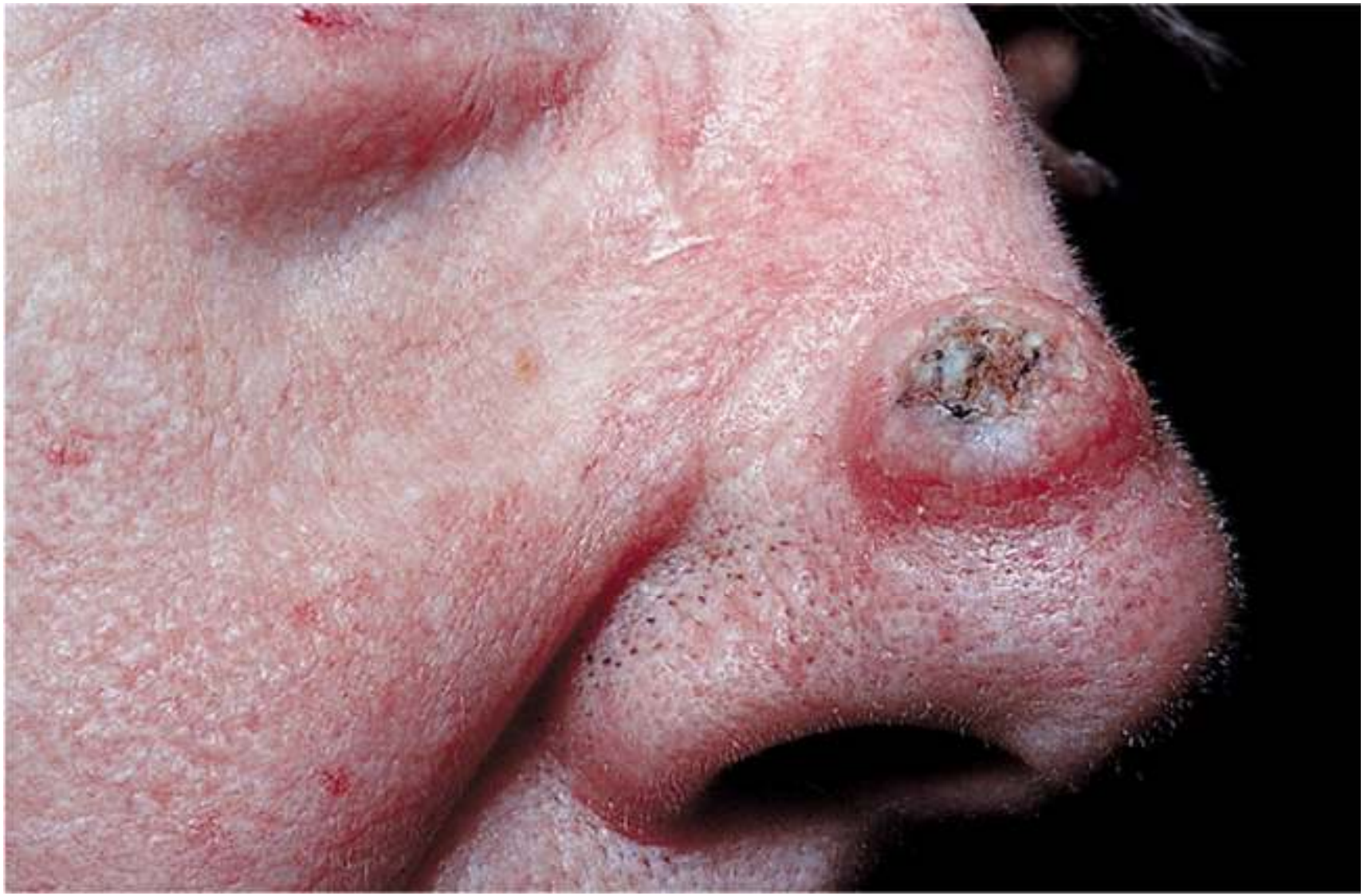
Verucă seboreică = keratoză seboreică:



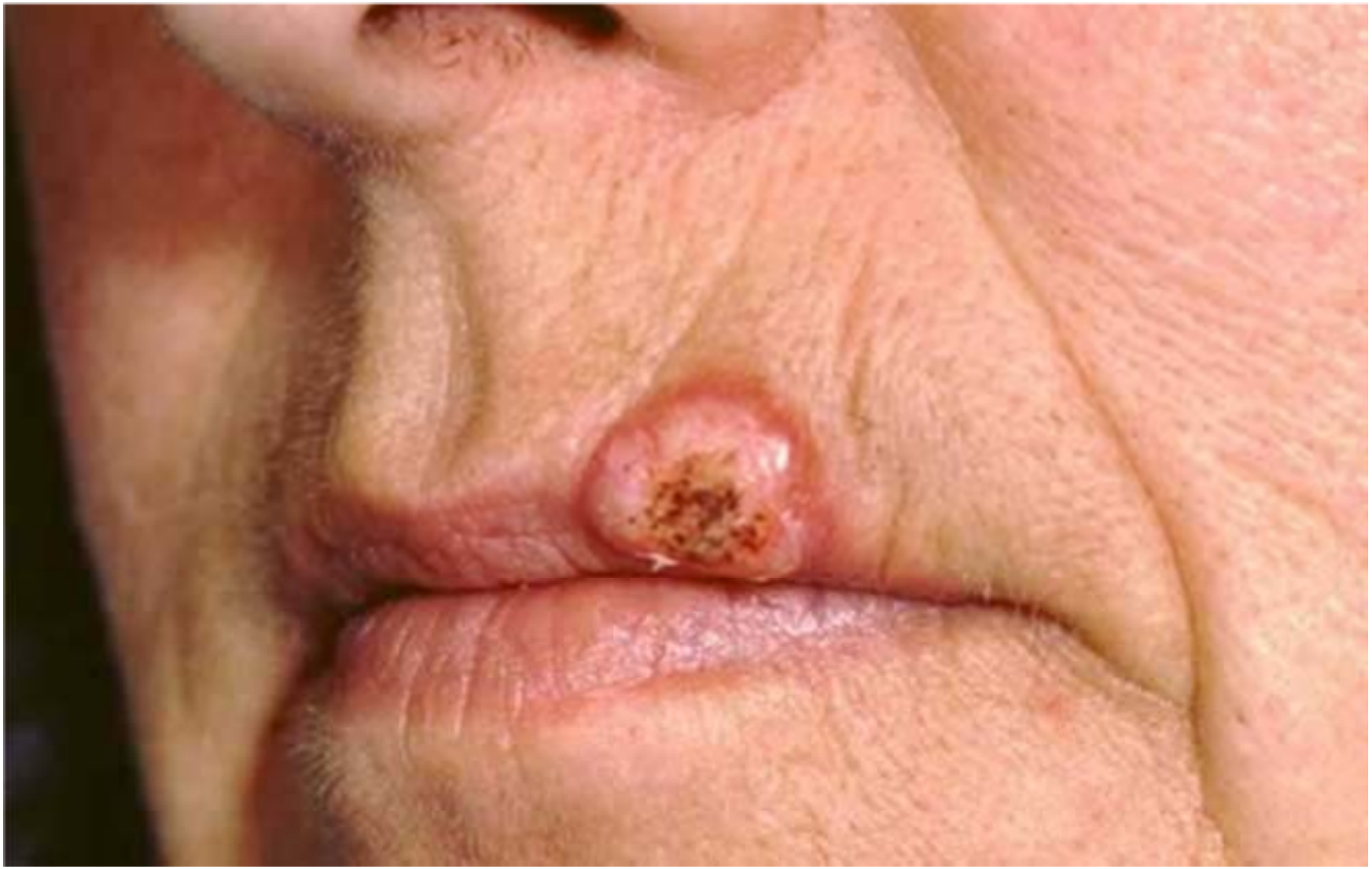
Keratoze seboreice – “flori de cimitir”:



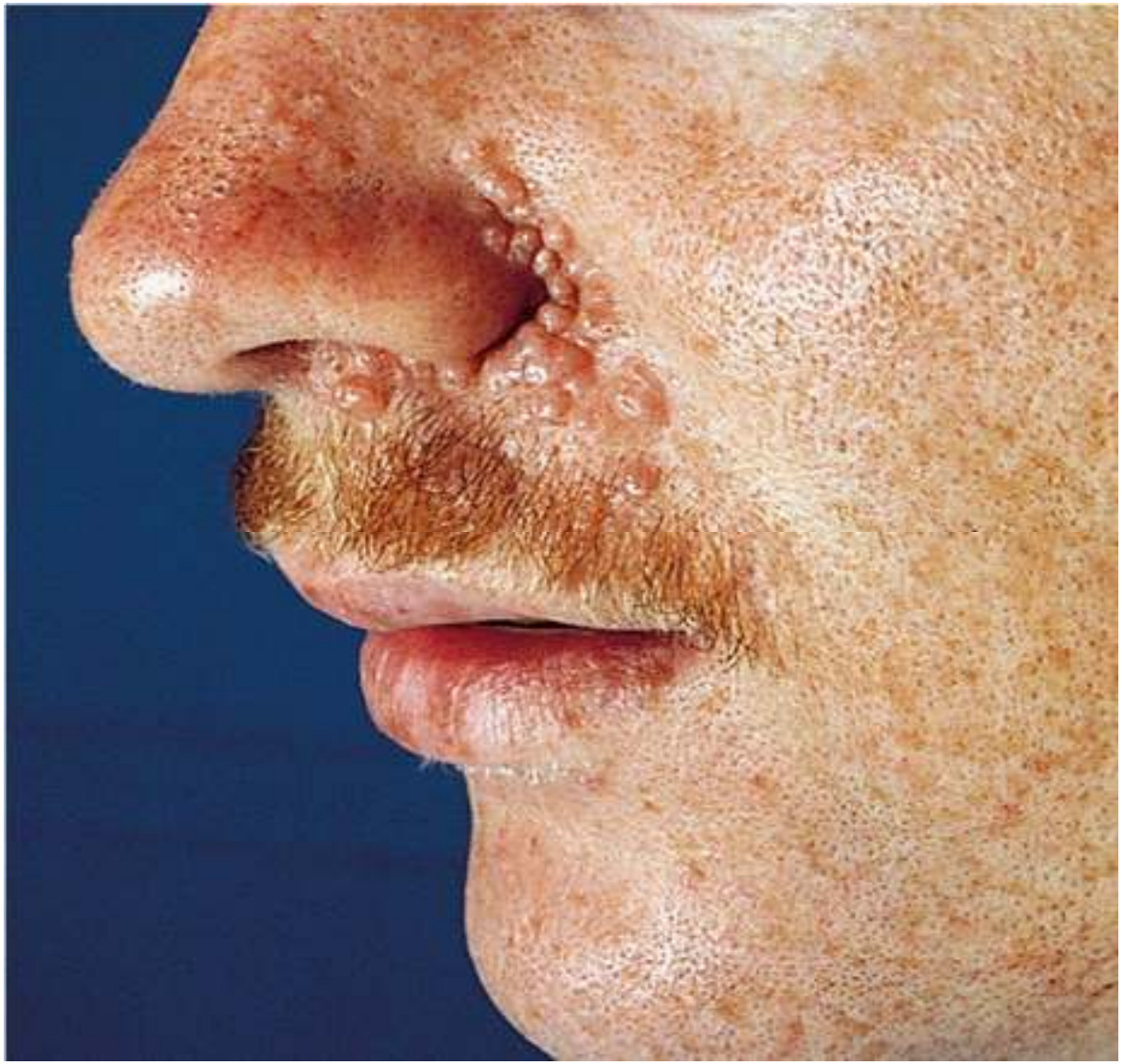
Keratoacantom al nasului:



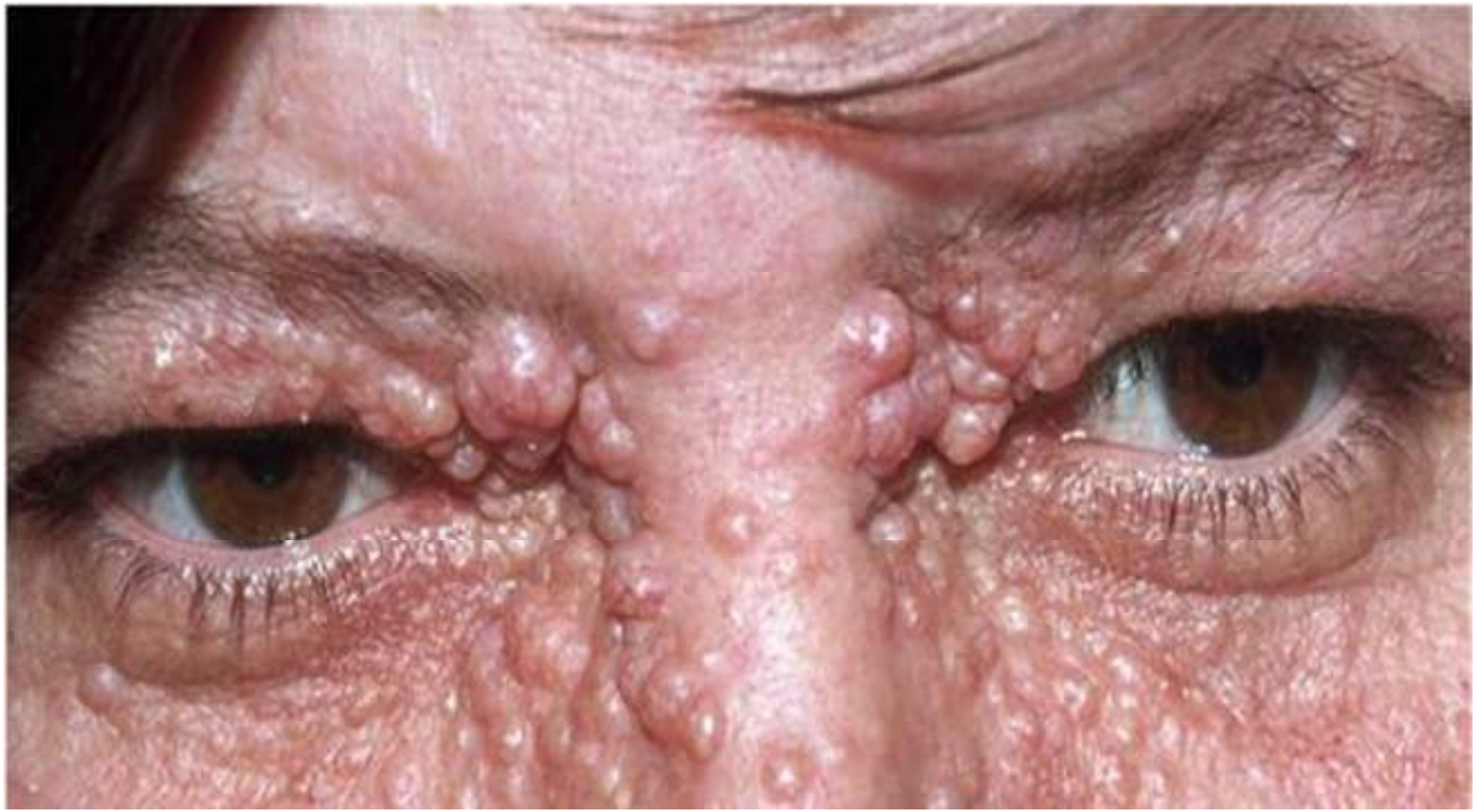
Keratoacantom al buzei superioare:



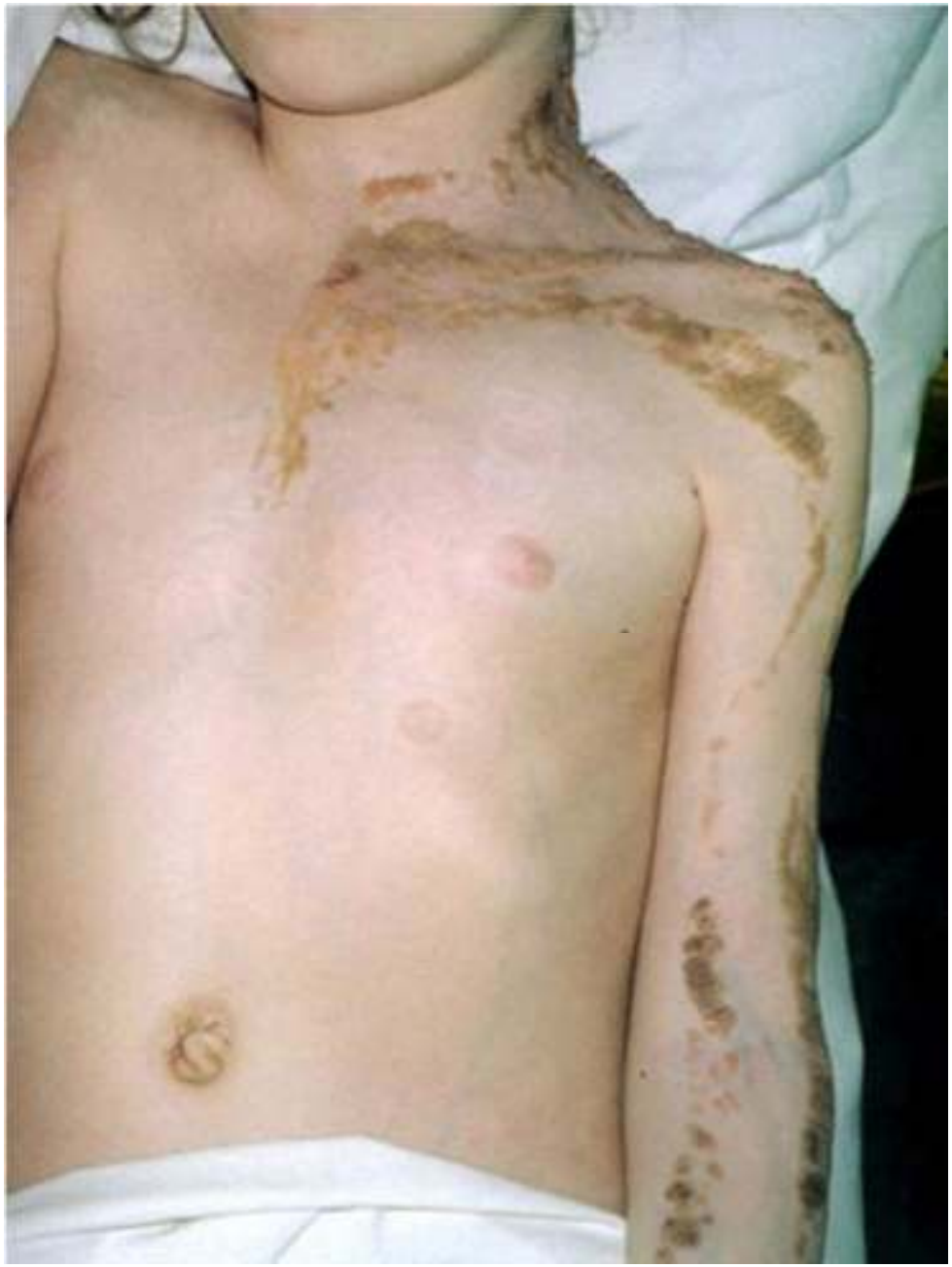
Trichoepitelioame pliul nazo-labial:



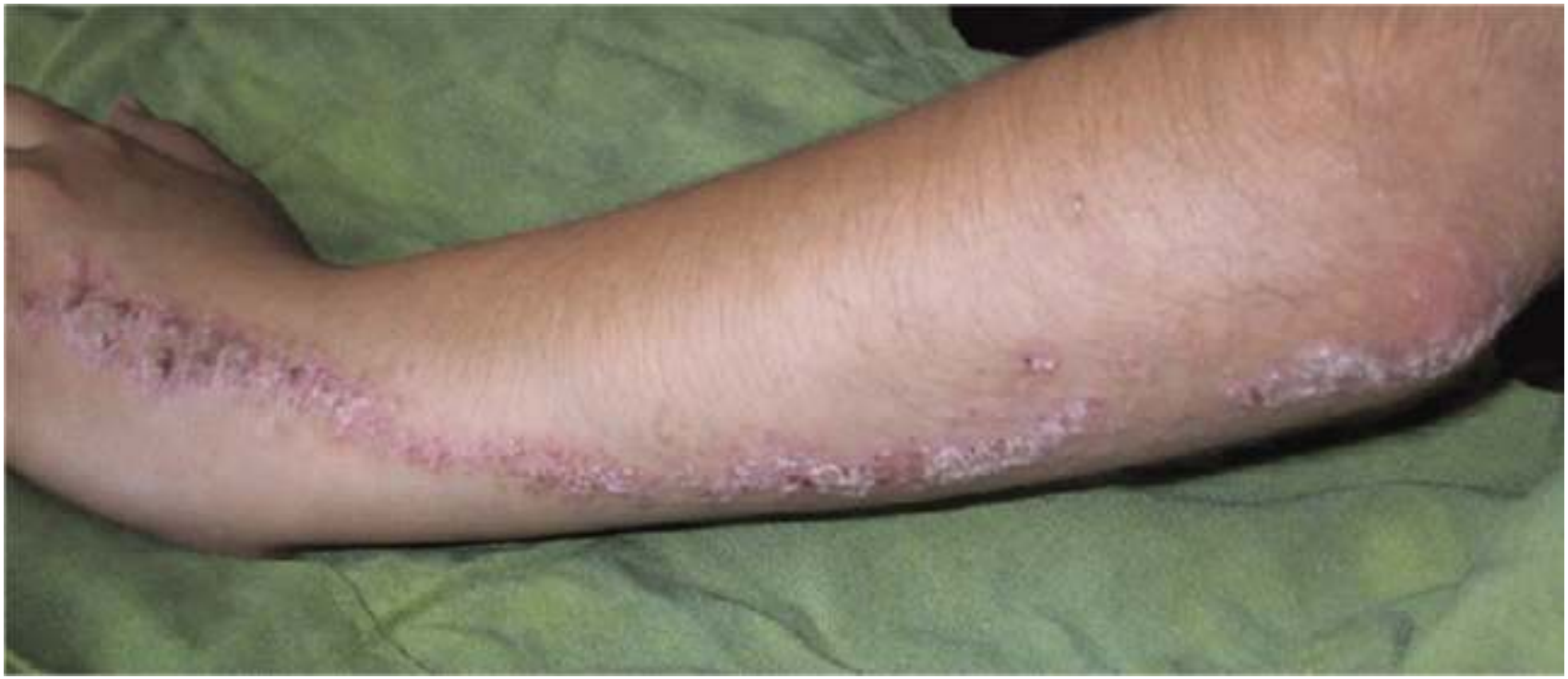
Trichoepitelioame multiple:



NEVIL:



Nevus epidermal = psoriasis nevoid:

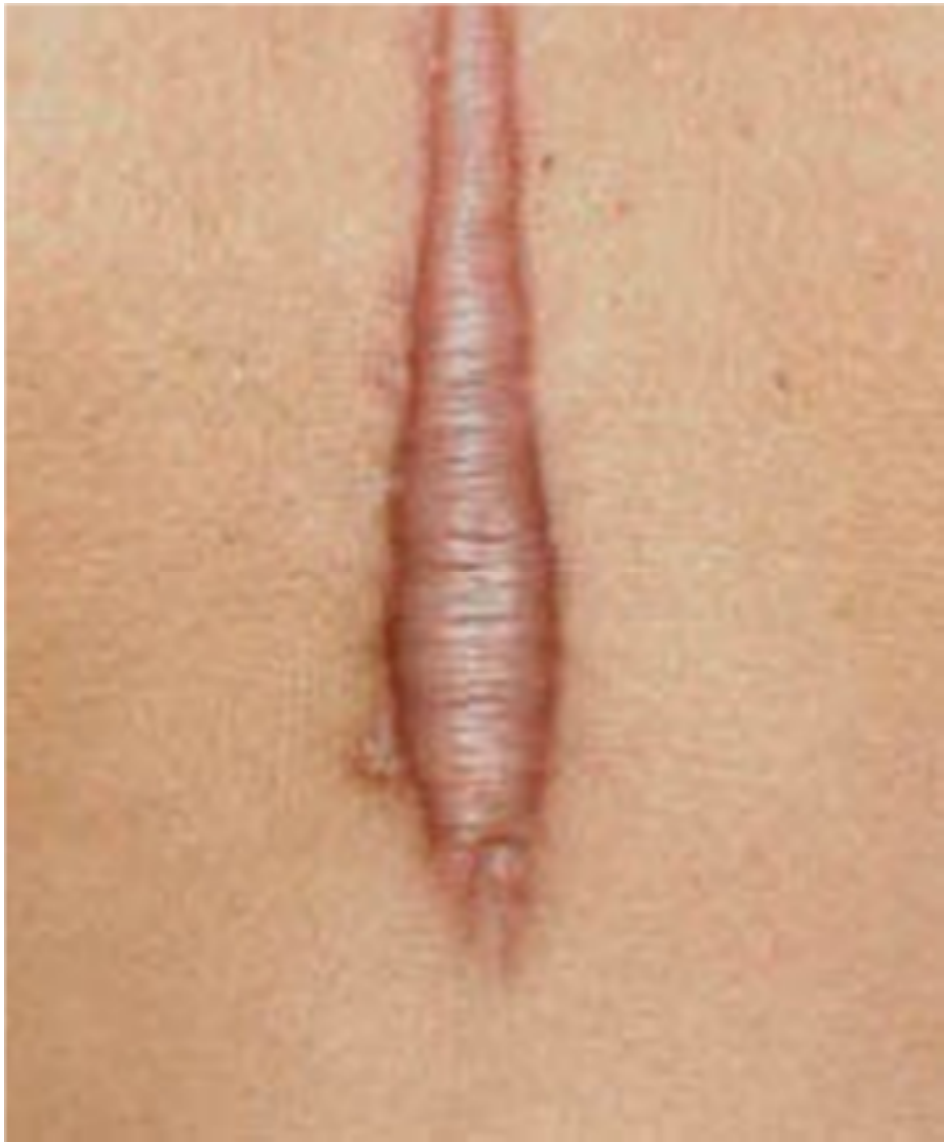


Benign tumors of the skin

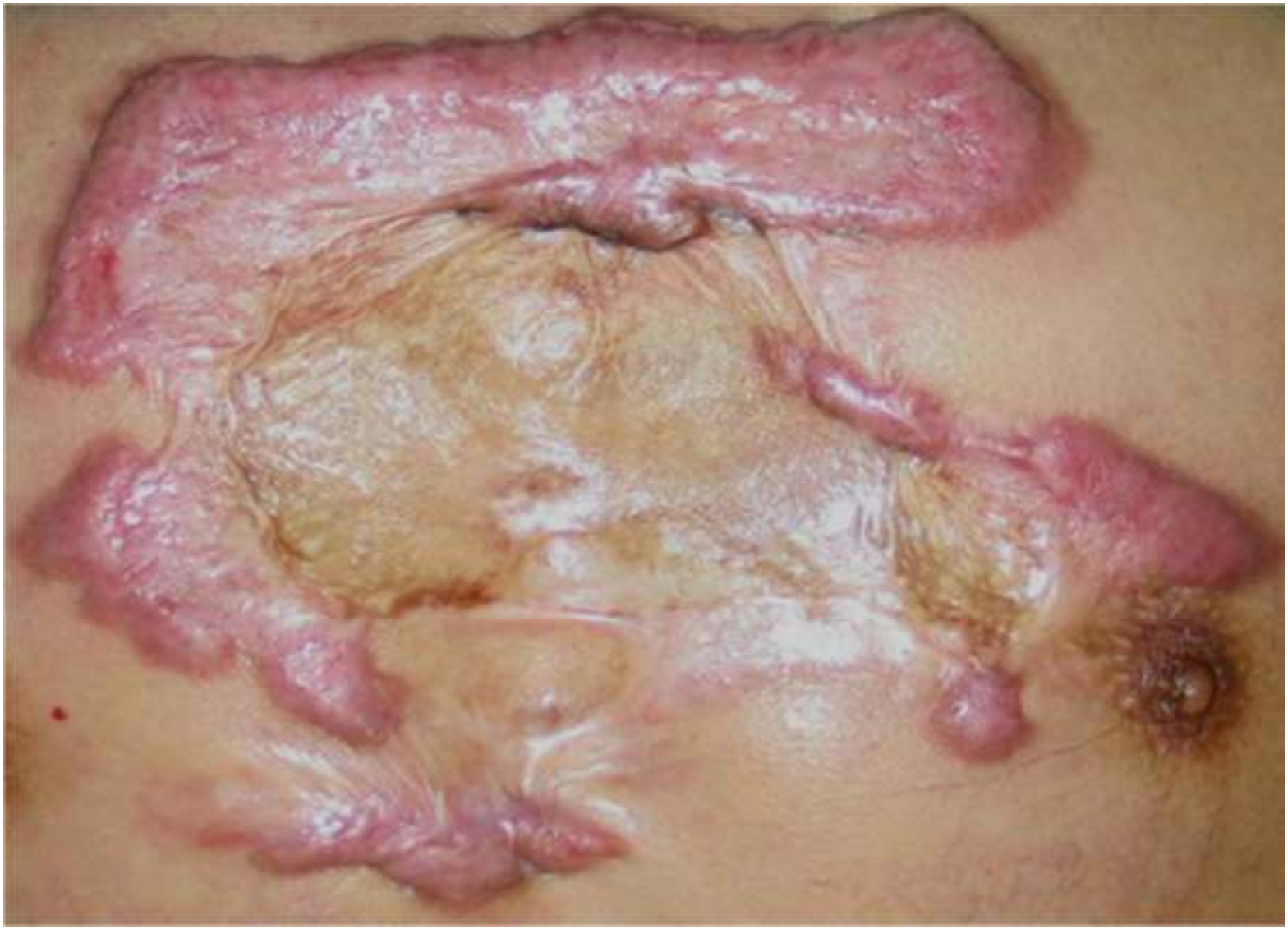
2. Mesenchymal origin:

- **Keloid, fibroma;**
- **Hemangioma;**
- **Lymphangioma;**
- **Lipoma;**
- **Leiomyoma, etc.**

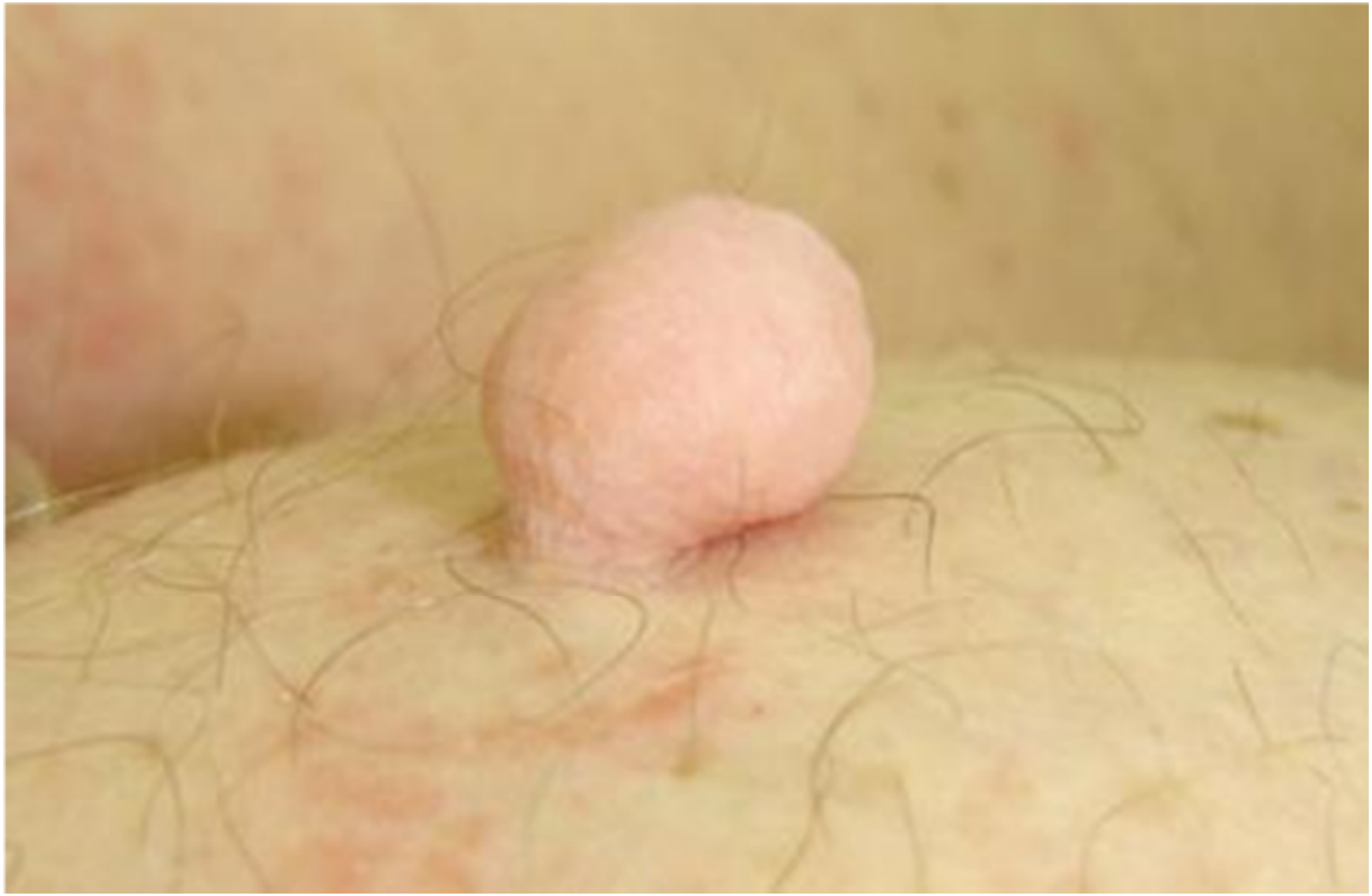
Keloid liniar – reacție postoperatorie:



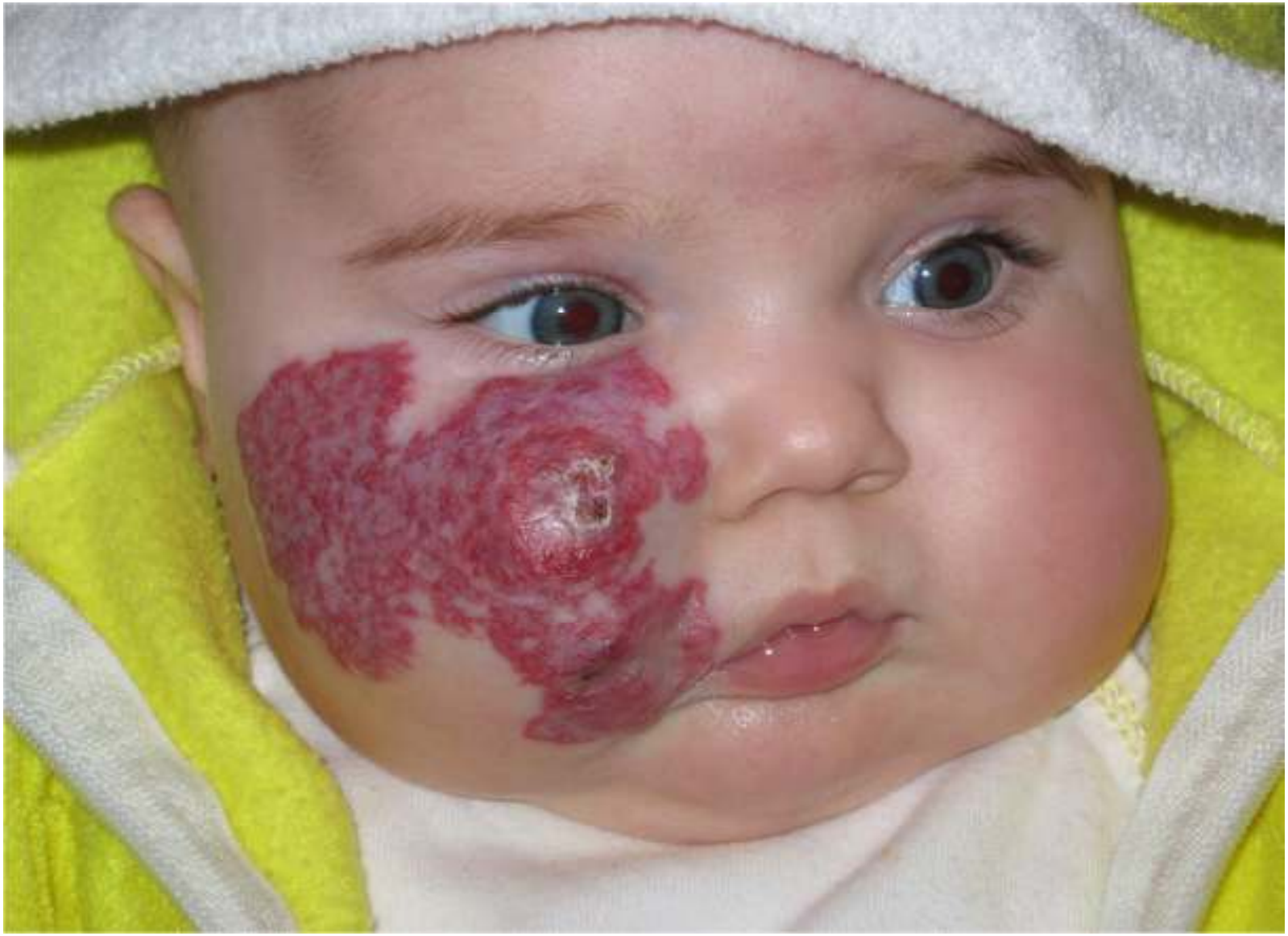
Keloizi multipli – post acnee, post furuncul:



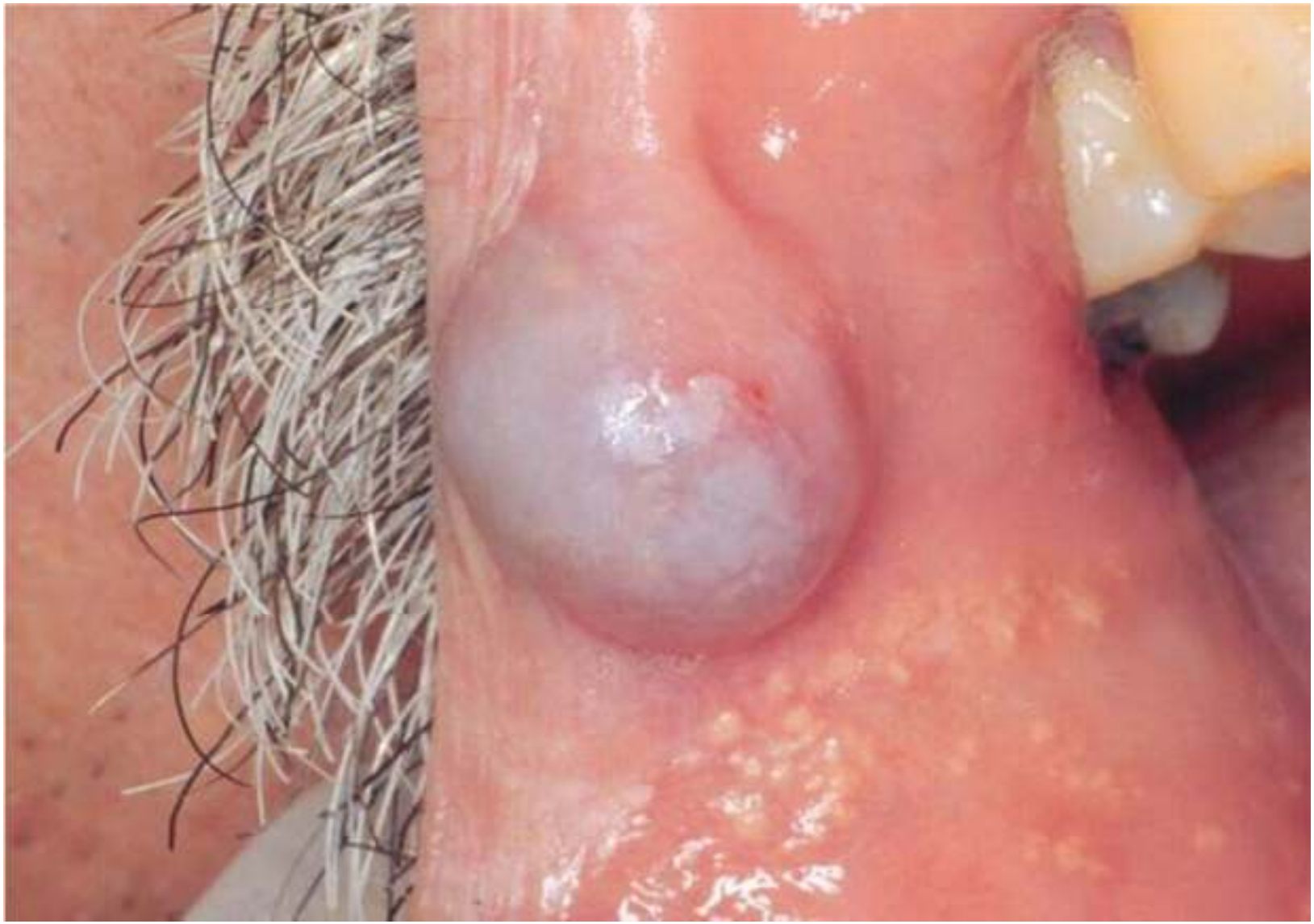
Fibrom:



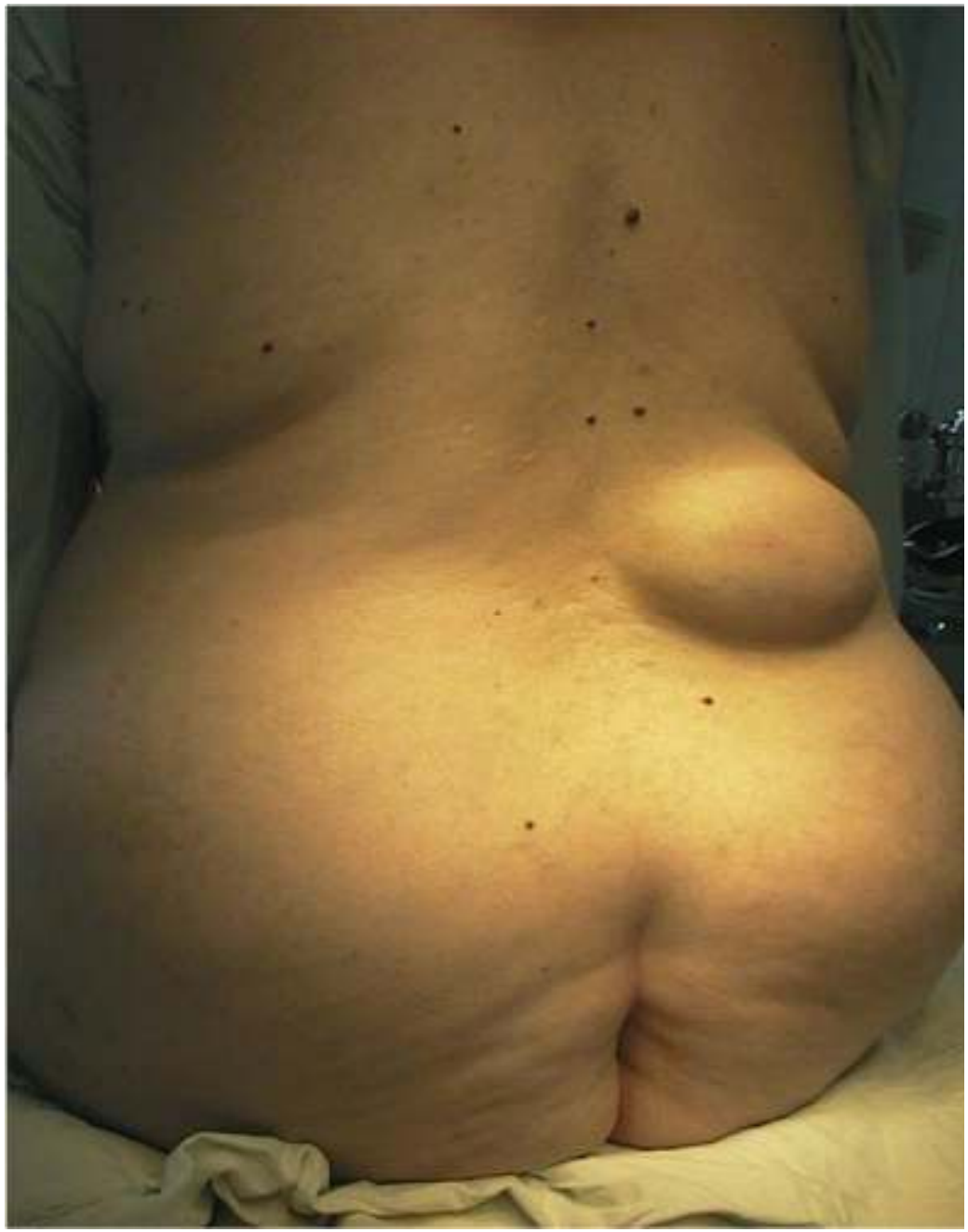
Hemangiom:



Limfangiom:



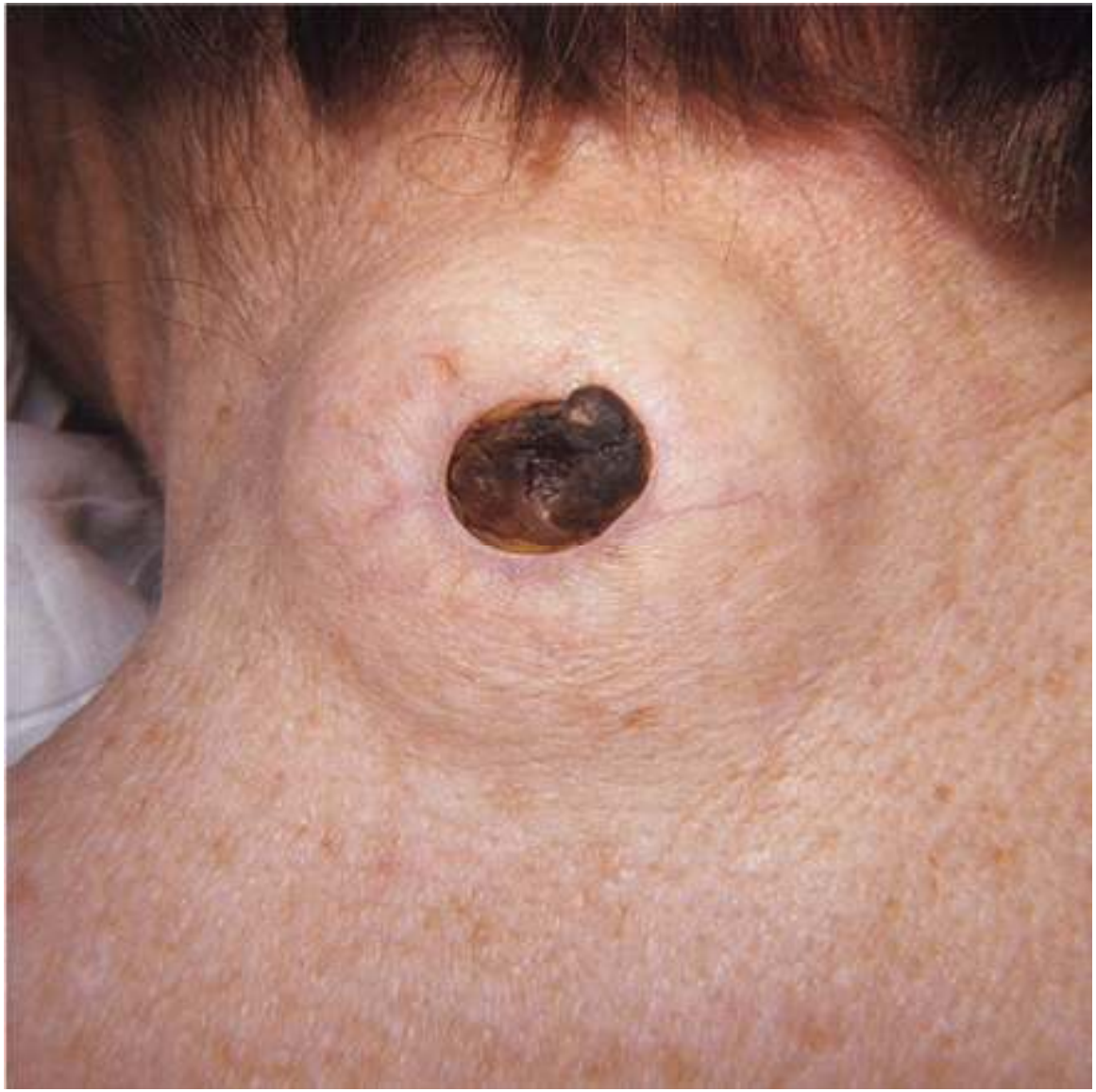
Lipom:



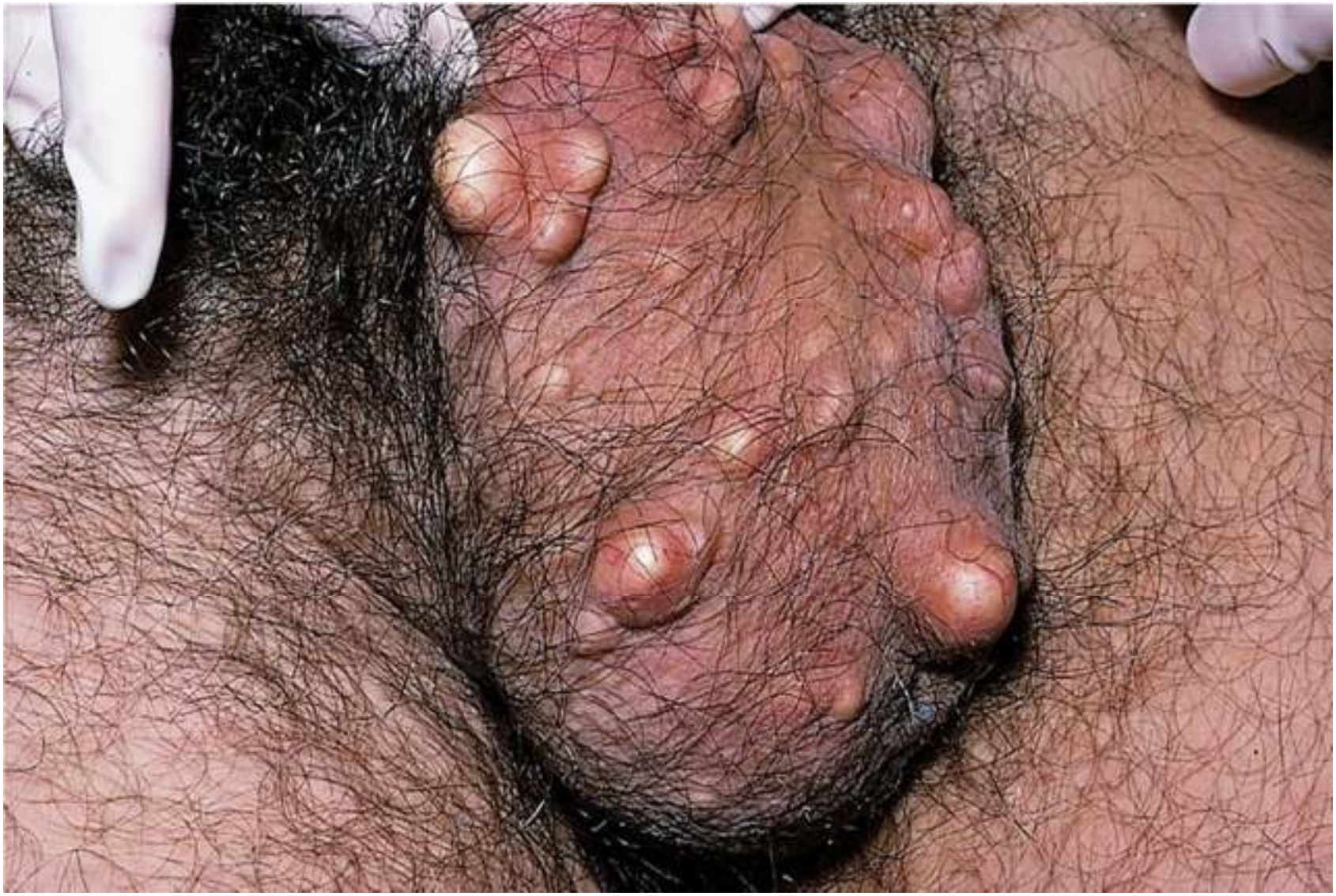
Benign tumors of the skin

- **3. Cysts:**
  - **Cysts epidermal;**
  - **Cysts sebaceous;**
  - **Cysts sweat gland, etc.**

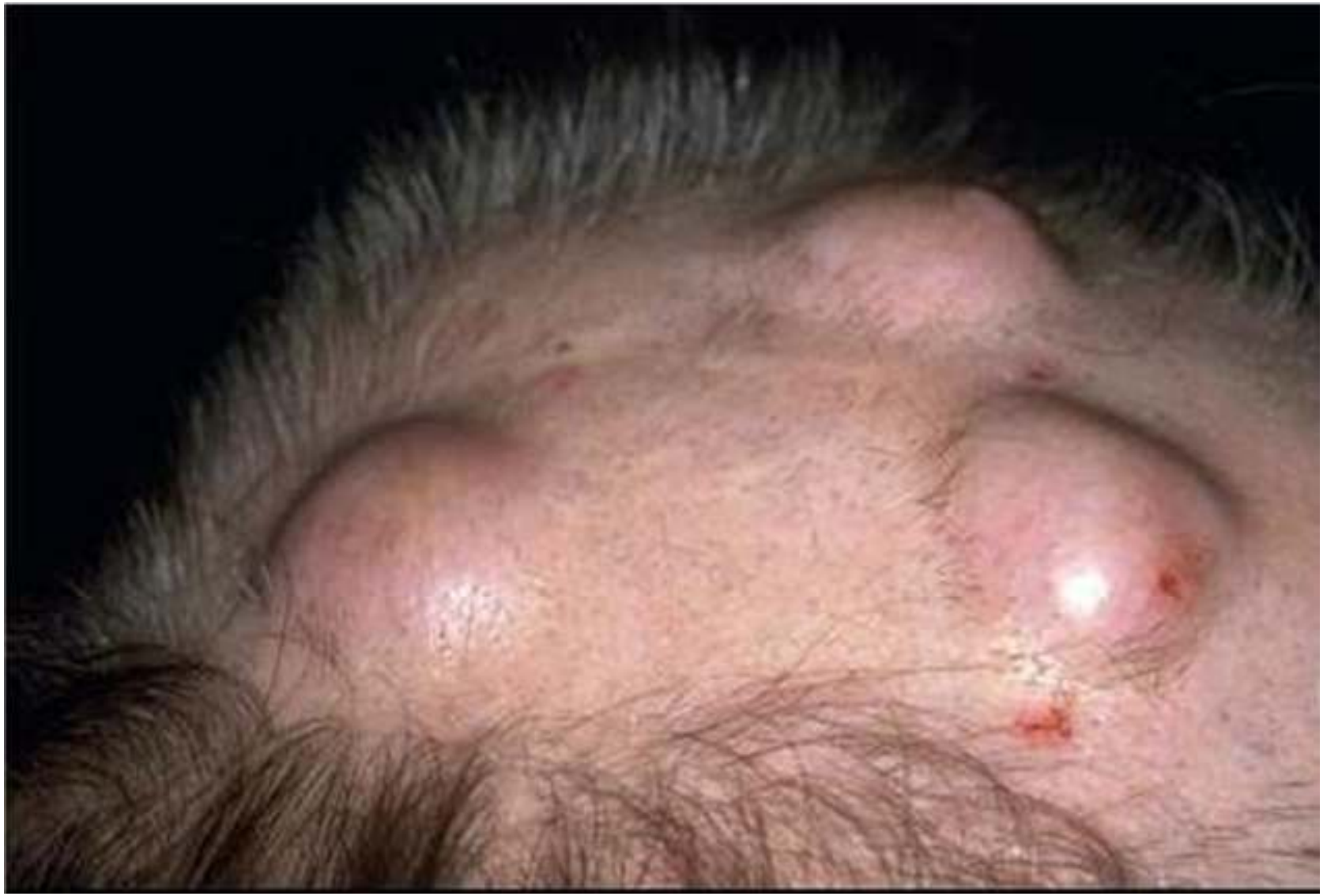
Chist epidermal:



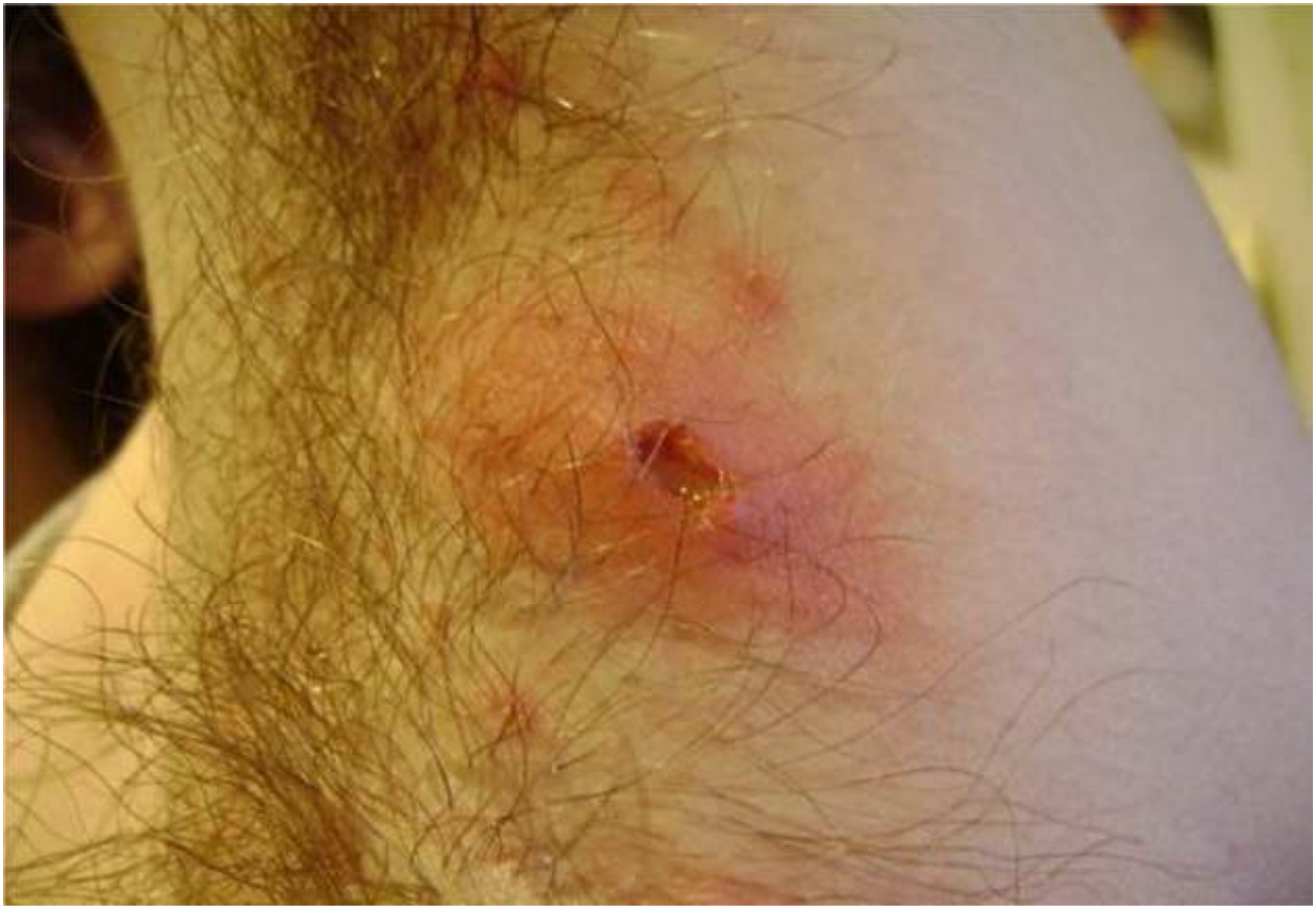
Chist epidermoid al scrotului:



Chisturi sebacee ale scalpului:



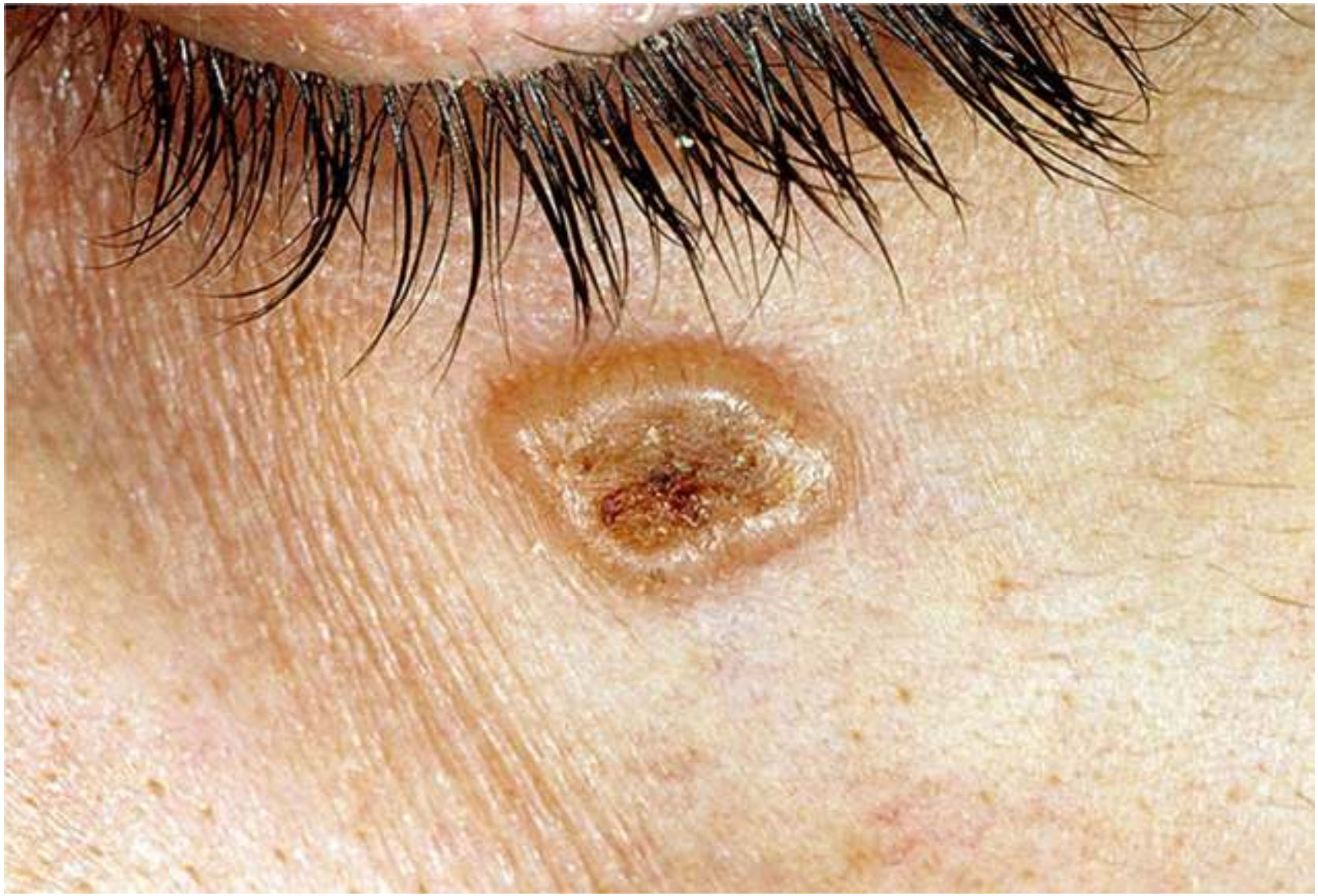
Chist sudoripar:



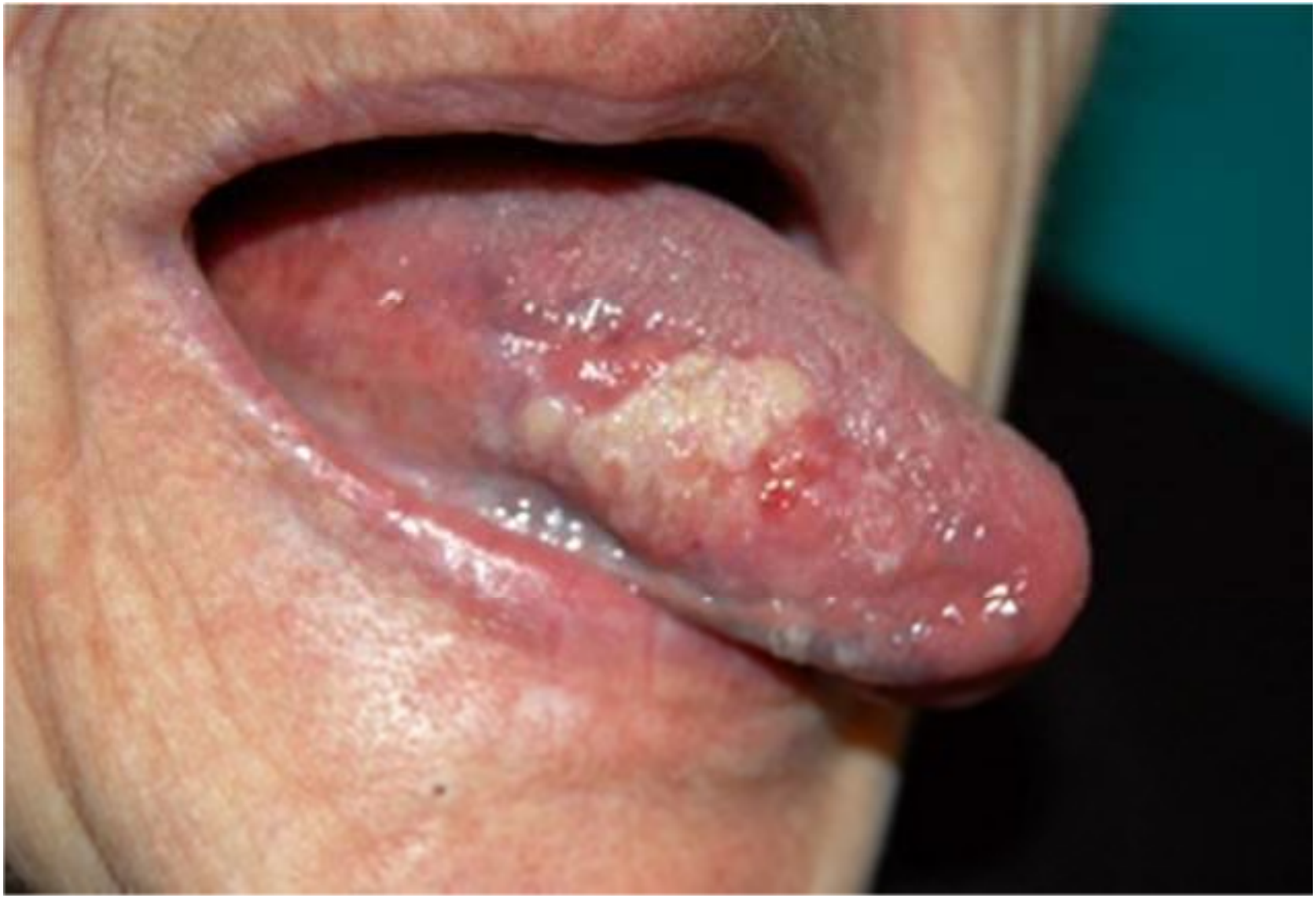
Malign tumors:

- **1. Epithelial origin:**
  - **BCC;**
  - **SCC.**

EBC sau bazaliom:



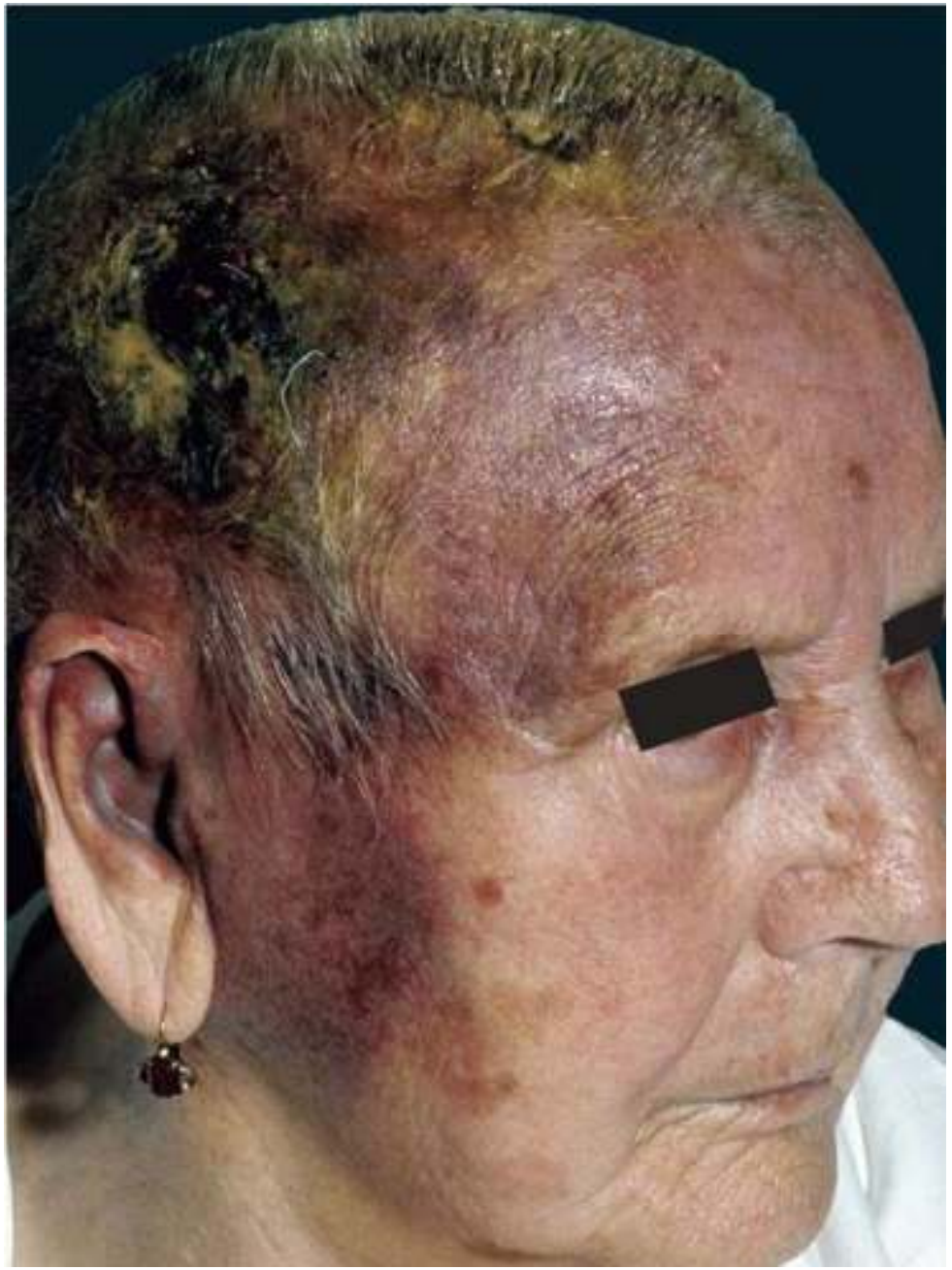
ESC sau spinaliom:



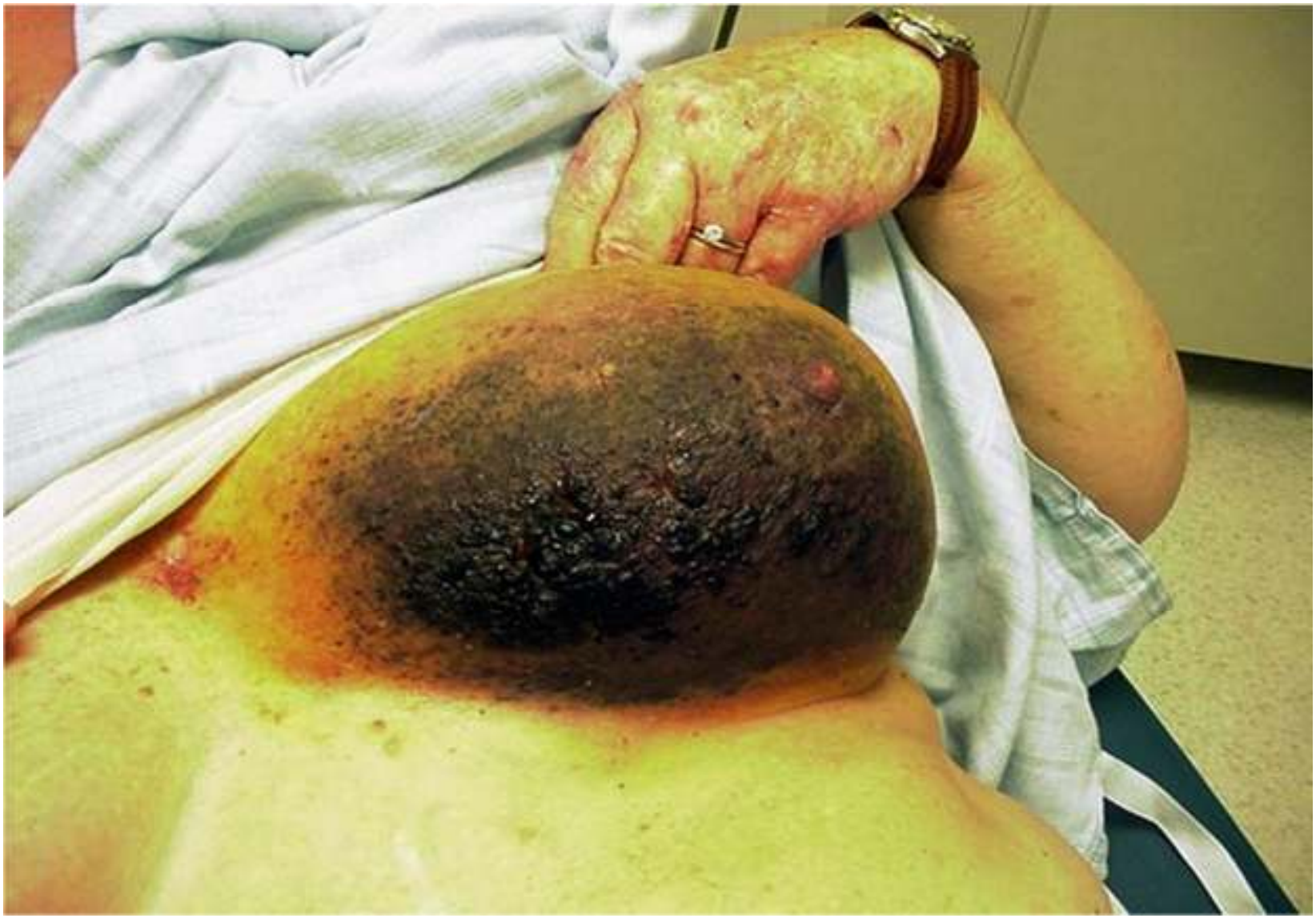
Malign tumors

- **2. Mesenchymal origin:**
  - **Angiosarcoma;**
  - **Lymphosarcoma;**
  - **Fibrosarcoma;**
  - **Liposarcoma;**
  - **Osteosarcoma;**
  - **Reticulosarcoma, etc.**

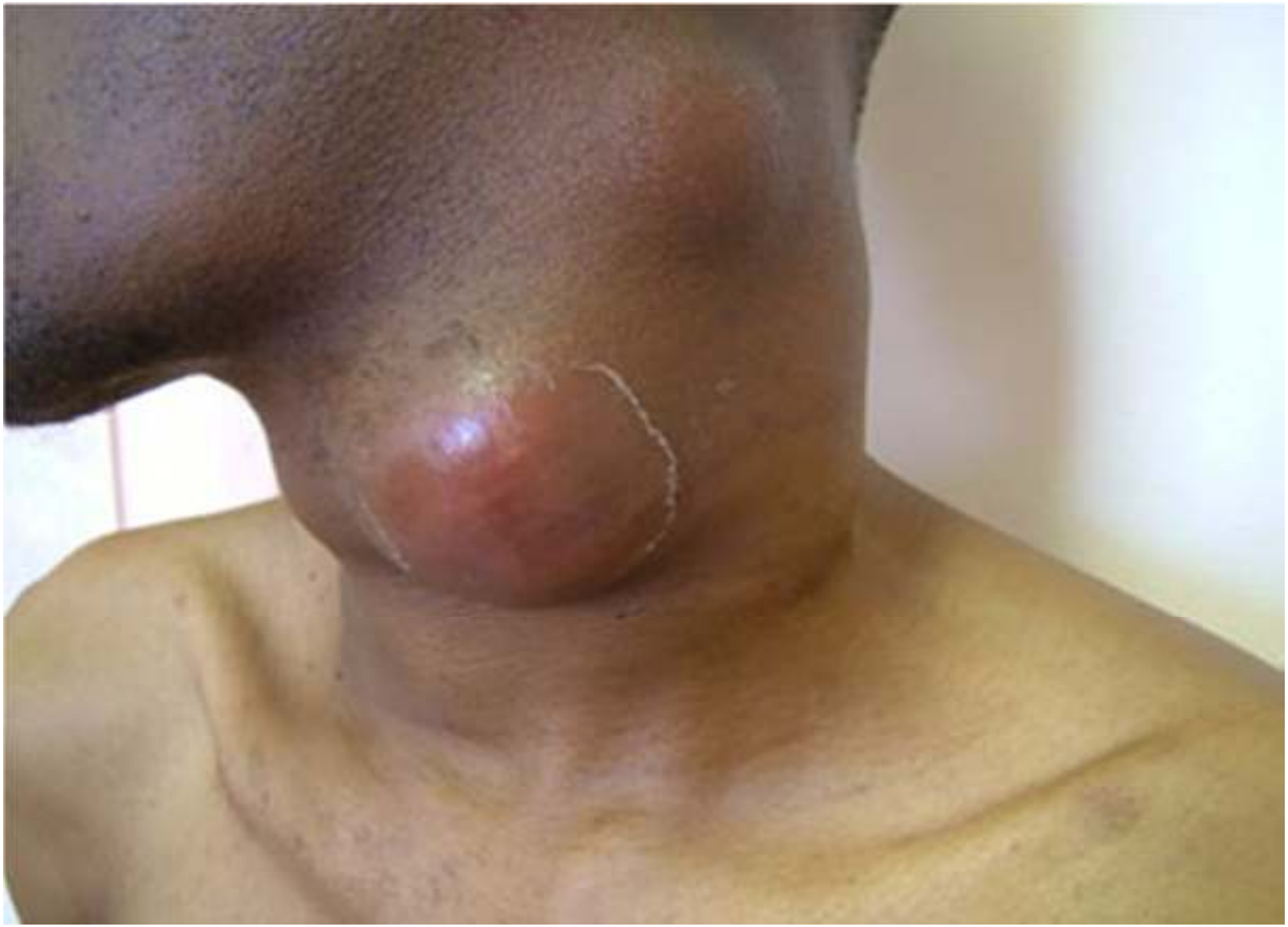
Angiosarcom:



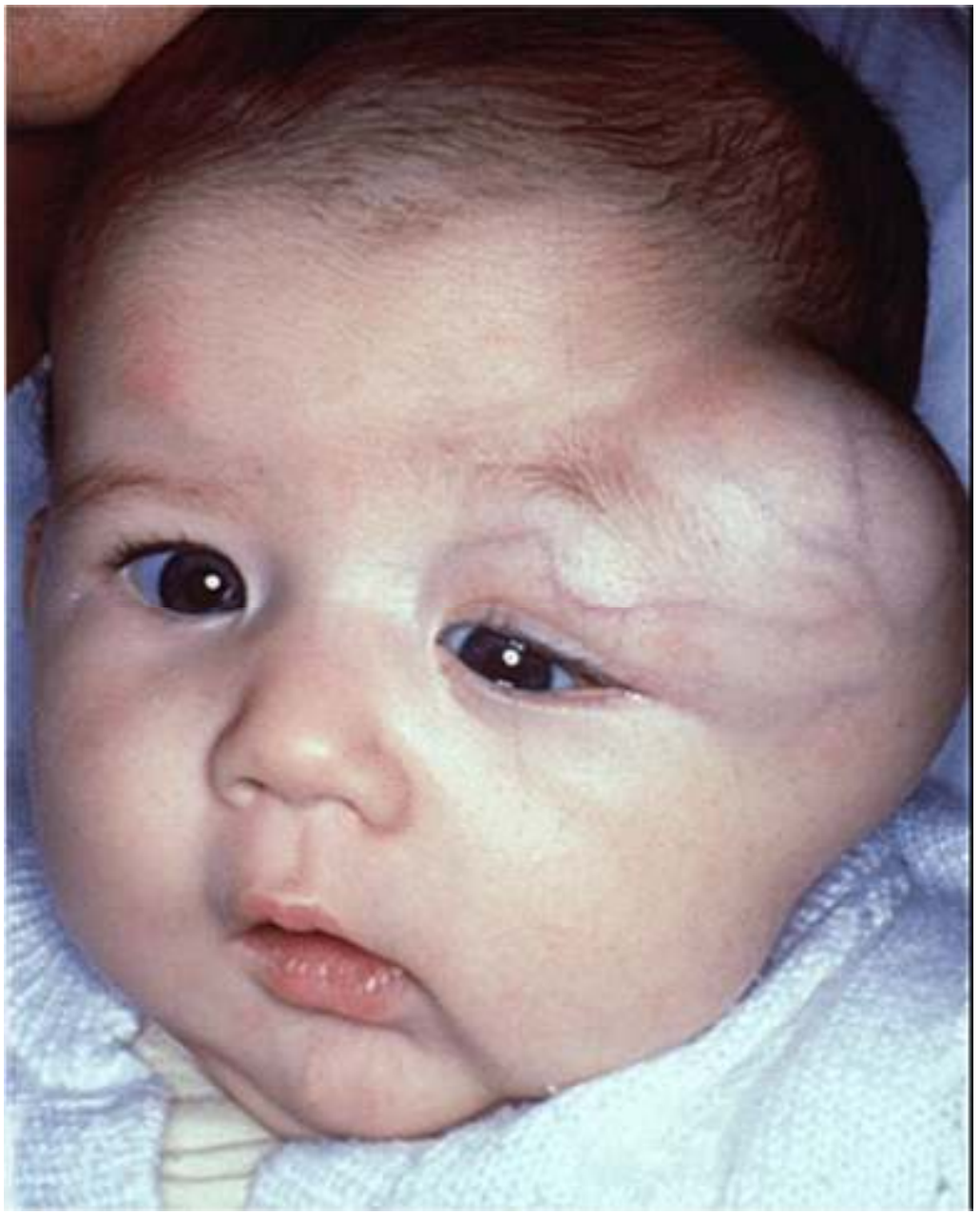
Angiosarcom:



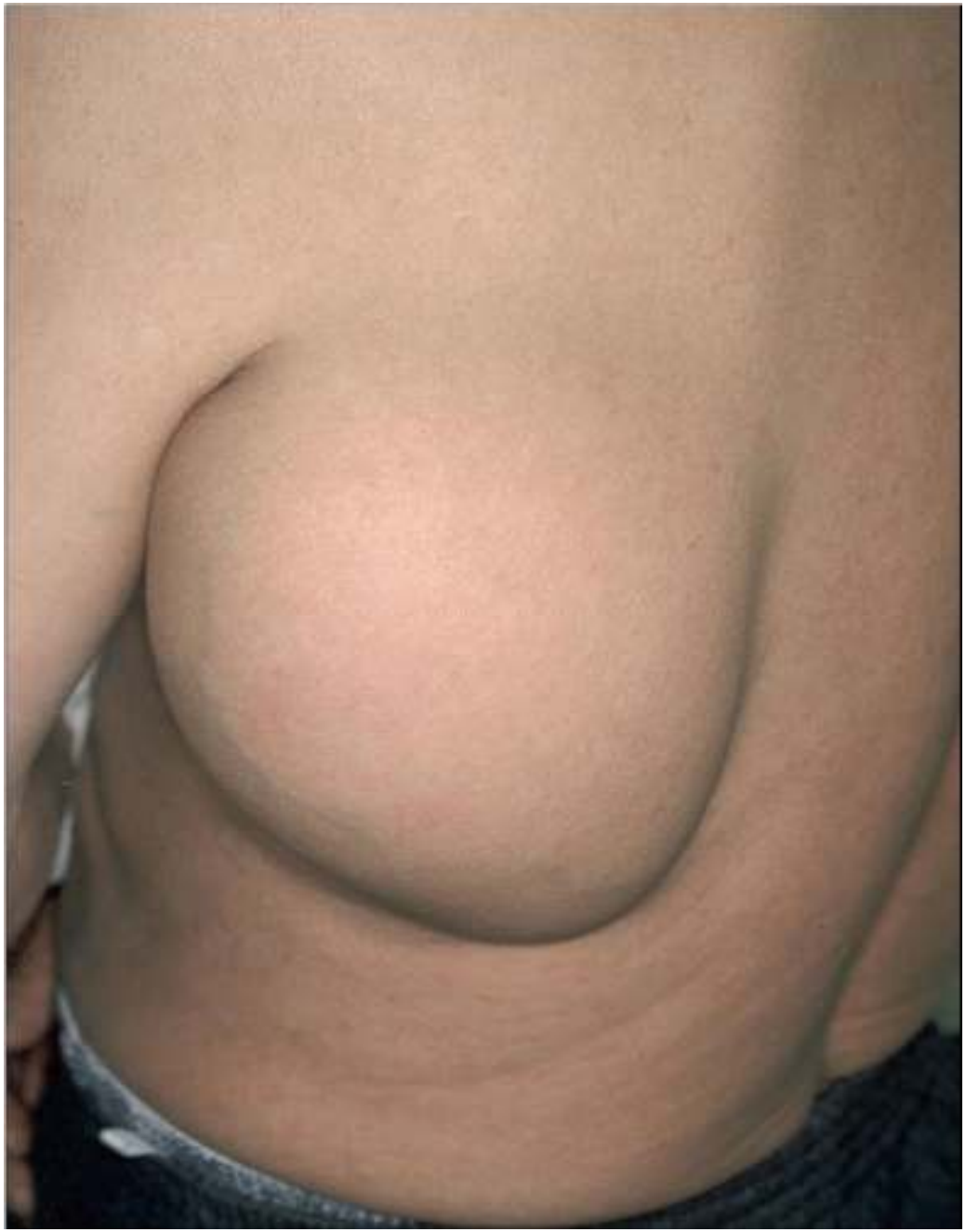
Limfosarcom:



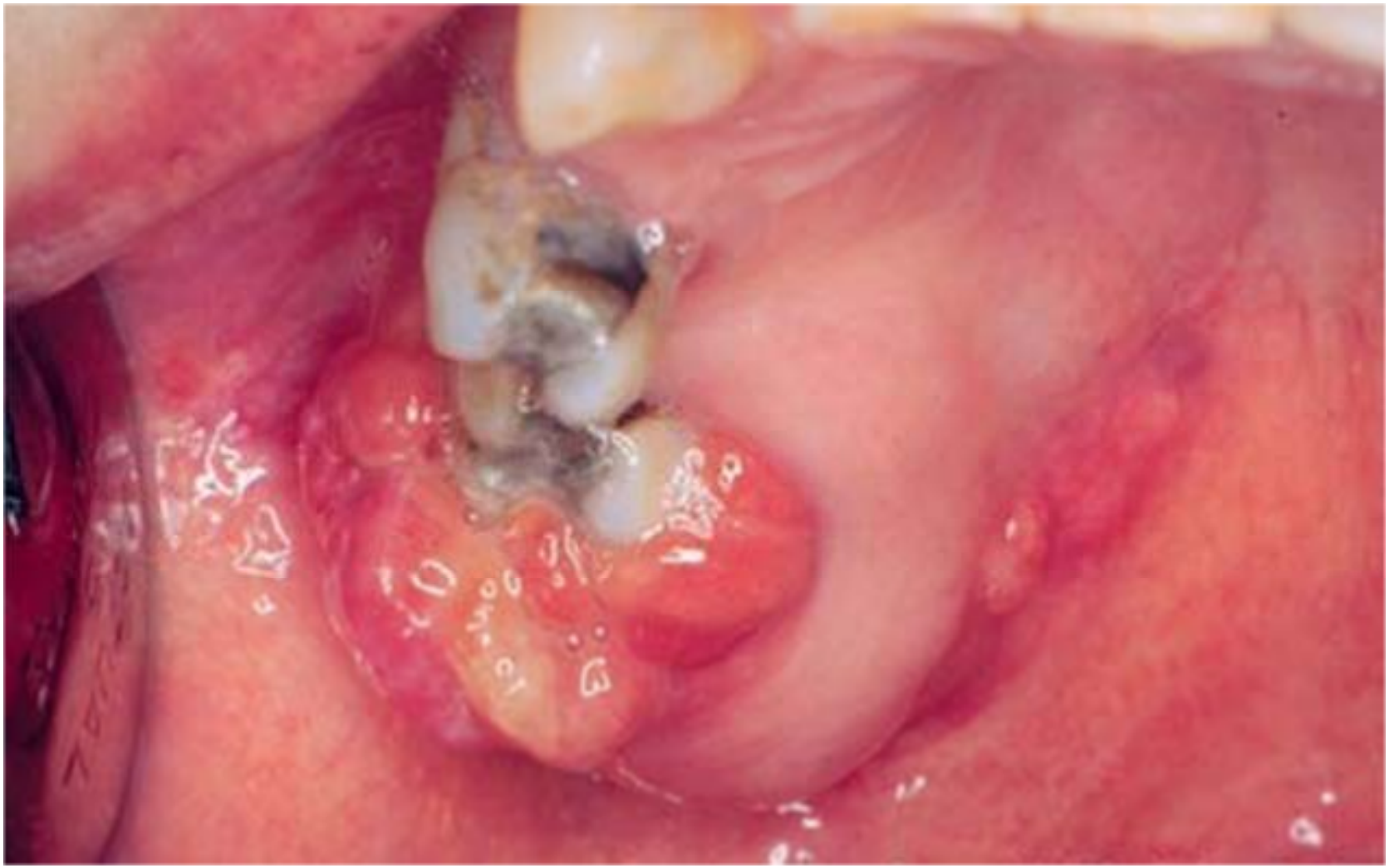
Fibrosarcom:



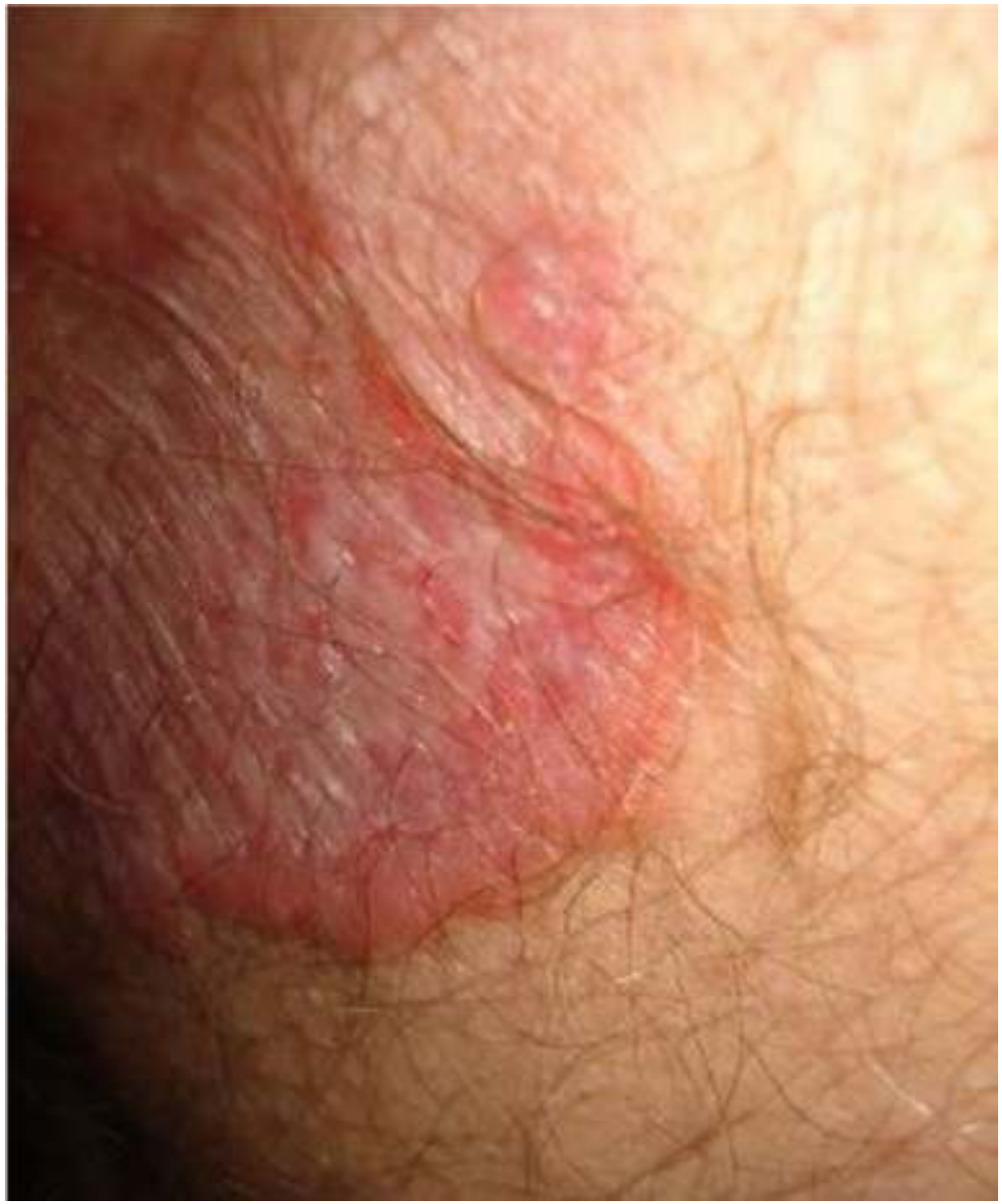
Liposarcom:



Osteosarcom:



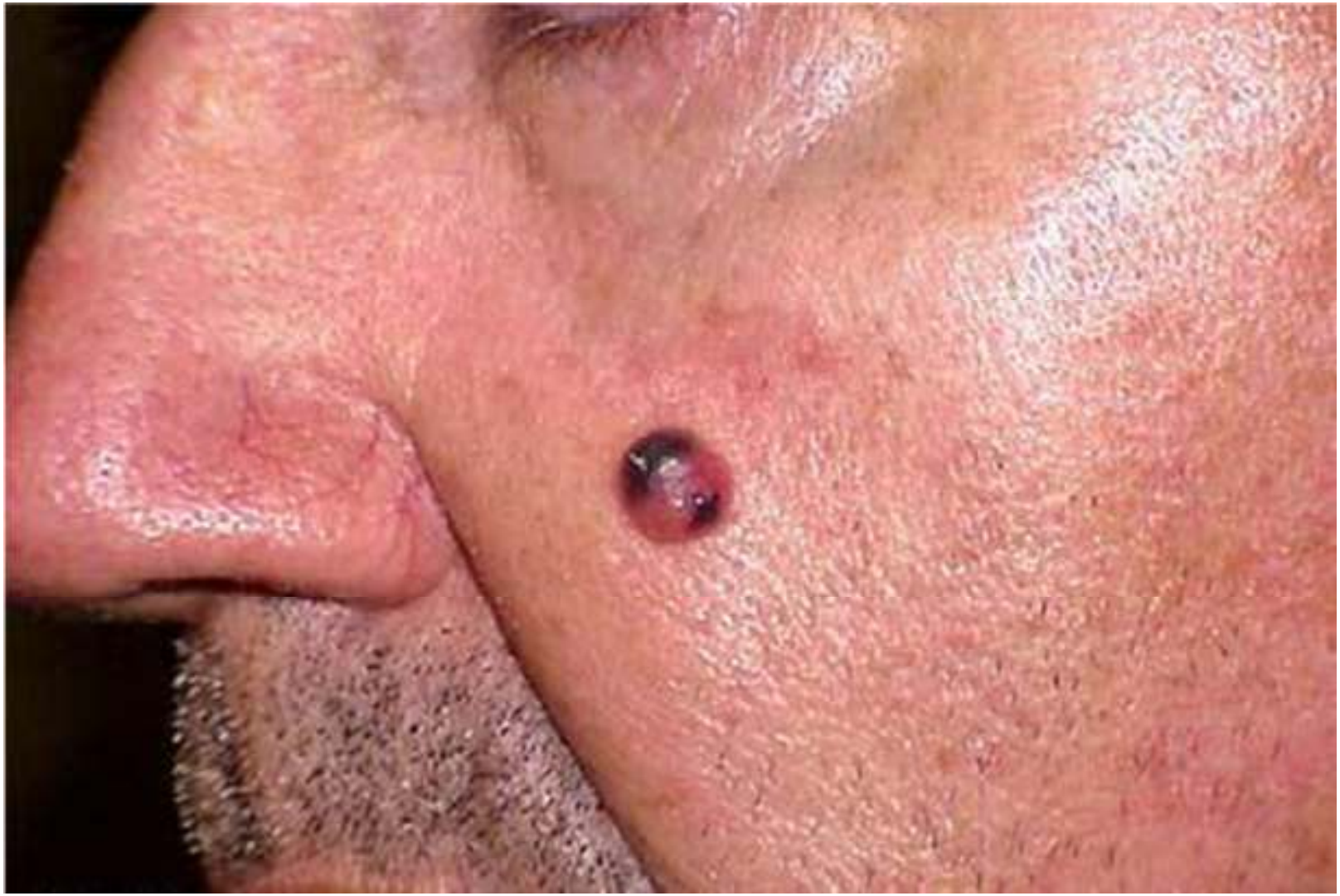
Reticulosarcom:



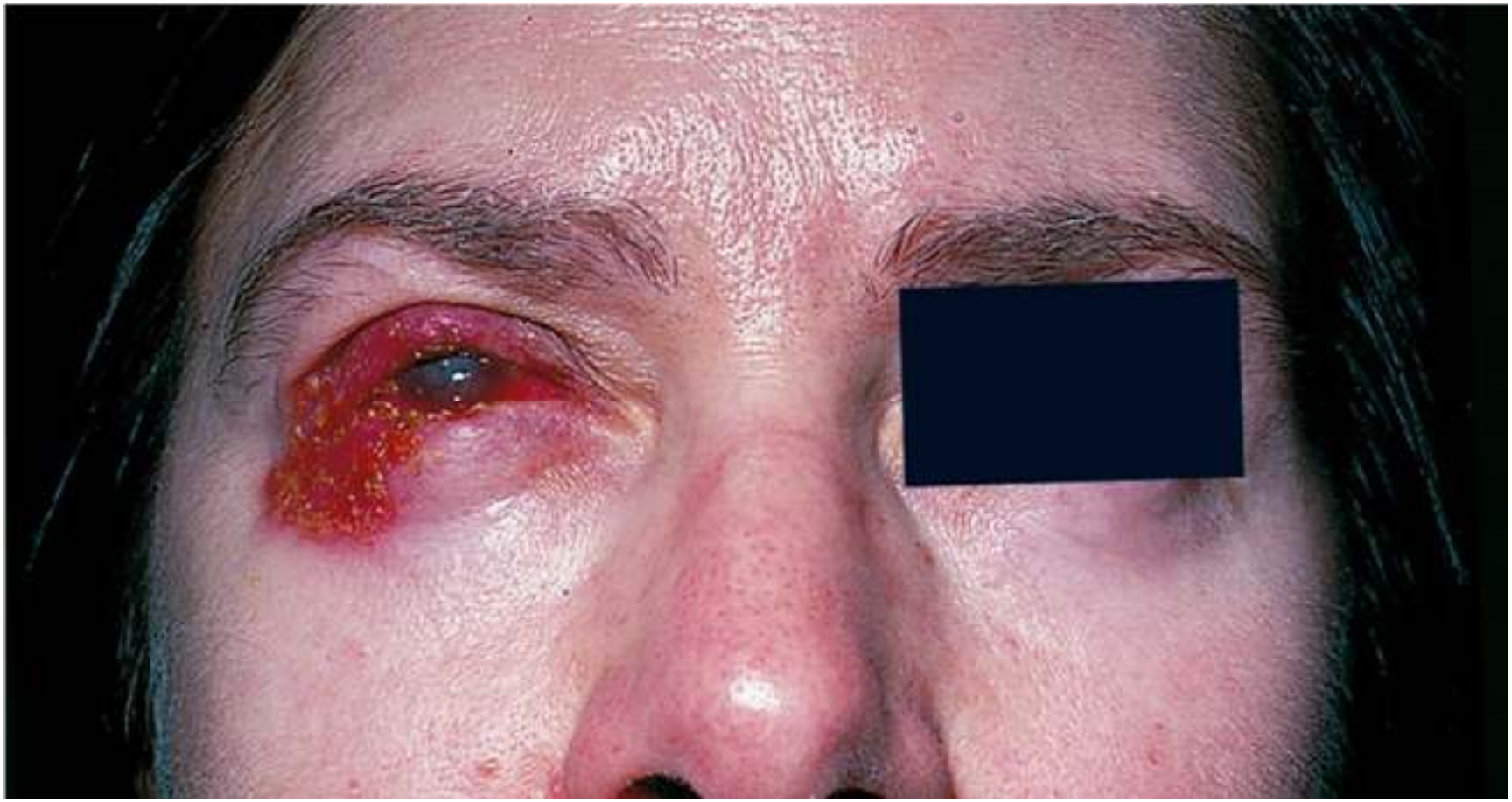
Malign tumors of different origin

- **3. Naevic / neuroblastic:**
  - **Melanoma;**
- **4. Appendageal :**
  - **Sebaceous carcinoma**
  - **Sweat glands' carcinoma.**

Melanom:



Carcinom sebaceu palpebral:



Porocarcinom:

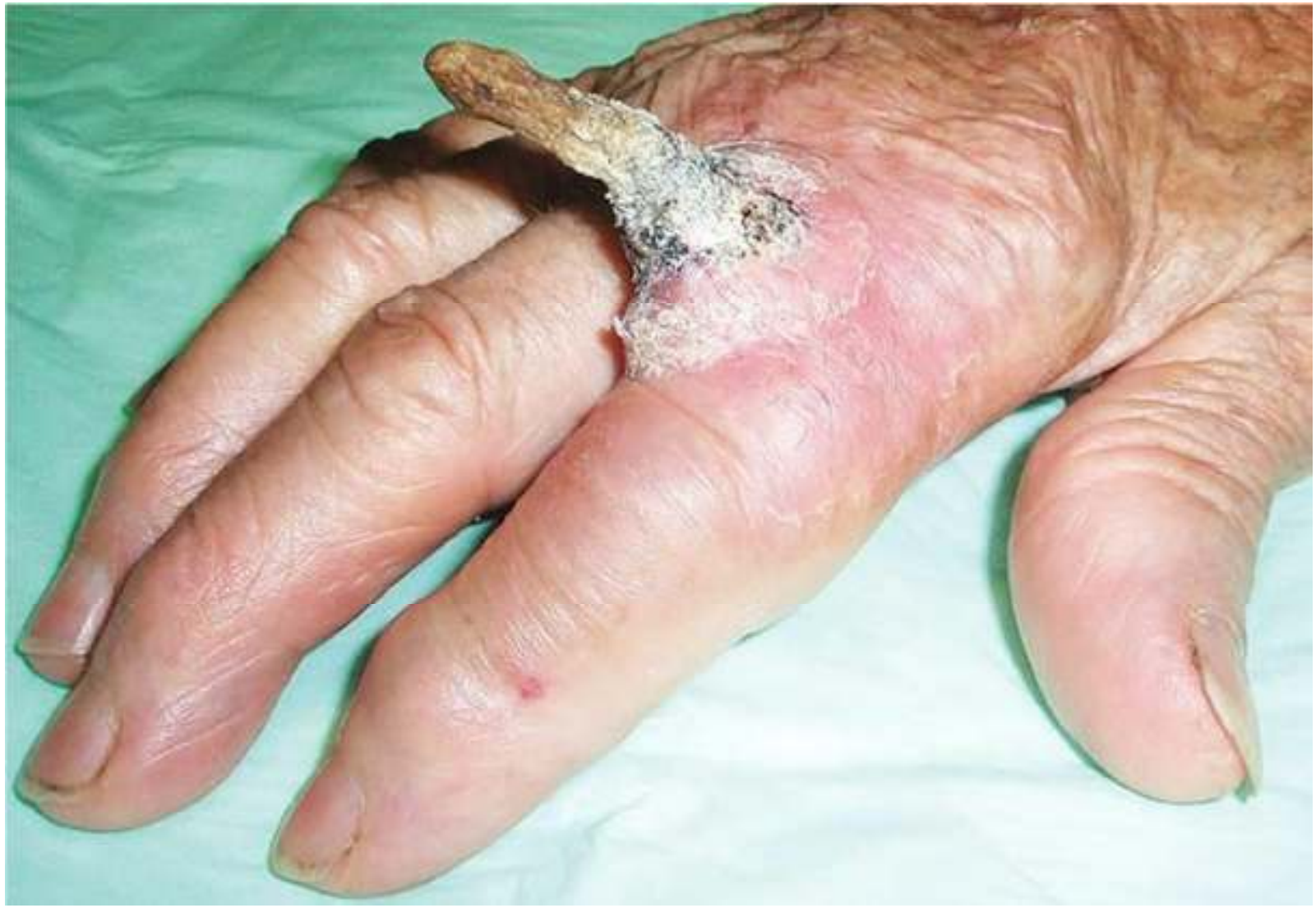
C. Cutaneous precancers

- **erythemato-scuamous**
- **hyperkeratozic**
- **papillomatous**
- **erosive-ulcerative, etc.**

Precancers – entities

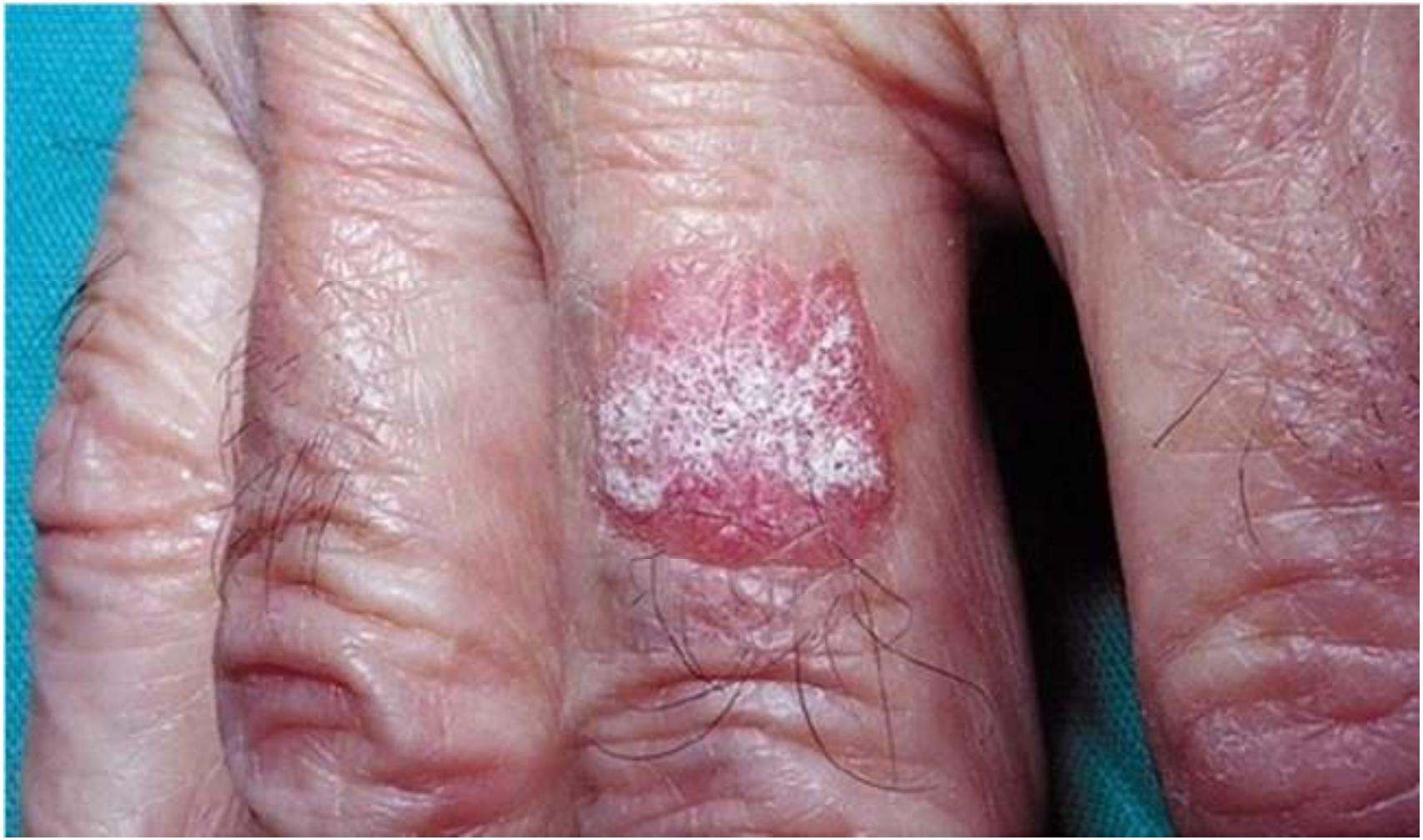
- Cutaneous horn;
- Erythroplasia;
- Leucoplasia;
- Bowen disease;
- Paget disease;
- LE, lichen sclerosus and atrofic;
- Lupus tbc;
- Tertiary syphilis, etc.

Corn cutanat:

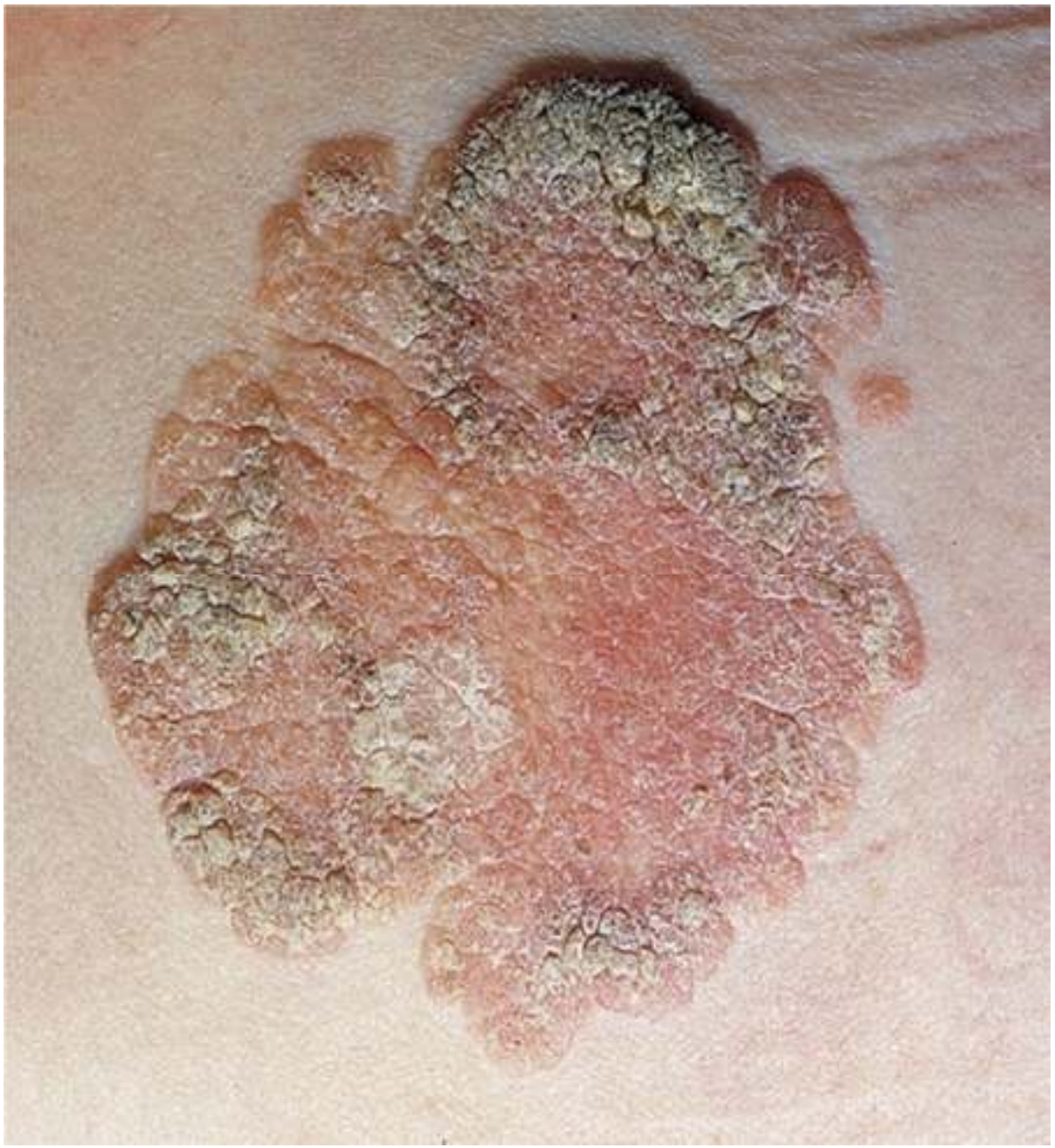


Corn cutanat:
Pacienta Z.R., 101 ani, China (foto – a. 2009)

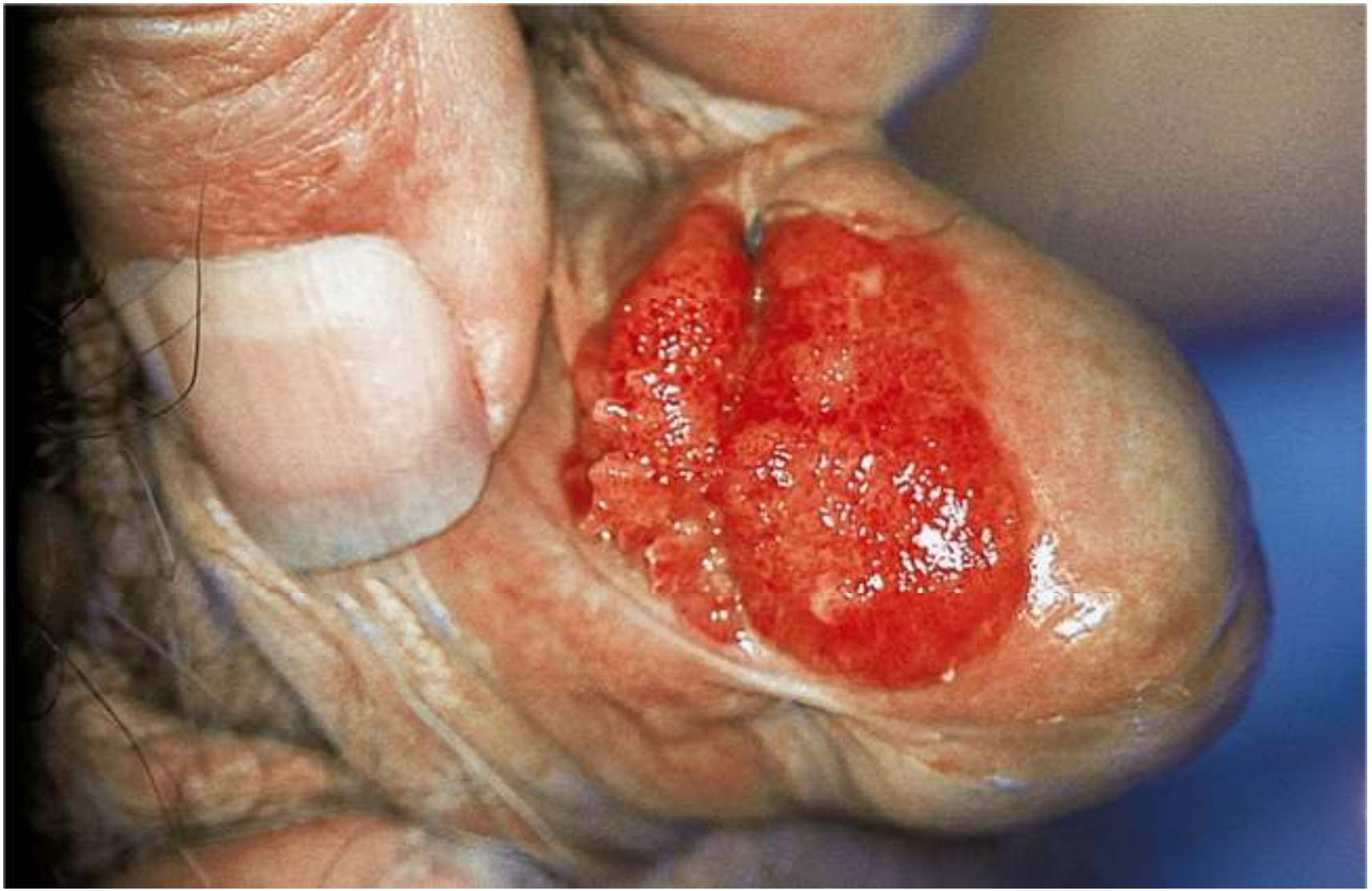
Boala Bowen:



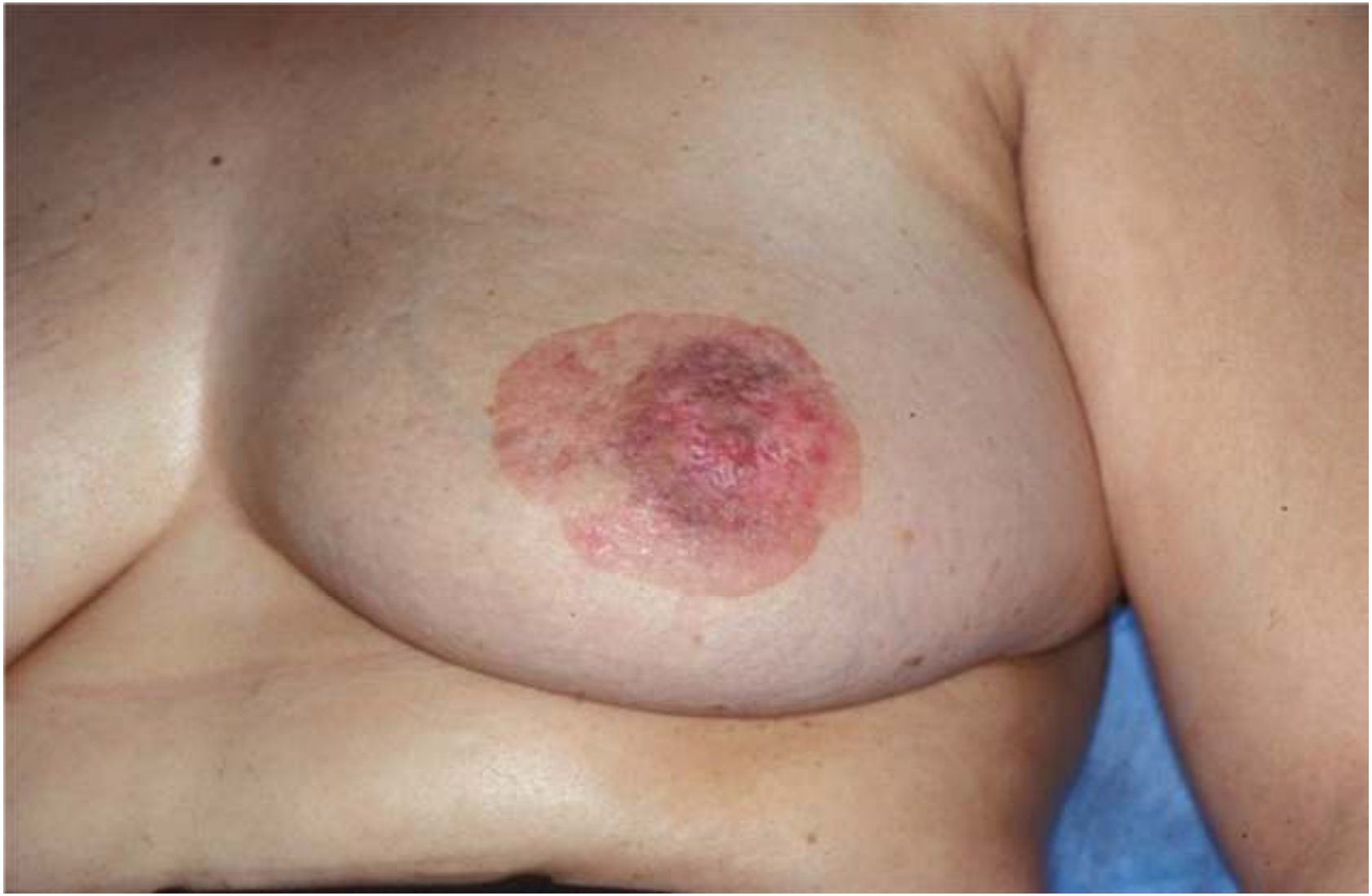
Boala Bowen:



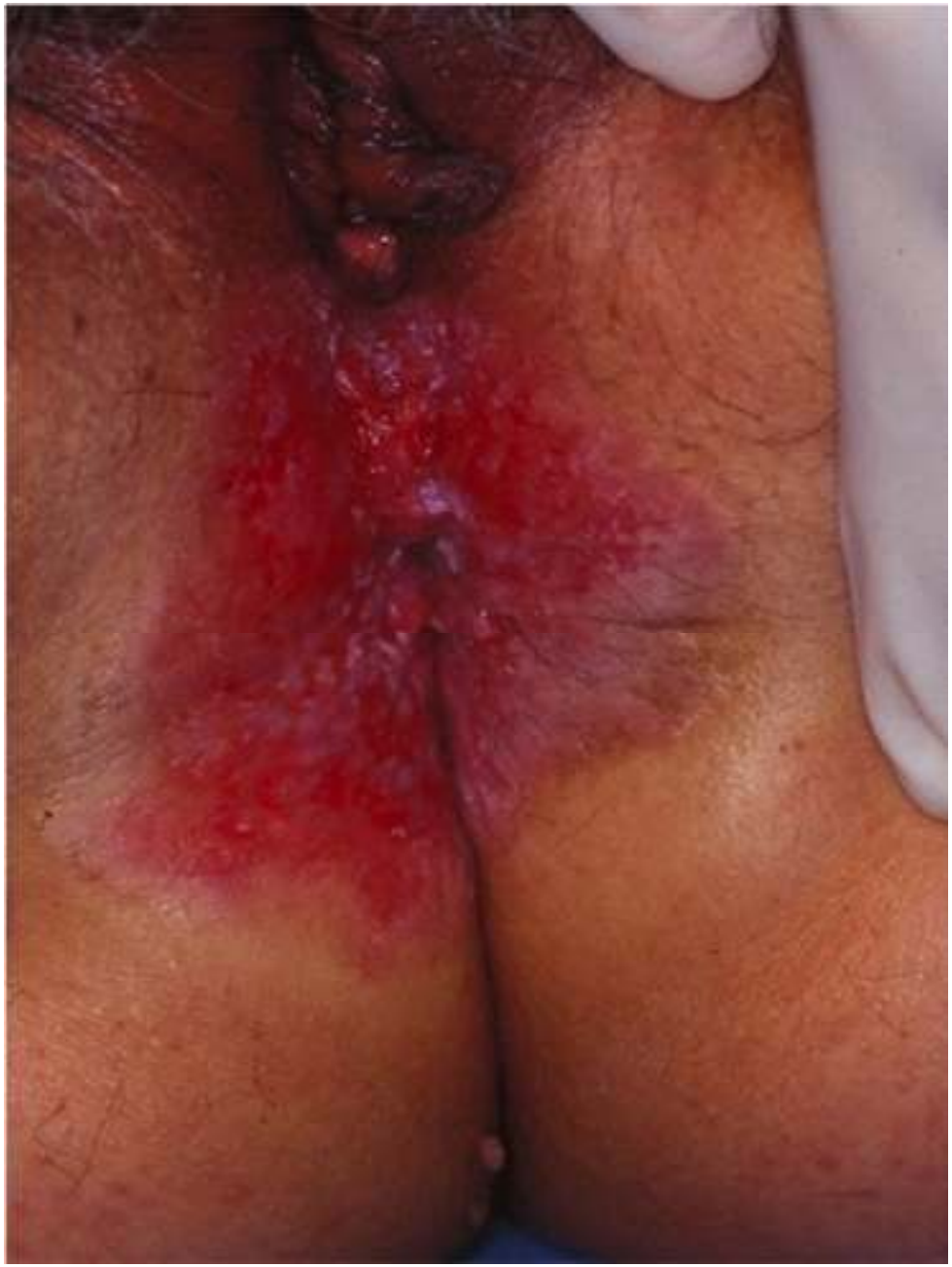
Boala Bowen genitală = eritroplazia Queyrat:



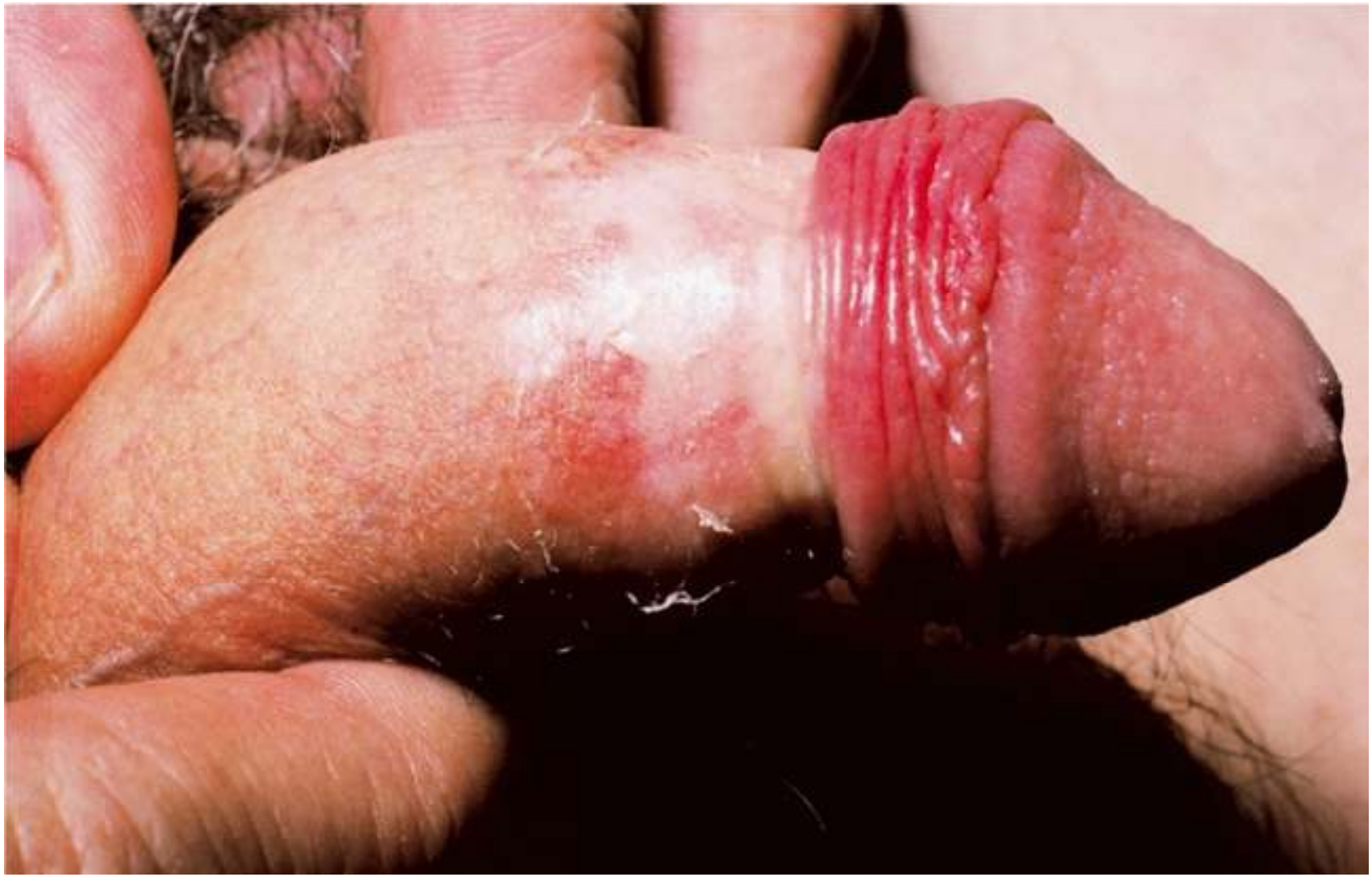
Boala Paget:



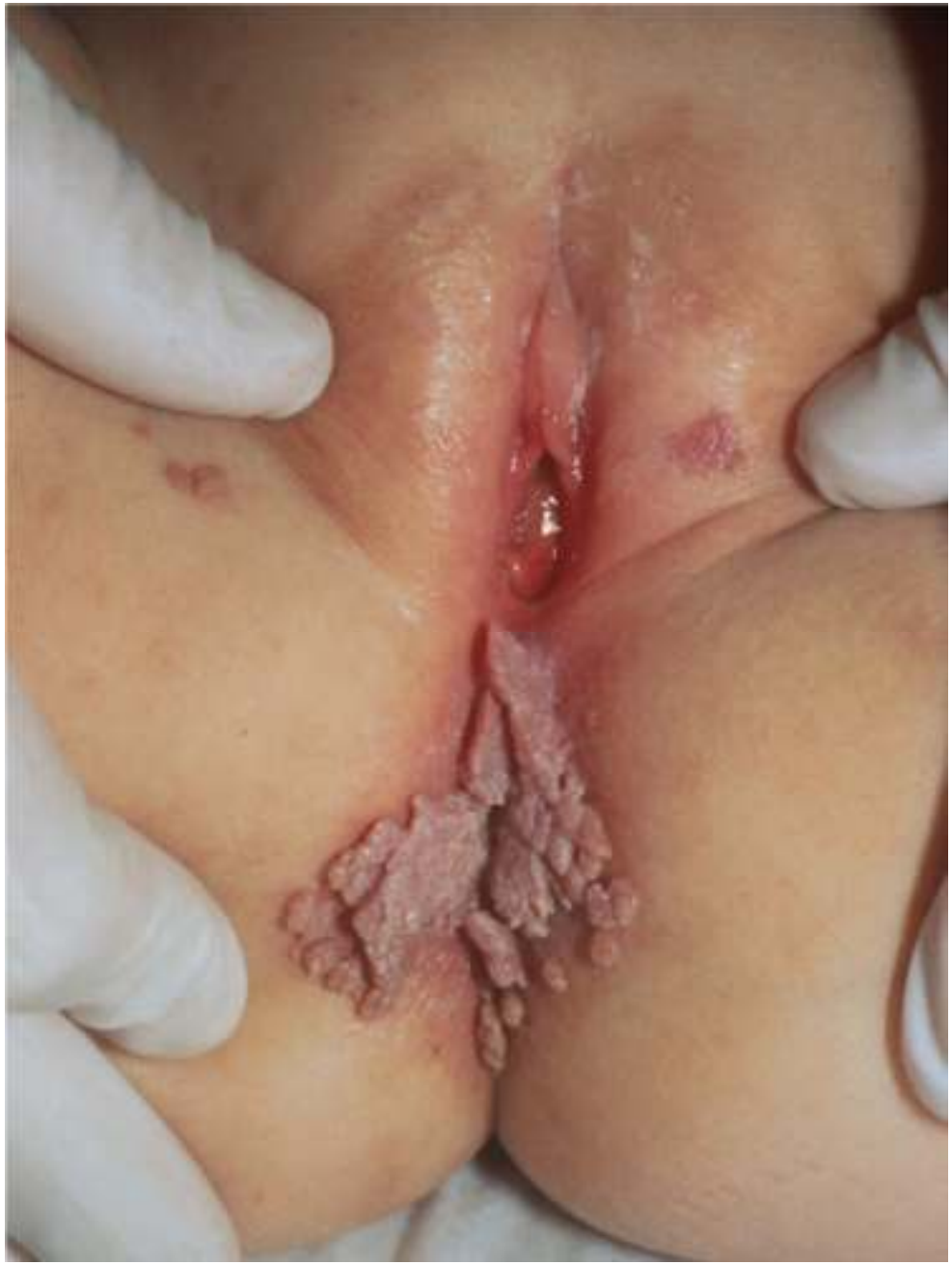
Boala Paget:



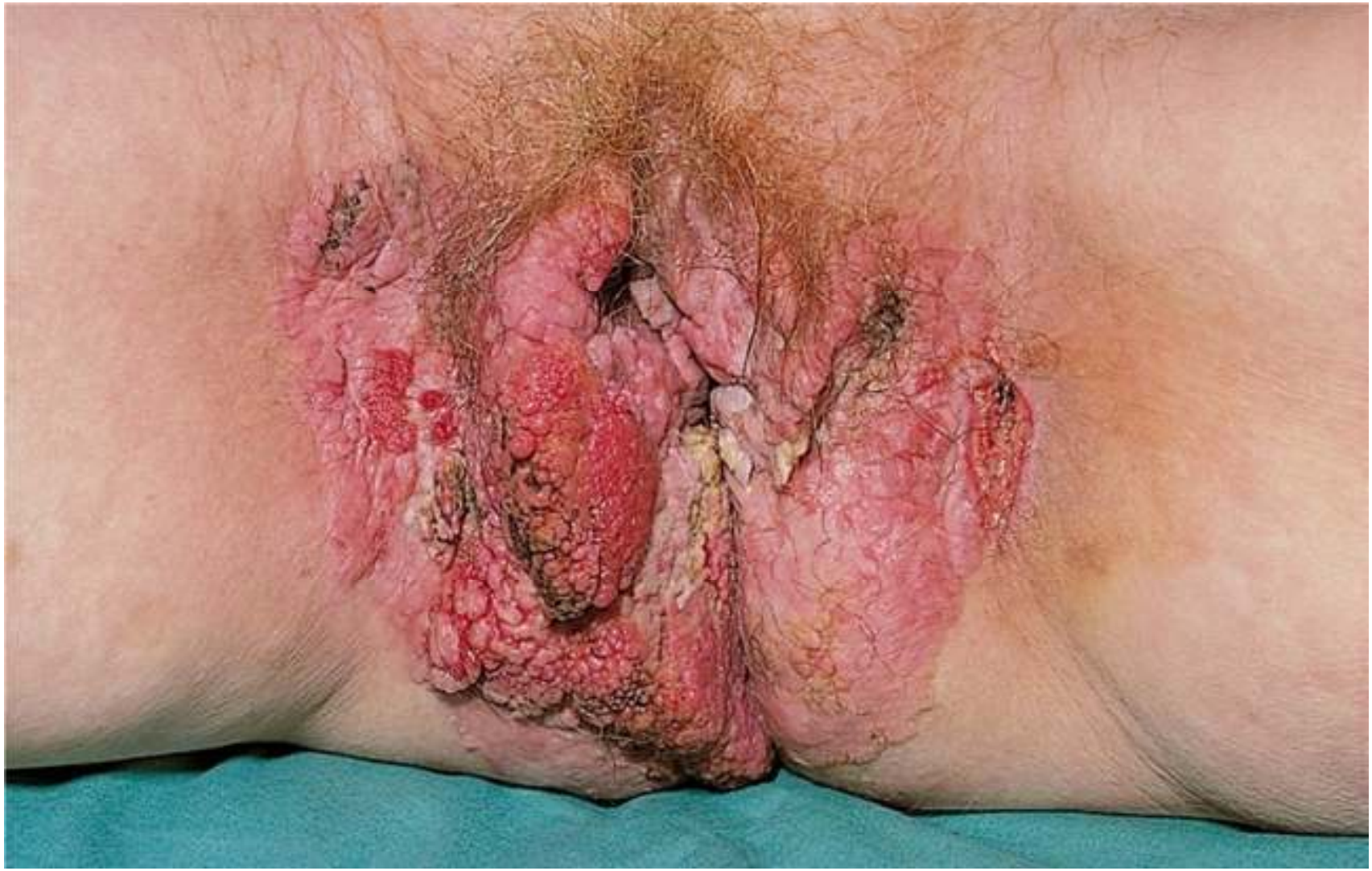
Lichen sclero-atrofic – balanită sclerotică obliterantă:



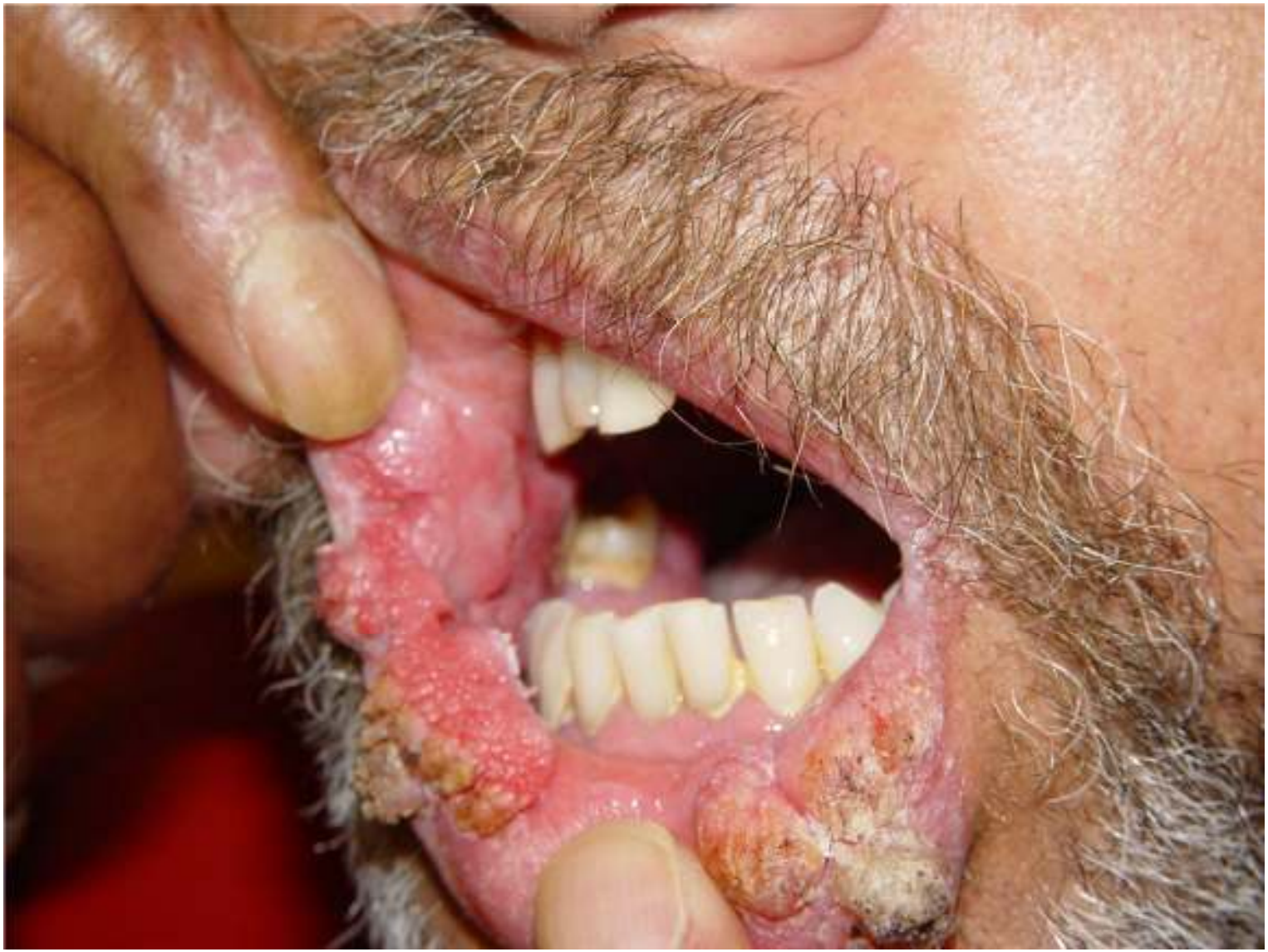
Condiloame acuminate:



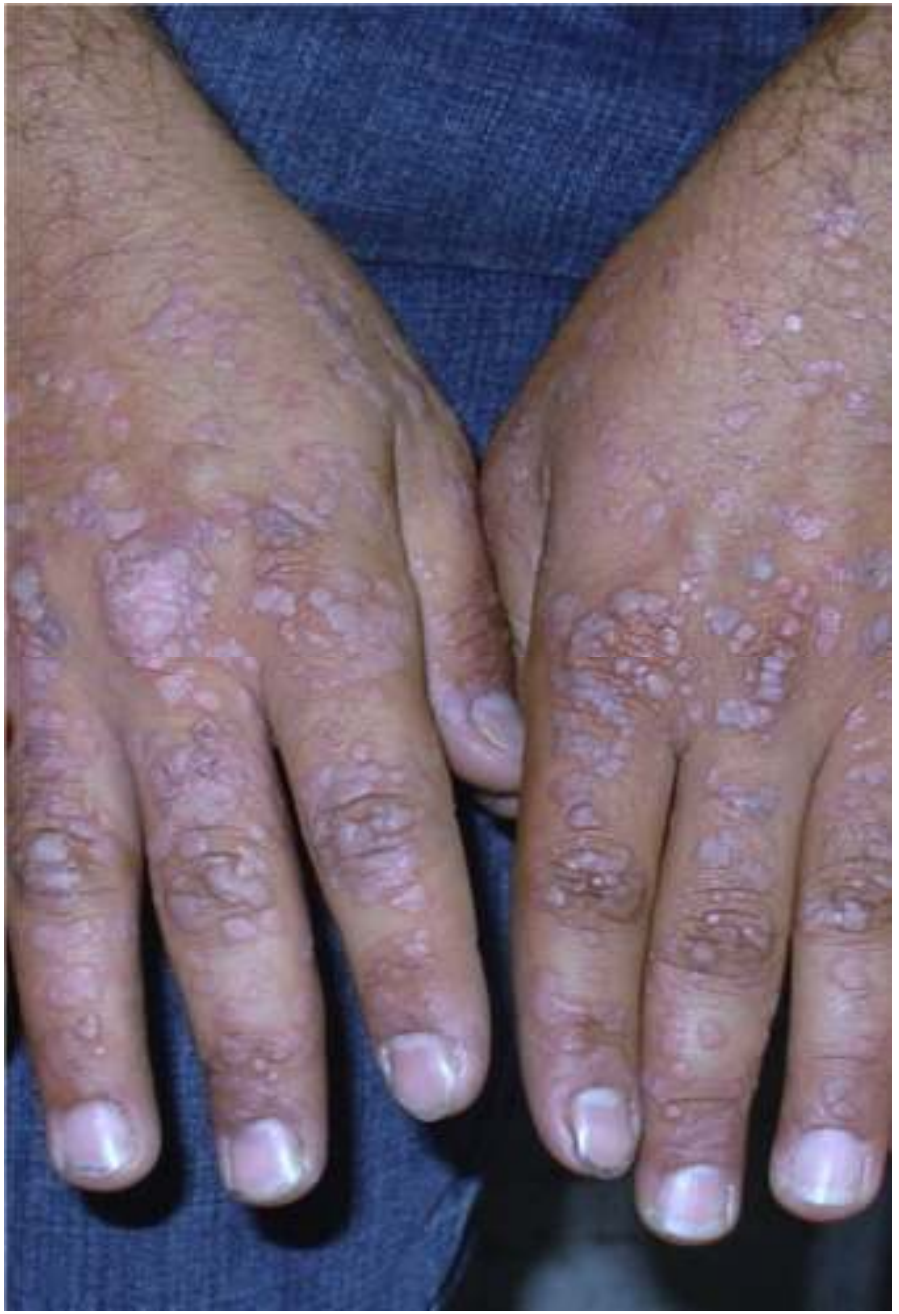
Condilomatoza gigantă Buschke-Löwenstein:



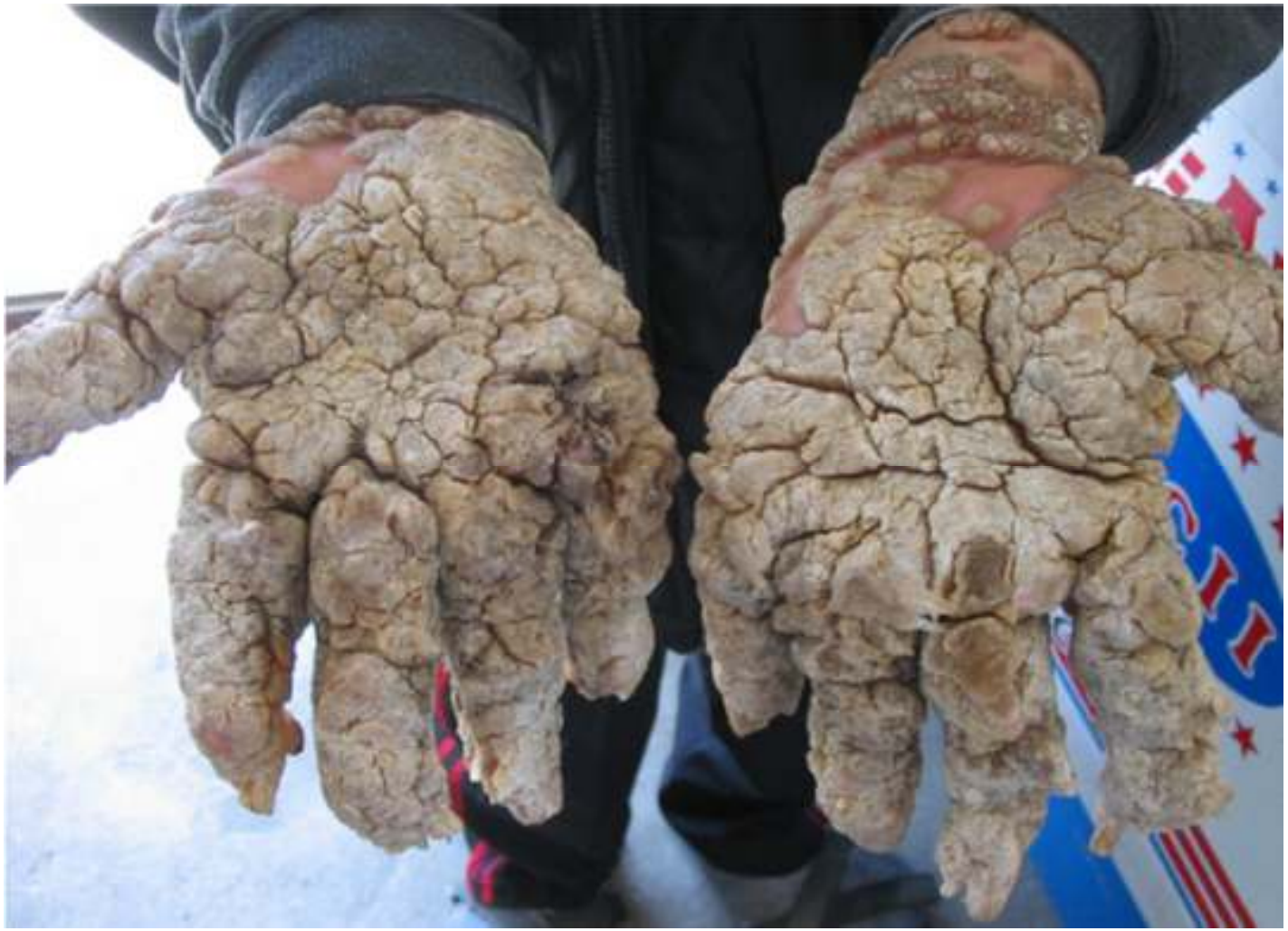
Condilomatoză bucală:



Epidermodisplazia veruciformă Lutz-Lewandowsky:



Epidermodisplazia veruciformă Lutz-Lewandowsky:



Epidermodisplazia veruciformă Lutz-Lewandowsky.

Omul copac:
Pacientul D.K., 38 ani, Indonezia
(foto – a. 2010)

Three most common types of skin cancer

- **Basal cell carcinoma (BCC),**
- **Squamous cell carcinoma (SCC)**
- **Cutaneous malignant melanoma (CMM)**

Skin cancers' epidemiology

- BCC and SCC, otherwise known as "nonmelanoma skin cancer" (NMSC), develop in keratinocytes and CMM develops in melanocytes
- At this time, between 2 and 3 million nonmelanoma skin cancers and approximately 132, 000 melanoma skin cancers occur globally each year
- Alarmingly, one in every three cancers diagnosed is a skin cancers
- More than 1 million NMSC occur in the US each year and more than 56,000 CMMs
- It has been estimated that every year 2.75 million new cases of nonmelanoma skin cancer will be diagnosed worldwide
- Although skin cancer is generally considered to be benign, deaths from melanoma are the most rapidly growing of cancers deaths in the US
- Most skin cancers has a higher incidence among light skin individuals and is less common among dark-skinned individuals.

Epidemiology of nonmelanoma skin cancer

- There has been an increase in NMSC incidence during the last several decades
- Mortality is generally low in NMSC, but does occur among the relatively few aggressive SCCs
- **Risk factors includes:** sun sensitive phenomenon; immunologic factors; UV-radiation; arsenic exposure; viral exposures, such as HPV.

Epidemiology of melanoma

- The incidence of cutaneous malignant melanoma has increased among light-skinned individuals worldwide
- Mortality rates have increased among old males, but have plateaued or declined among some age groups
- Risk factors include multiple nevi, atypical nevi, immune factors, intermittent sun exposure, and possibly metal exposure
- Genetic factors are under intensive investigation, and seem to be important in the development of melanoma.

Mayo Clinic, Minnesota, USA

- **1970:**
  - **4,8 / 100.000 melanoma cases.**
- **2010:**
  - **30,8 / 100.000 melanoma cases.**

****

- **Under 40 years age:**
  - **More in females.**
- **After 40 years age:**
  - **More in males.**

Beach suits for women

anii 1890-1900

Beach suits for women

anii 1920-1930

Beach suits for women

anii 1950-1960

Beach suits for women

anii 1980-1990

Beach suits for women

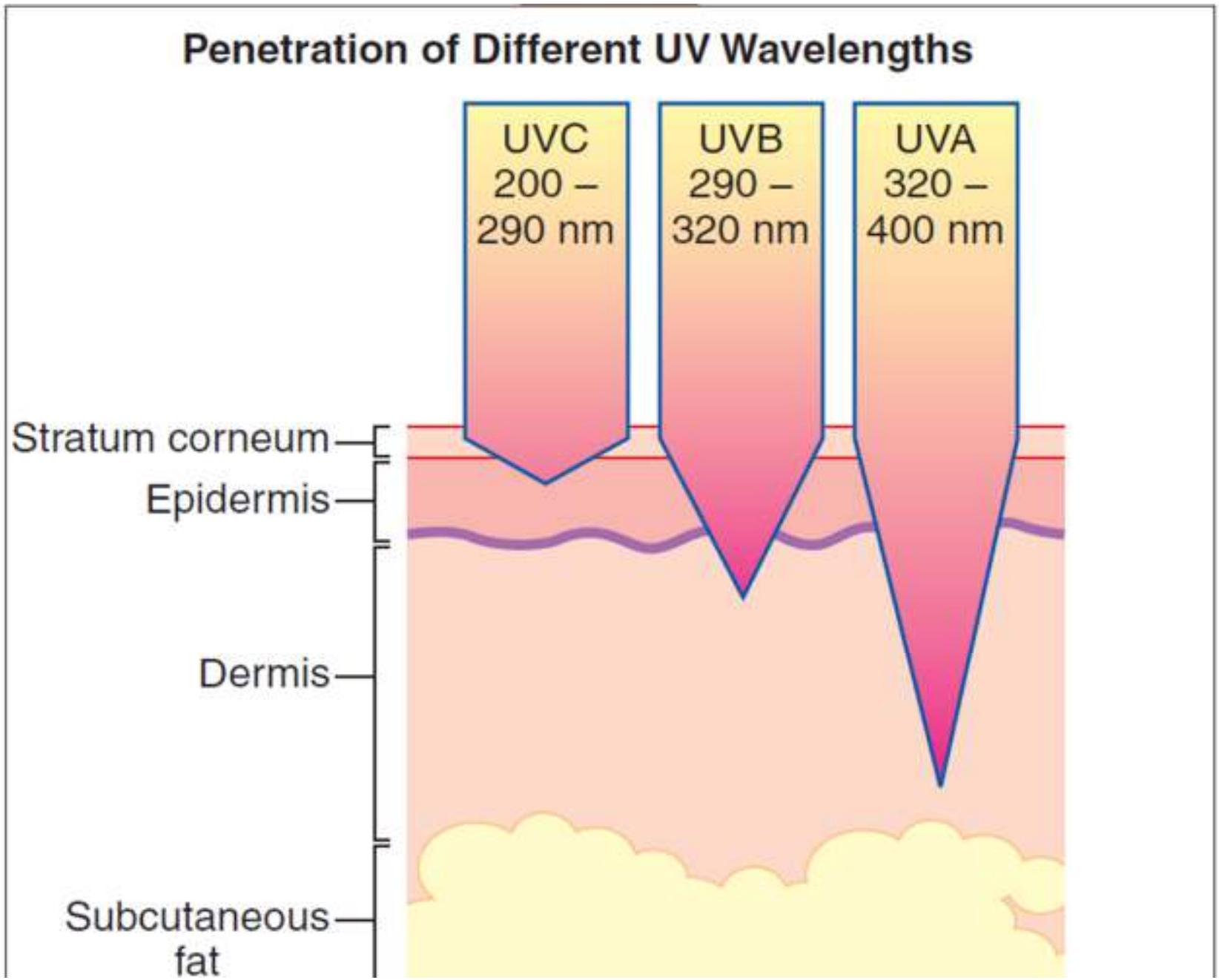
anii 2000-prezent

ETIOLOGY OF SKIN CANCER

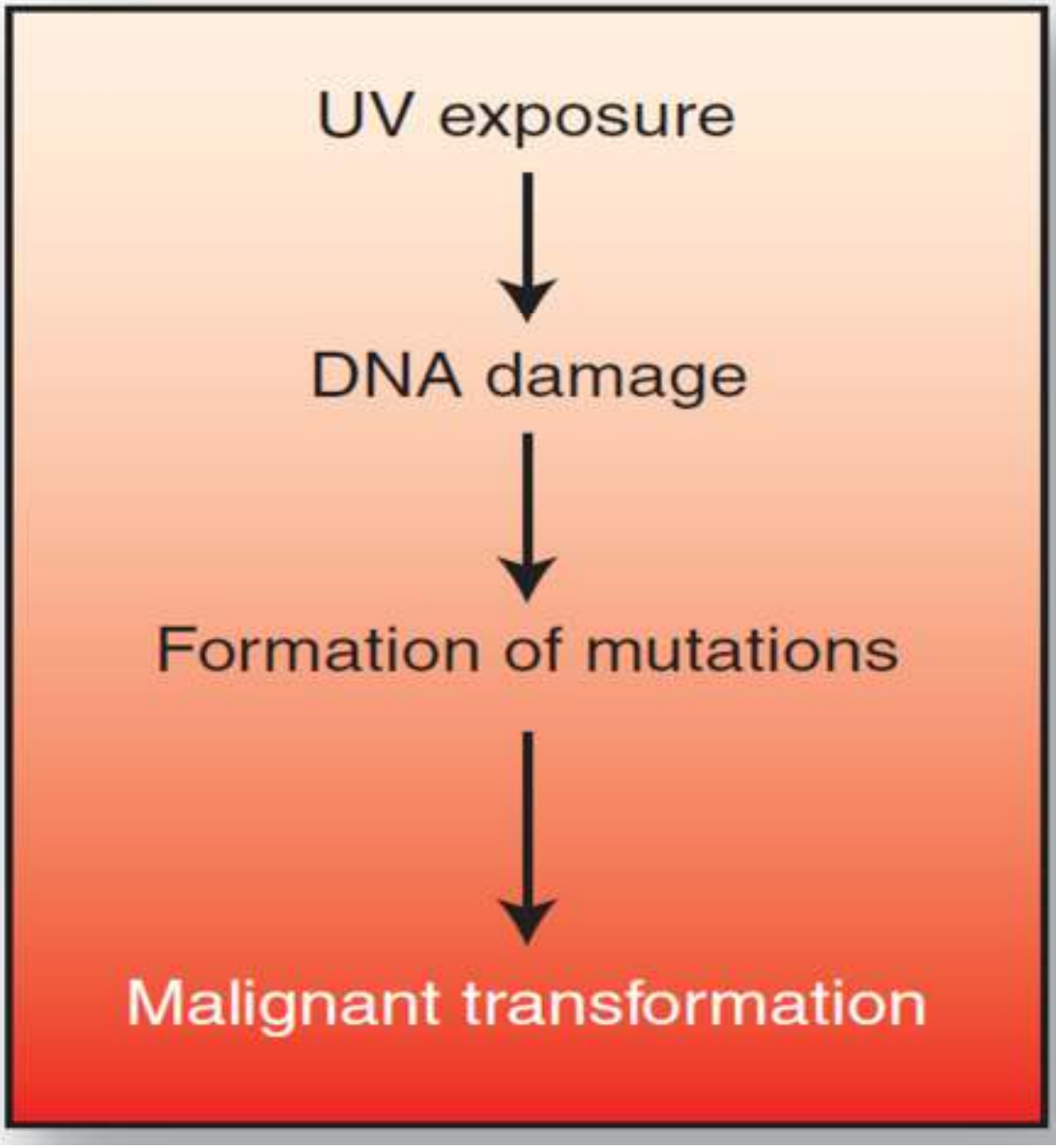
Predispositions

- Skin cancer develops in people of all colors , from the palest to the darkest;
- However, skin cancer is most likely to occur in individuals who have fair skin, blonde or red hair, atendency to burn or freckle when exposed to the sun, multiple moles, a history of sun exposure, and light colored eyes. These individuals are at the increased risk due to the fact that they have less melanin production;
- Ultraviolet radiation induces skin cancers by three mechanisms:
  - direct DNA damage leading to mutation;
  - production of activated oxygen molecules that in turn damage DNA and other cellular structures;
  - localized immunosupression blocking the body's natural anticancer defenses;
- The ultraviolet radiation wavelenghts primarily responsible for skin cancers are the UVB (280-320nm) and UVA (320-400nm) range.

Human Skin Phototypes (SPT)		
Skin Phototype	**Unexposed Skin Color**	**Sun Response History**
I	White	Always burns, never tans
II	White	Always burns, minimally tans
III	White	Burns minimally, tans gradually and uniformly
IV	Light brown	Burns minimally, always tans well
V	Brown	Rarely burns, tans darkly
VI	Dark brown	Never burns, tans darkly
*Those in SPT groups I & II are at highest risk for skin cancer.		


Penetration of Different UV Wavelengths
UVC
200 –
290 nm
UVB
290 –
320 nm
UVA
320 –
400 nm
Stratum corneum
Epidermis
Dermis
Subcutaneous
fat

Photocarcinogenic Cascade

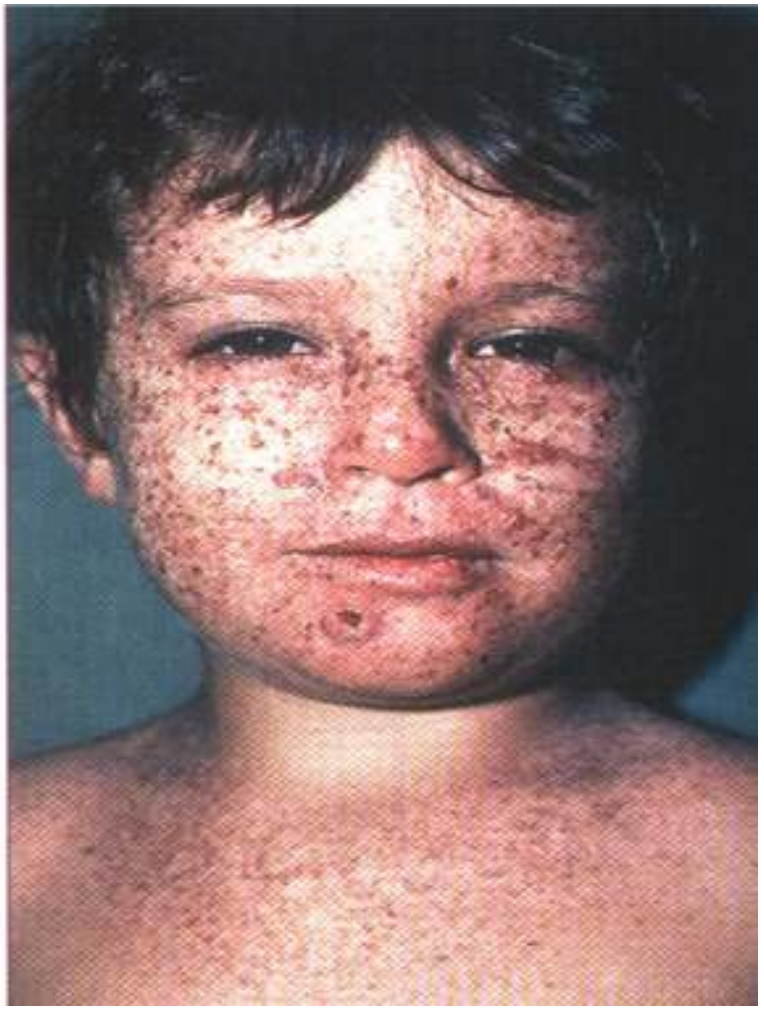


ETIOLOGY OF SKIN CANCER
Predispositions

- A second risk factor for development of skin cancer is age
- Elderly individuals are more susceptible to the development of skin cancers than younger individuals
- The risk of developing skin cancer increases with age, primarily because many skin cancers develop slowly; the damage that occurs during chilhood or adolescence may not become apparent until middle age
- Thirdly, men are at 2 to 3 times greater risk than women for developing skin cancer; according to the Skin Cancer Foundation, the majority of individuals diagnosed with melanoma are white men over the age of 50 years and is curently leading cancer in men over the age of 50 years;
- Finally, a personal or family history of skin cancer portends a greater risk of developing skin cancer

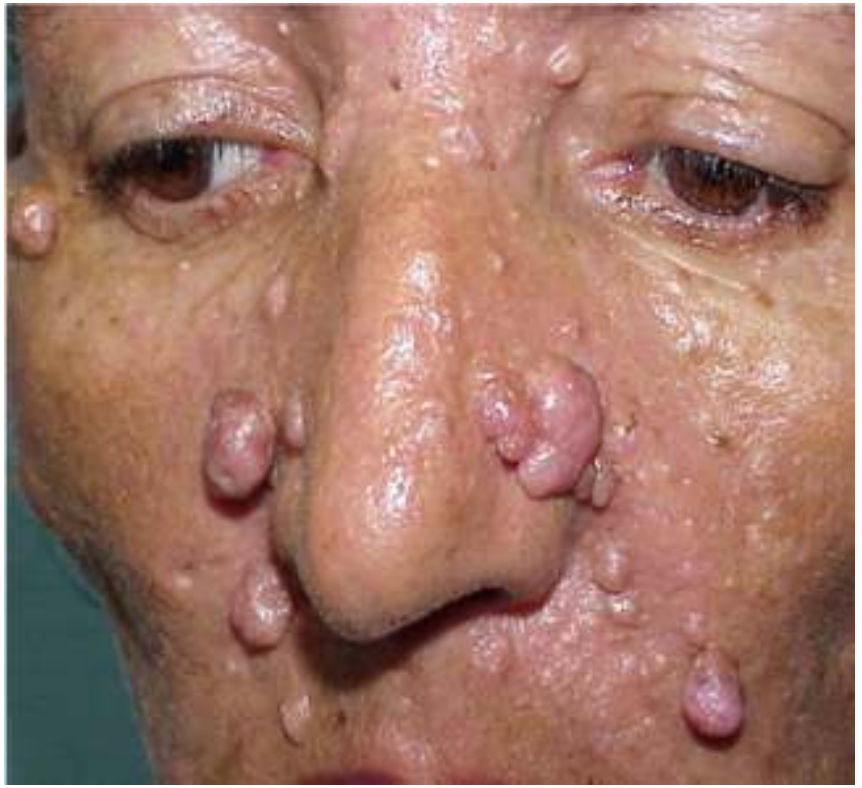
ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Xeroderma pigmentosum** is a rare autosomal recessive disorder characterized by:
  - skin malignancies
  - premature skin aging
  - photosensitivity
  - pigementary changes



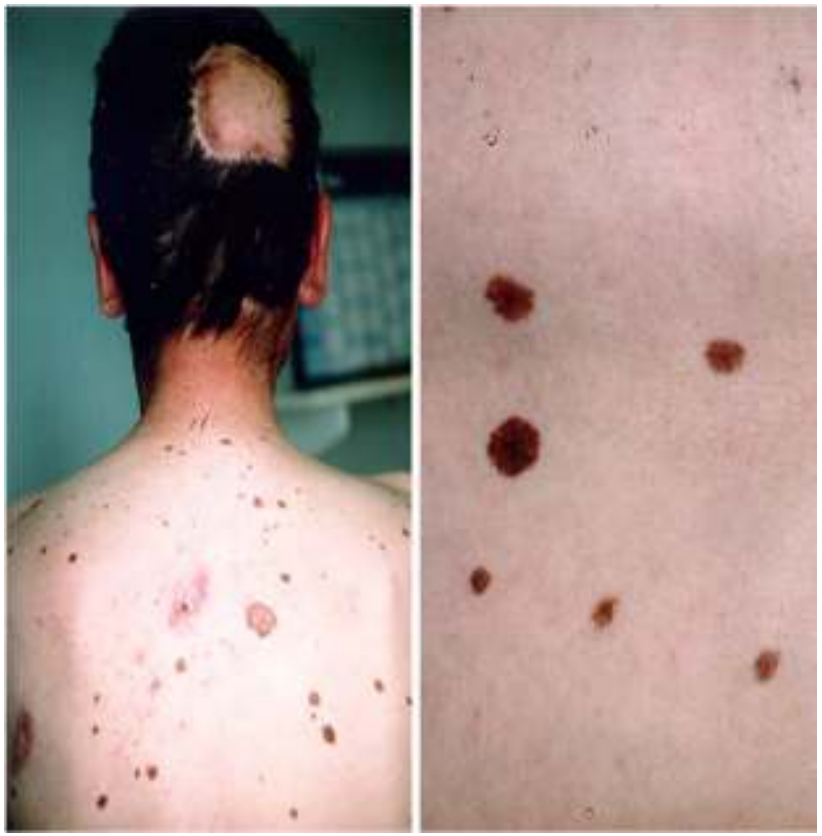
ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Gorlin syndrome** is an autosomal dominant disorder characterized by extreme sensitivity to ionizing radiation; a gene mutation leading to an increased risk for basal cell carcinoma
- These patients have a higher risk of developing multiple neoplasms, especially basal cell carcinomas and medulloblastoma



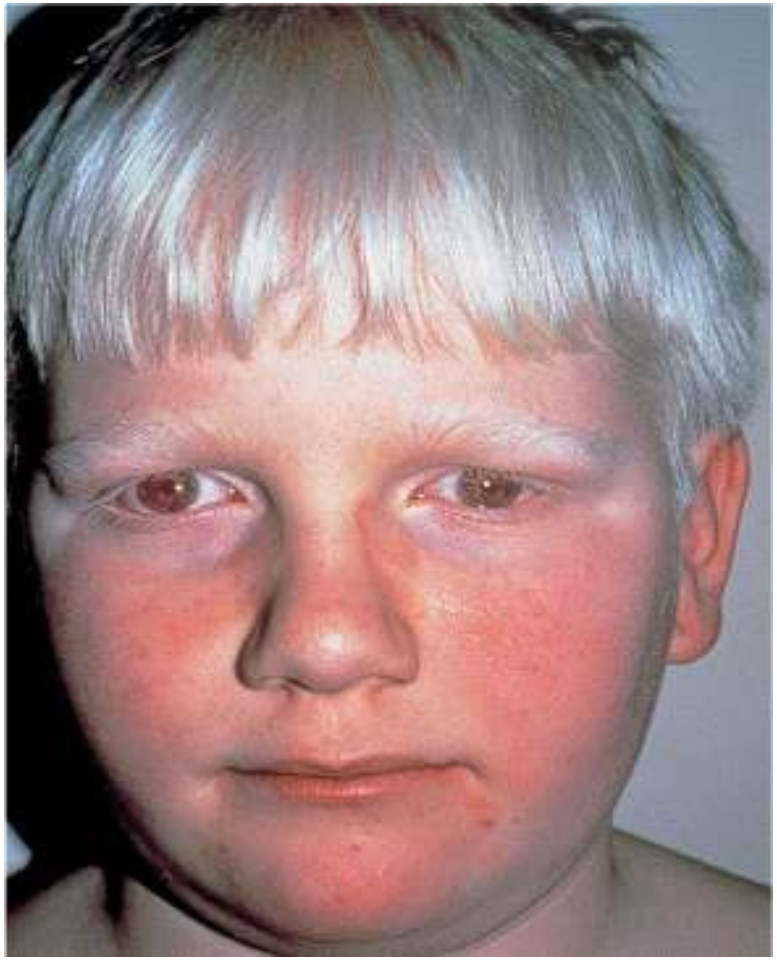
ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Familial atypical multiple mole melanoma syndrome**, as the name suggests, is a genetic disorder characterized by patients with an extensive family history of malignant melanoma;
- Affected persons may have over 100 nevi, present dominantly on trunc and in sun-exposed areas



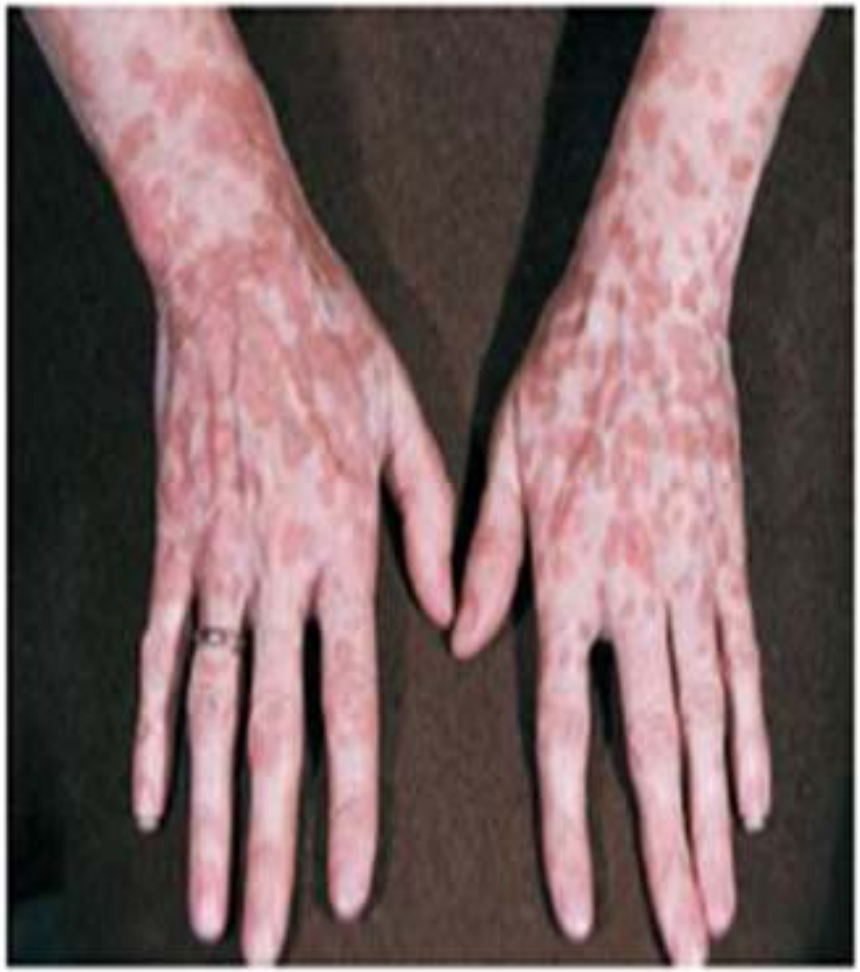
ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Albinism** is a genetic disease caused by a lack of melanin production or distribution, leading to a complete or patchy lack of pigment in the skin;
- These patients can present with either an absence of pigment from the hair, skin or iris;
- Because melanin protects the skin from the sun, people with albinism are very prone to sunburn and, therefore, to skin cancer



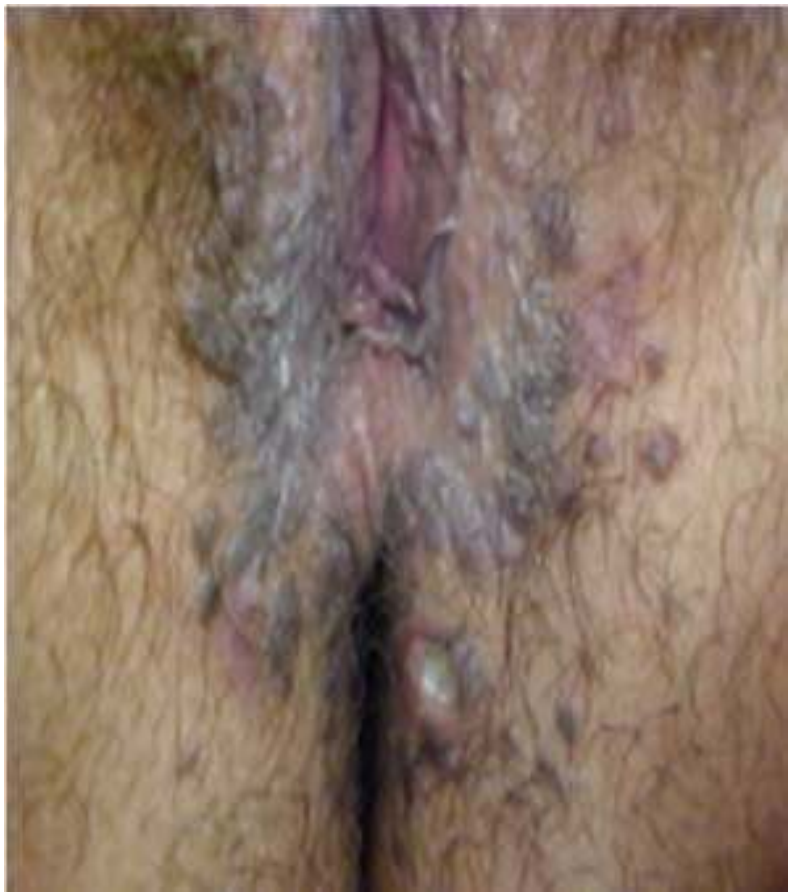
ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Epidermodysplasia verruciformis** is a rare, autosomal recessive hereditary disorder characterized by extreme susceptibility to cutaneous human papillomavirus (HPV) infection and squamos cell carcinoma;



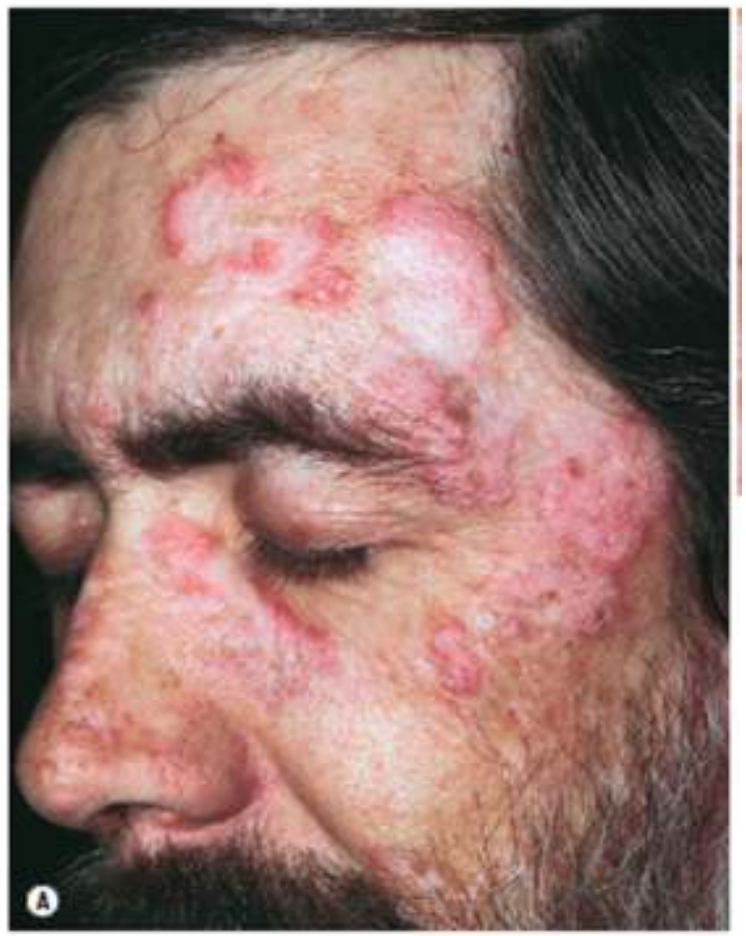
ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Bowenoid papulosis** is a focal epidermal hyperplasia and dysplasia induced by human papilomavirus infection (most commonly by HPV-16) and localized on genitalia



ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Discoid lupus erythematosus** is a chronic and recurrent photosensitive disorder primarily affecting the skin and characterized by sharply circumscribed macules and plaques displaying erythema, follicular plugging, scales, telangiectasia,and atrophy, can cause persistent inflammation and may eventually lead to the development of skin cancers;



ETIOLOGY OF SKIN CANCER
Disorders and diseases

- **Chronic inflammation**, it has been shown that there is a tumor-promoting role of inflammation (due to NF-kB activity and inhibition of apoptosis) in the development and progression of the epithelial skin cancer, approximately 1% of skin cancers arise in chronically inflamed skin and about 95% of these are SCCs

ETIOLOGY OF SKIN CANCER
Chemical carcinogenesis

- Arsenic exposure through drinking water or occupationally has been linked to causing a variety of cancers, nonmelanoma skin cancers included;
- Creosote, found in coal tar used for road paving and insecticides, can lead to skin cancer;
- Smokers are at increased risk for developing squamous cell carcinoma perhaps due to its immunosuppressive effects;
- PUVA may induce skin cancer by: photomutagenicity, photoinduced immunosuppression, use of other immunosuppressive agents along with PUVA, and possible HPV infection

ETIOLOGY OF SKIN CANCER
Environmental and lifestyle concerns

- Ozone layer depletion has allowed an increased penetrance of UVB, thereby increasing its chance for causing cancer harmful sunburns;
- UVB radiation damages DNA and disables it from repair, thereby permitting uncontrolled cell growth and allowing the development of skin cancer;
- Indoor tanning and sunlamp usage, though meant to provide an alternative to natural UV exposure, is also harmful due to overusage and disregard for regulations

Basal cell carcinoma
Introduction

- NMSCs are the most common forms of cancer in the US and account for nearly 90% of all skin cancers diagnosed in the world
- Out of NMSCs, basal cell carcinoma is the most frequently occurring cancer
- **Basal cell carcinoma (BCC) is described as** an abnormal growth of epidermal keratinocytes immediately above the basement membrane in the form of indolent malignant neoplasm of the hair follicle.

Basal cell carcinoma
Epidemiology

- Approximately 75% of all diagnosed skin cancers in the US are BCCs
- The incidence of BCC in the US, Canada, Australia, and Europe increases roughly by 3 to 6% per year
- In a large multicenter southern European study, “Helios”, a tendency to sun burn, an inability to tan, and a history of sunburn at youth were warning flags for an increased incidence of BCC
- BCC is no longer associated with the middle-aged or elderly population. Unfortunately, it has now encroached upon younger age groups because of the dangerous and unprotected levels of sun exposure
- Primary (previously untreated) BCCs also have a tendency to recur
- Nearly two-thirds of BCCs will recur in the following 3 years after treatment
- The American Cancer Society has reported that patients with a single basal cell lesion will develop a new skin tumor within the next 5 years

Basal cell carcinoma Pathogenesis

- Usually, BCCs emerge from keratinocyte stem cells, in hair follicles, sebaceous glands, or interfollicular basal cells
- Generally, most BCC cases are sporadic, but BCCs may also appear in genetic disorders such as Gorlin's syndrome and xeroderma pigmentosum
- The majority of sporadic cases are induced by sunlight, specifically UVB rays
- The radiation from the UV rays induces DNA mutations in certain genes within cells
- The most frequent UVB – induced alteration seen is the C-T, CC-TT base substitutions at dipyrimidine sites
- These unique dimmers have been titled as the "UV signature" because of their frequency in photodamaged skin.

Basal cell carcinoma Pathogenesis

- The mutation in the p53 and PTCH1 genes is present
- The p53 and PTCH1 are tumor suppressor genes
- **The p53 gene** is responsible for encoding a protein that controls the cell cycle and apoptosis
- UVB irradiation causes direct alteration to the p53 tumor suppressor gene, which eventually inhibits apoptosis and starts the development of skin cancer
- **The PTCH1 gene** is located on chromosome 9q22.3 and is responsible for the repression of genes that direct embryonic cell development, growth, and differentiation, such as hedgehog gene
- The mutation of the PTCH1 gene inactivates the suppressor function, leading to the cell proliferation and tumor formation

Basal cell carcinoma
Diagnosis

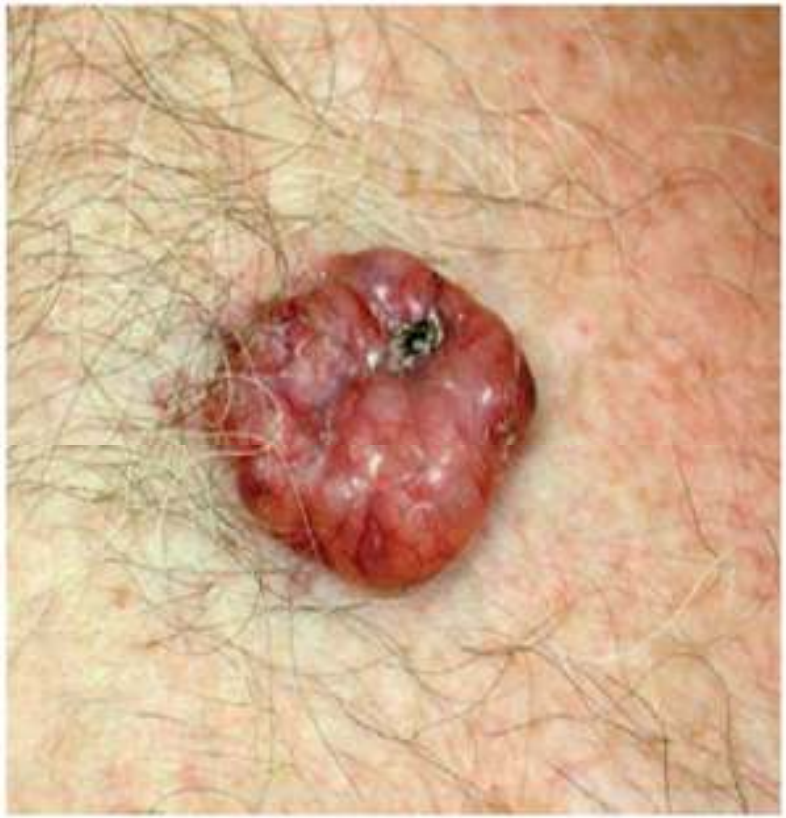
- As with many dermatologic entities, BCCs can be recognized clinically
- Although these lesions have typical characteristics, the clinical presentations can vary
- A definitive diagnosis can't be established until a biopsy is taken and proven to be a BCC
- A shave biopsy is usually adequate for most BCC lesions, such as nodular and superficial types
- However, if an infiltrative or morpheaphorm-type is suspected, a punch or excisional biopsy should be taken to verify the diagnosis
- Numerous subtypes of BCCs exist and are usually found on hear-bearing skin; they almost never occurs on mucous membranes
- Clinically and histologically, numerous forms can be differentiated, and the most common types are described below

Basal cell carcinoma
Clinical classification

- Nodular/noduloulcerative basal cell carcinoma
- Superficial multifocal basal cell carcinoma
- Pigmented basal cell carcinoma
- Morpheaform (sclerosing or fibrosing) basal cell carcinoma
- Infiltrative basal cell carcinoma
- Infundibulocystic basal cell carcinoma
- Giant basal cell carcinoma
- Controversial entities: basosquamos (metatypical) carcinoma, micronodular basal cell carcinoma, field fire basal cell carcinoma, fibroepithelioma Pinkus

Basal cell carcinoma
Diagnosis

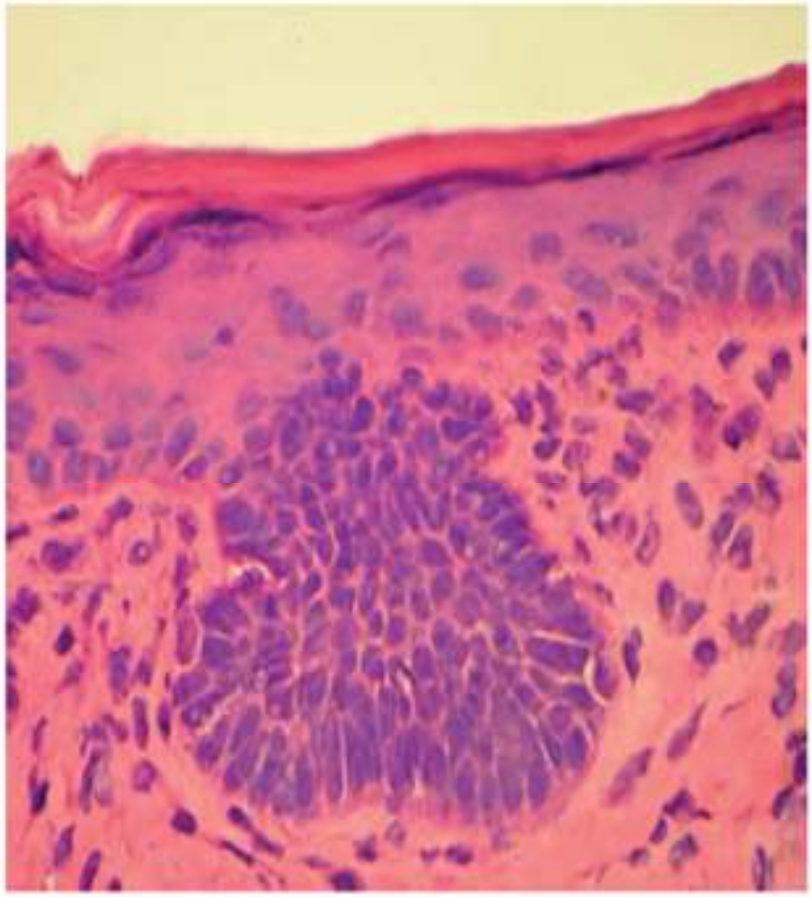
- **Nodular/noduloulcerative basal cell carcinoma**
- Clinical presentation
- They usually appear as red to pink papules with raised, roller borders that slowly enlarge
- Typically, they are described as having a pearly, waxy, or translucent appearance
- Telangiectasias are prominent features on the surface of the tumor that can sometimes present with bleeding
- Noduloulcerative BCCs have indurated edges and central painless ulcerations that are covered with crust: “rodent crust”.



▲ **FIGURE 6-2** Typical nodular BCC with rolled borders decorated with prominent telangiectasia.

Basal cell carcinoma
Diagnosis

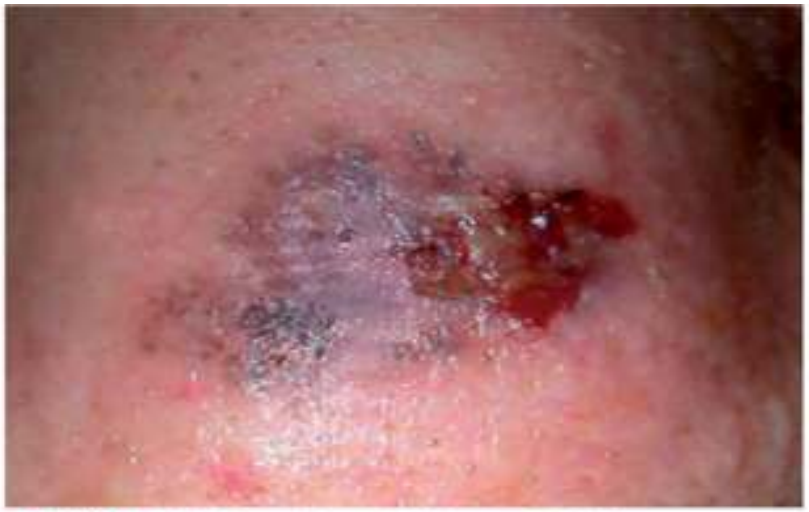
- **Nodular/noduloulcerative basal cell carcinoma**
- **<u>Dermatopathology</u>**
- Under microscopic examination, nodular/noduloulcerative BCCs are composed of well-defined, smooth-bordered basophilic staining islands of neoplastic cells
- The BCC cells have a high nuclear-to-cytoplasmic ratio and lack well-formed intercellular bridges
- **<u>Prognosis</u>**
- Most nodular BCCs grow at a slow rate and have only limited growth; however, than can invade local structures and cause significant damage
- The longer they are allowed to grow, the greater the potential for morbidity and destruction
- For example, on the face, nodular BCCs can invade the nose or eyes to an extent that these structures need to be removed to eradicate the tumor



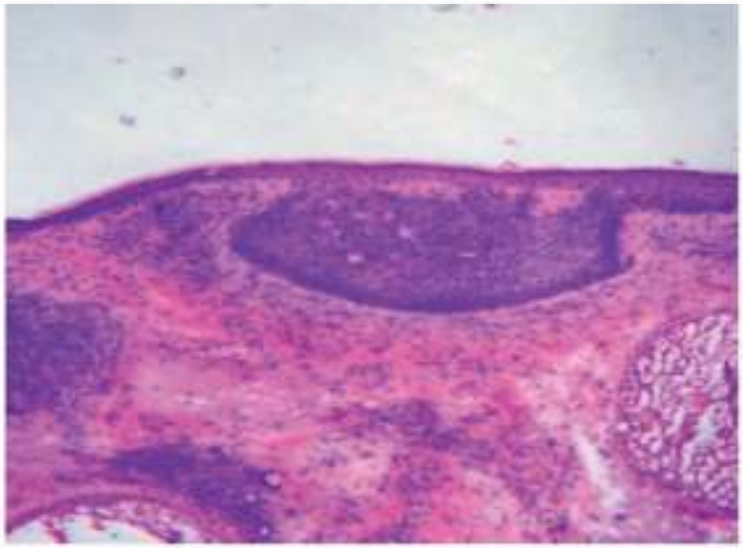
▲ FIGURE 6-4 BCC arising from surface epidermis H&E.

Basal cell carcinoma
Diagnosis

- **Superficial multifocal basal cell carcinoma**
- This subtype of BCC is the second most common with a frequency of 9 to 17,5% of all cases and presents more often on the trunk and extremities
- Clinically, lesions present as flat, red to pink, scaly patches with ulcerations and/or crusting
- Under microscopic examination, these BCCs have a single or multiple basophilic staining tumor sheets or buds extending from the lower part of the epidermis into papillary dermis
- Superficial BCCs usually don't extend into the deep dermis, and a nonspecific inflammatory infiltrate may be seen in the papillary dermis
- These tumors tend to grow laterally and can cause significant damage to local tissue and structures, if not treated.



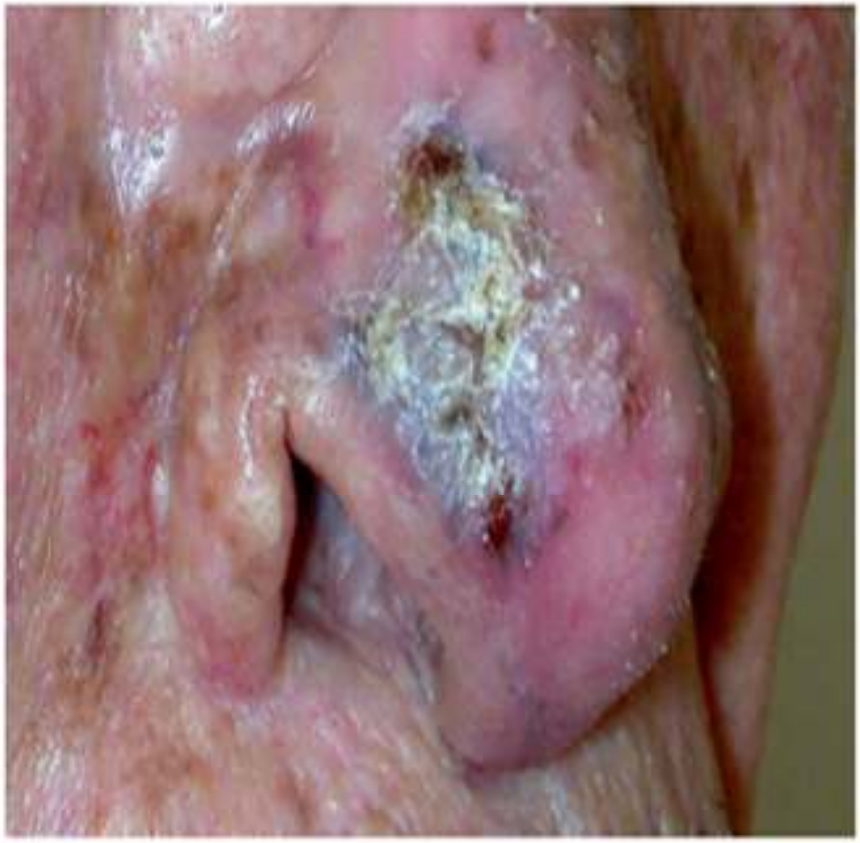
▲ **FIGURE 6-14** Pigmented superficial multicentric BCC.



▲ **FIGURE 6-15** Superficial multifocal BCC H&E.

Basal cell carcinoma Diagnosis

- **Pigmented basal cell carcinoma**
- These BCC are characterized with brown, black, or grayish blue pigmentation and constitute approximately 6% of all BCCs
- This form of BCC is localized on head, neck, trunk and/or extremities
- Pigmented BCCs can belong to either the nodular/ noduloulcerative/ micronodular subtypes or the superficial multicentric subtype
- The important differential diagnoses for this type of BCC are: pigmented nevi, melanoma, pigmented seborrheic keratosis, and pigmented Bowen's disease



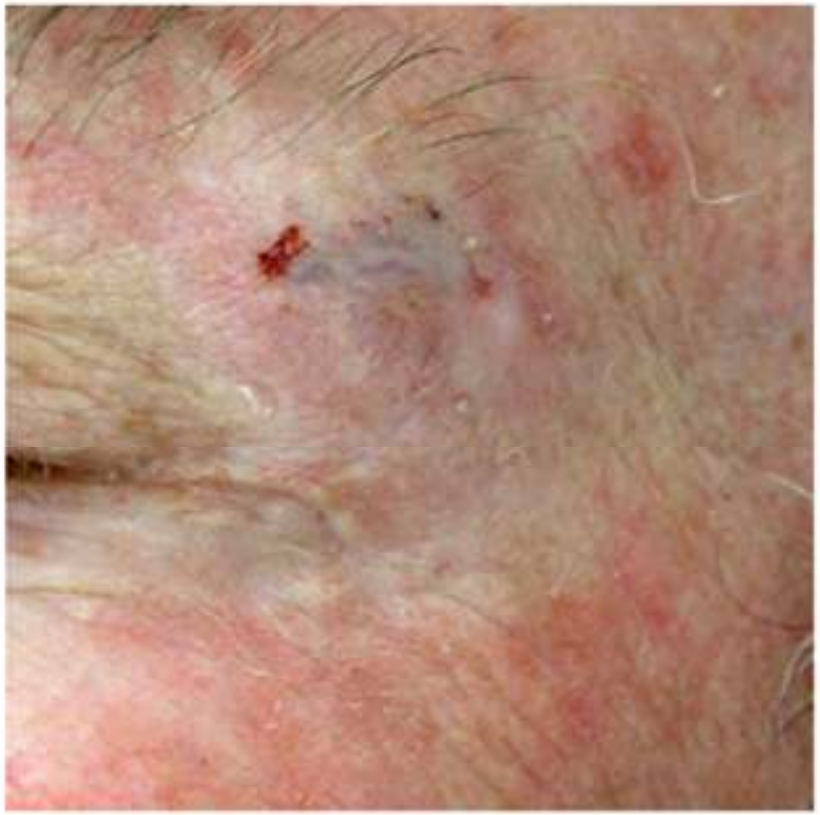
▲ FIGURE 6-13 Pigmented, recurrent infiltrative BCC on the nose.

Basal cell carcinoma
Diagnosis

- **Morpheaform (sclerosing or fibrosing) basal cell carcinoma**
- It occurs much less often than do the previous forms, with a frequency of about 2 to 3% of all BCCs diagnosed
- Morpheaform BCCs represent a more aggressive tumor that has a greater tendency to occur
- This subtype isn't as common and is found on the head and neck region
- Morpheaform BCC presents clinically as a skin-colored, pink, or white indurated plaque with poorly defined borders. The overall appearance is somewhat shiny and looks like a smooth scar. The underlying tumor may grow quite extensively before the overlying skin begins to ulcerate
- Unfortunately, these lesions are often misdiagnosed, leading to greater tumor growth and delayed treatment
- The tumor's extension is often underestimated, leading to incomplete excision
- Under the microscope, there is a fibrotic dermis that contains small, linear and branching collections of tumor cells
- It has BCC islands that are not well circumscribed and don't have prominent peripheral palisading of nuclei
- Histopathologically, morpheaform BCC cells can reach deep into the dermis

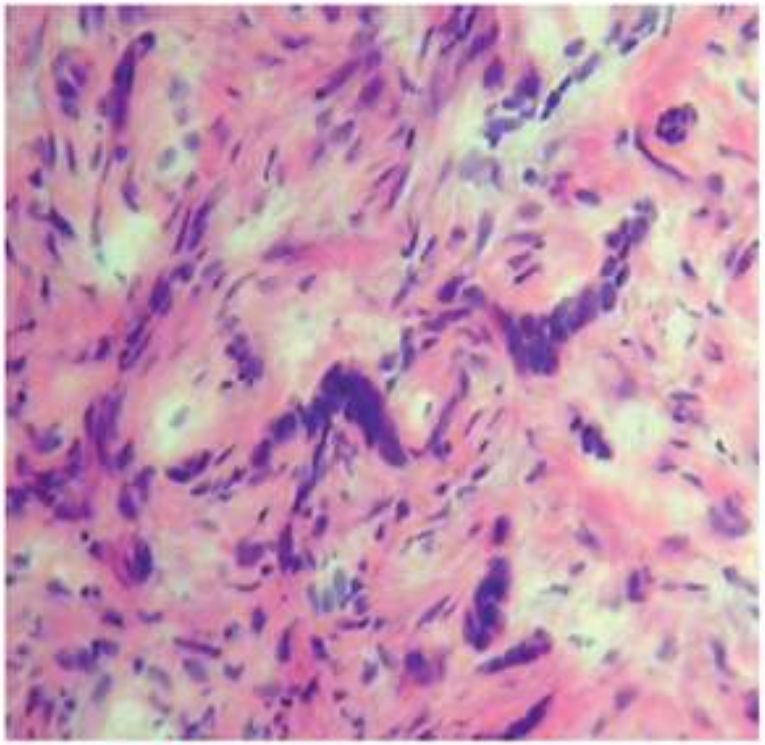
Morpheaform basal cell carcinoma

Clinical features



▲ FIGURE 6-16 Morpheaform BCC.

Dermatopathology



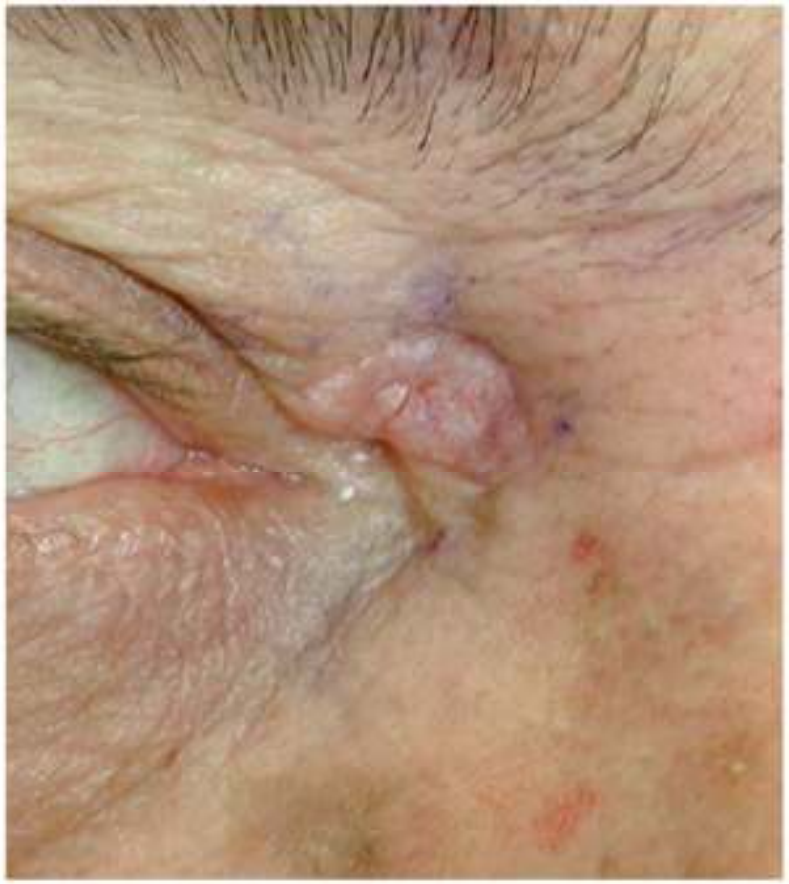
▲ FIGURE 6-17 Morpheaform BCC H&E high.

Basal cell carcinoma - Diagnosis

- **Infiltrative basal cell carcinoma**
- The infiltrative form of BCC is a more aggressive subtype than are some others, and is more likely to recurre
- The infiltrative subtype occurs solely or more frequently be a component of a mixed-type BCC
- Solely infiltrative BCCs have an opaque whitish yellow color papules
- They don't have a sharp or rolled border; and blend with the normal surrounding skin
- When present as a component of mixed-type BCC such as nodular, the clinical picture carries both characteristic findings
- Overall, this type of BCC clinically has less well-defined borders than do nodular types.
- Histopathologically, infiltrative BCCs present itself with basophilic staining, and elongated islands and strands of basaloid neoplastic cells with jagged or spiky borders
- Usually, the deep or peripheral portions of this neoplasms exhibit more of an infiltrative pattern with no prominent fibrosis in the stroma
- The latter finding differentiates infiltrative BCC from morpheaform BCC in which fibrosis in the stroma is an important finding.
- In addition to their infiltrative nature, these neoplasms are usually much larger than they appear clinically.

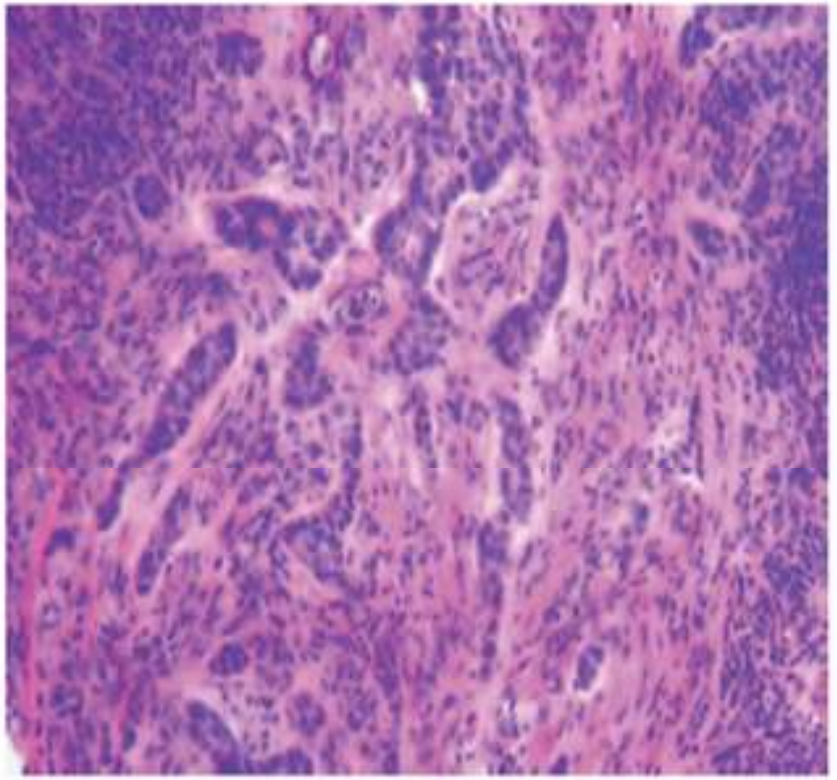
Infiltrative basal cell carcinoma

Clinical features



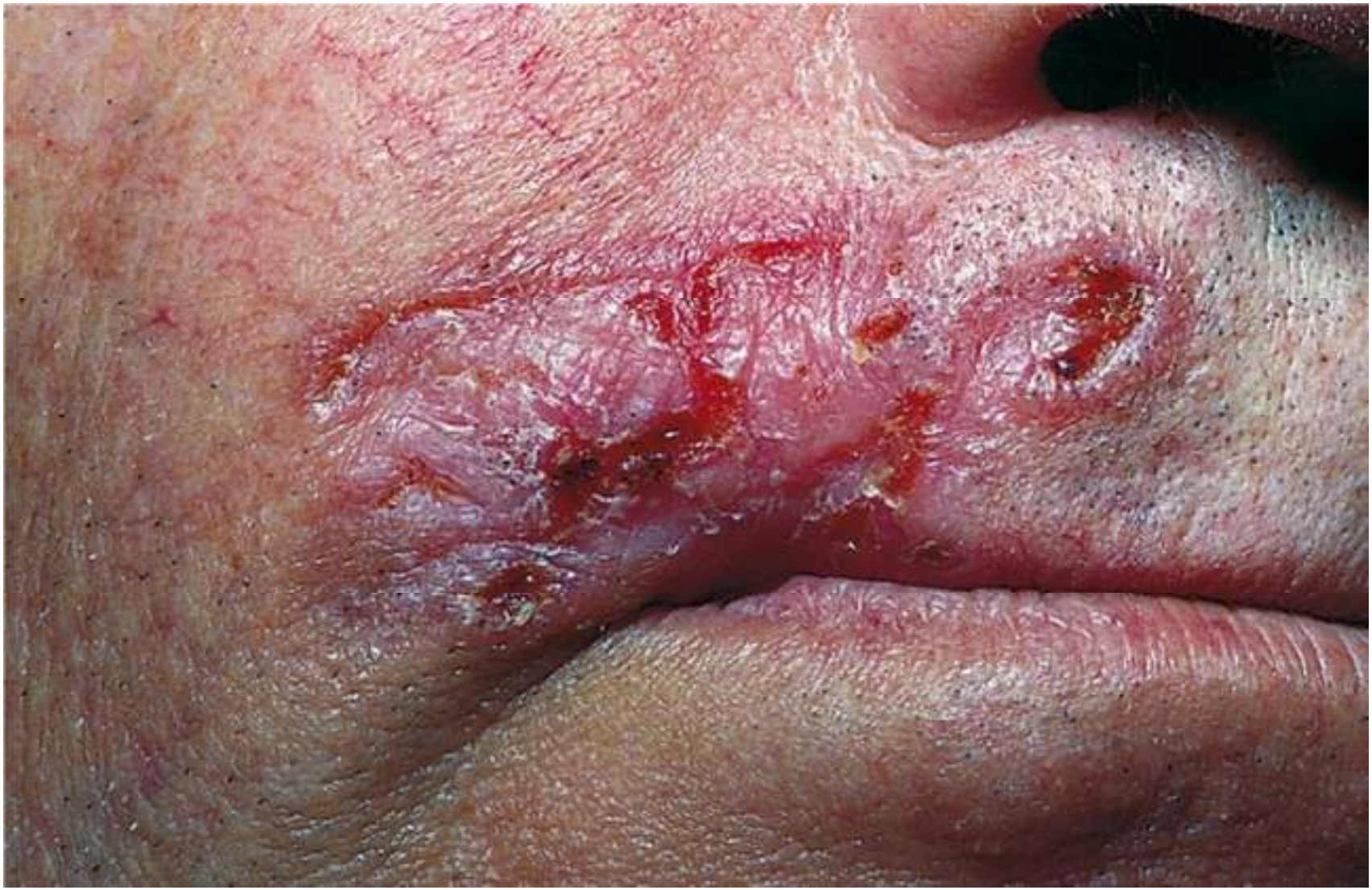
▲ FIGURE 6-18 Infiltrative BCC on inner canthus.

Dermatopathology

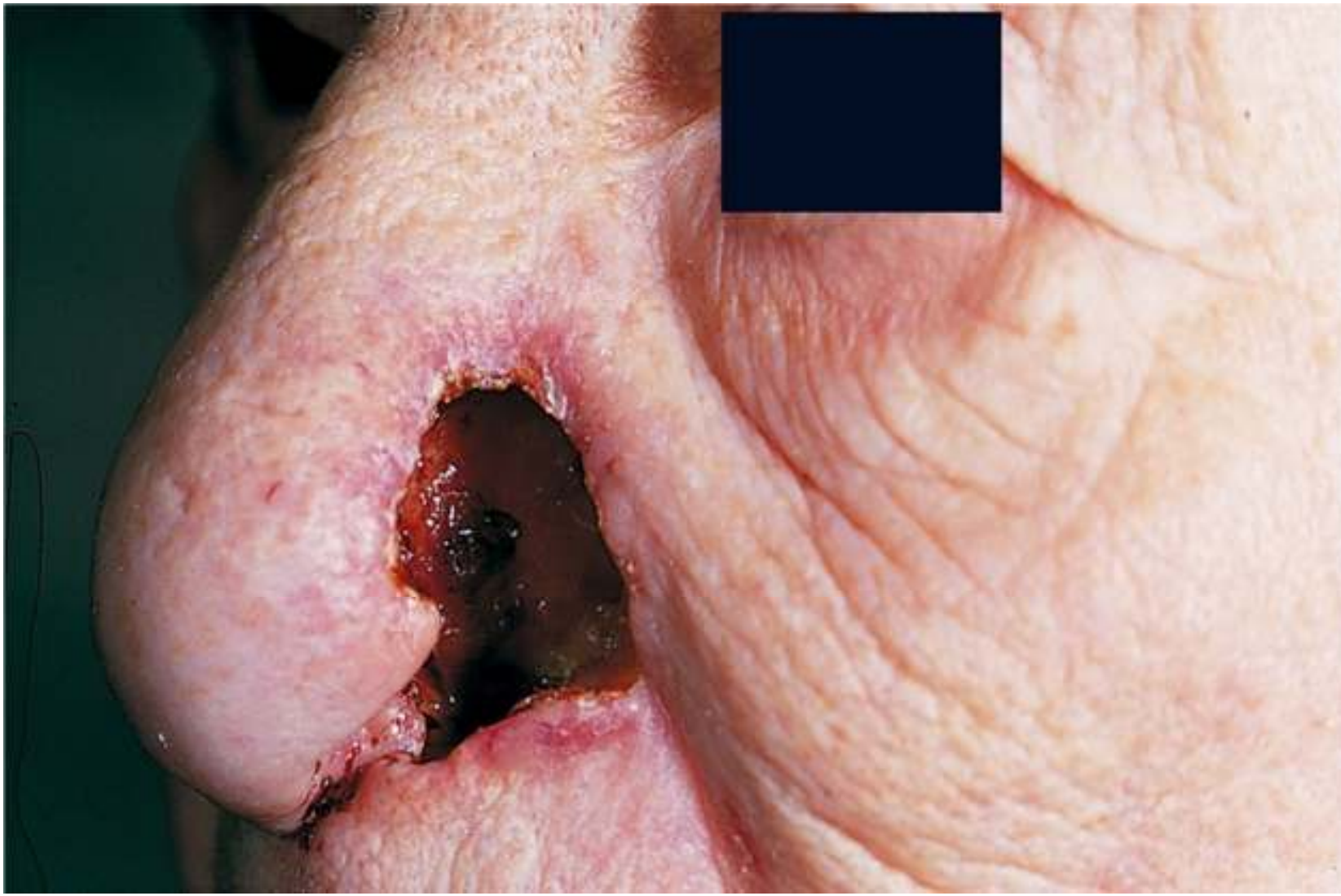


▲ FIGURE 6-19 Infiltrative BCC among lymphocytes and coarse collagen bundles.

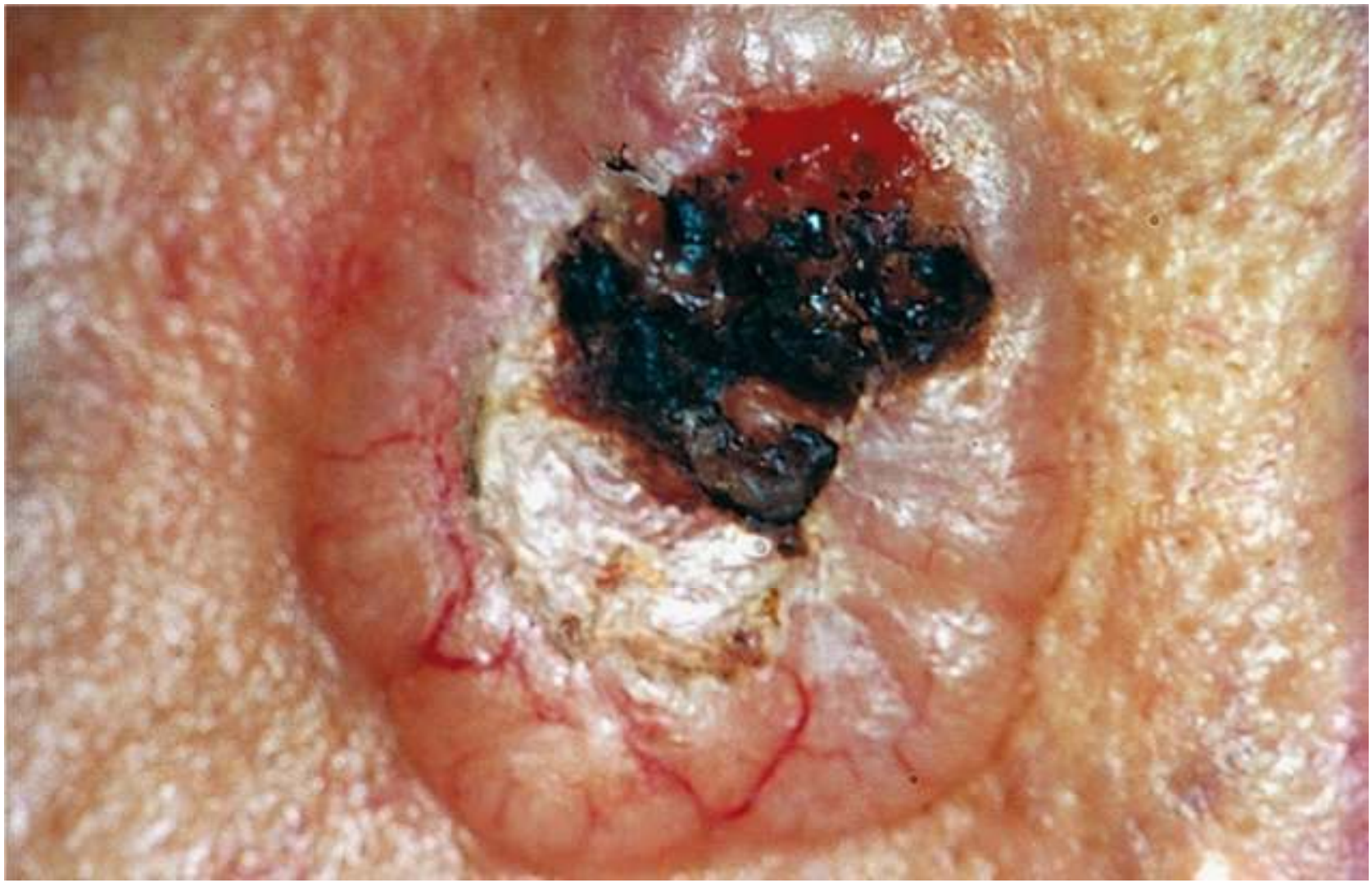
1. EBC plan cicatriceal:



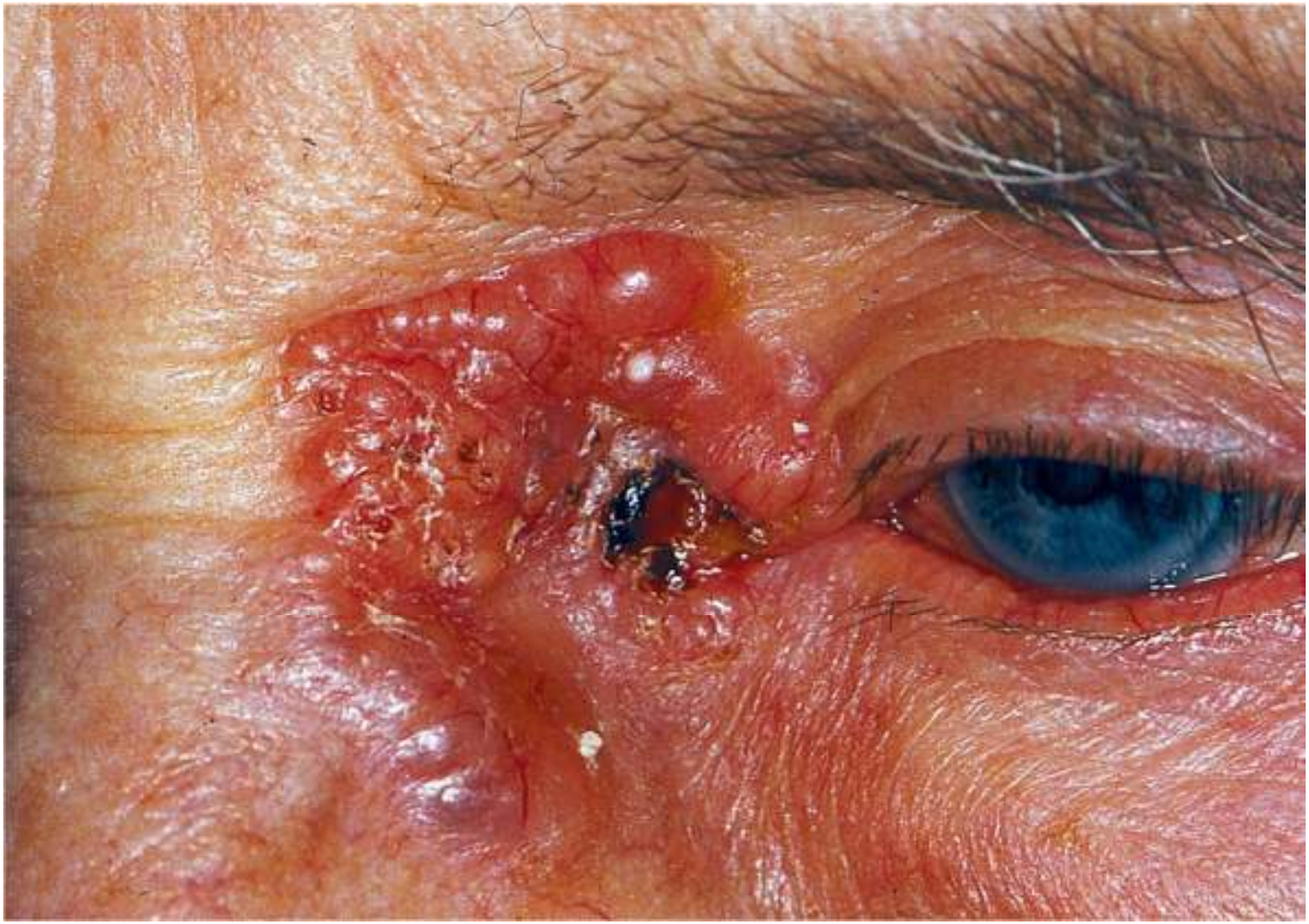
2. EBC ulceros – “ulcus rodens”:



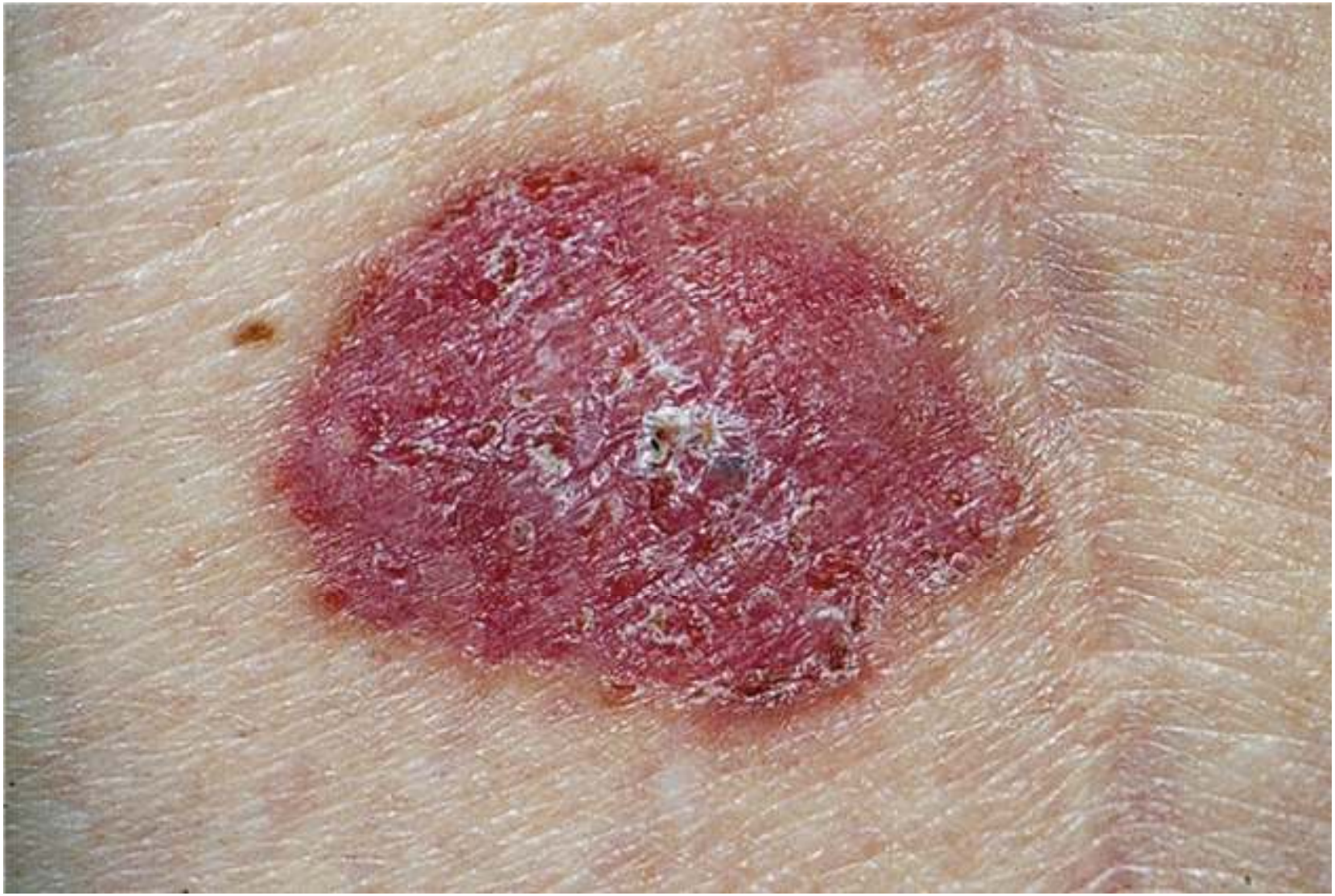
3. EBC nodular cu ulceraţie centrală:



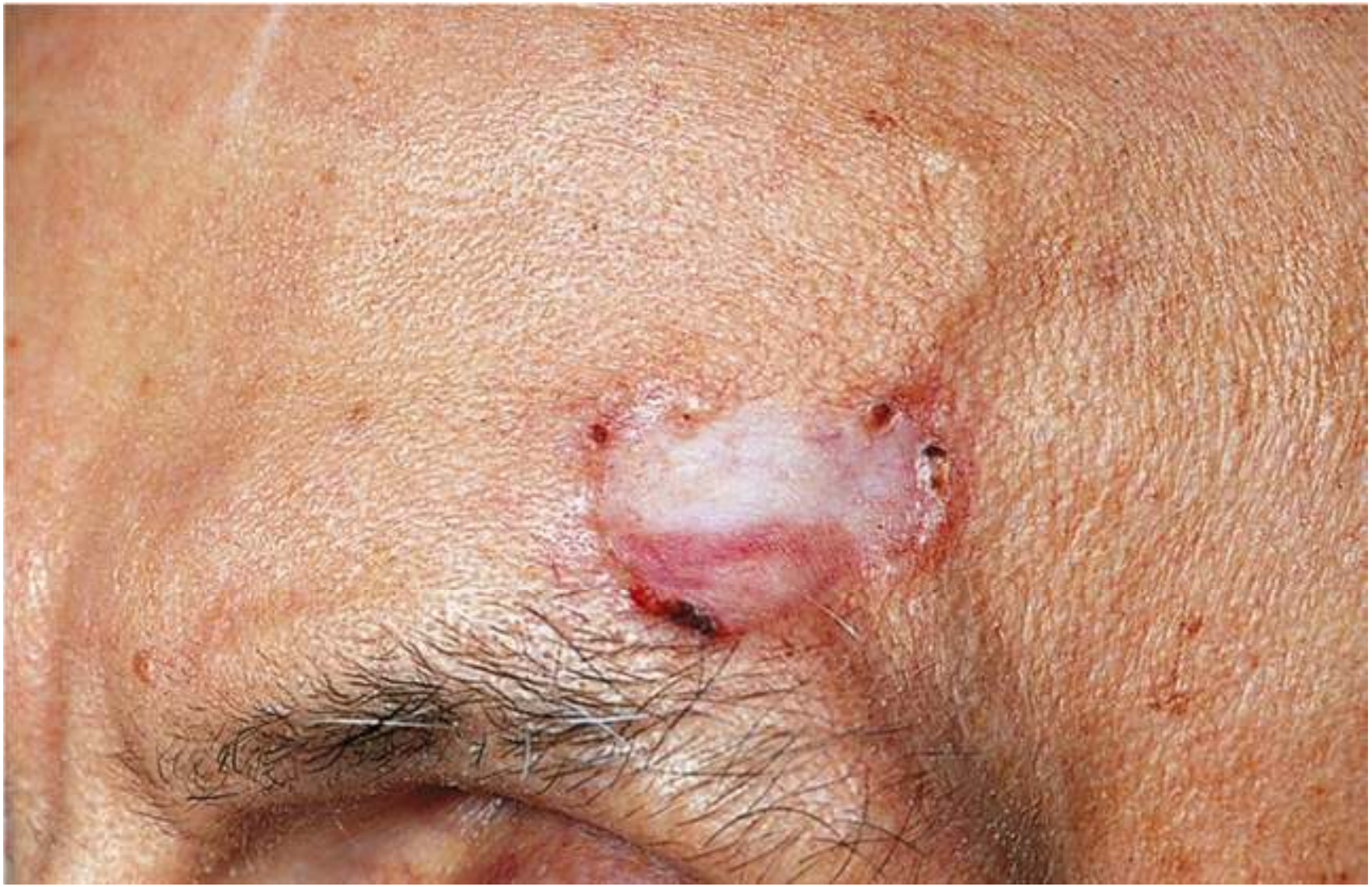
4. EBC multinodular cu ulceraţie:



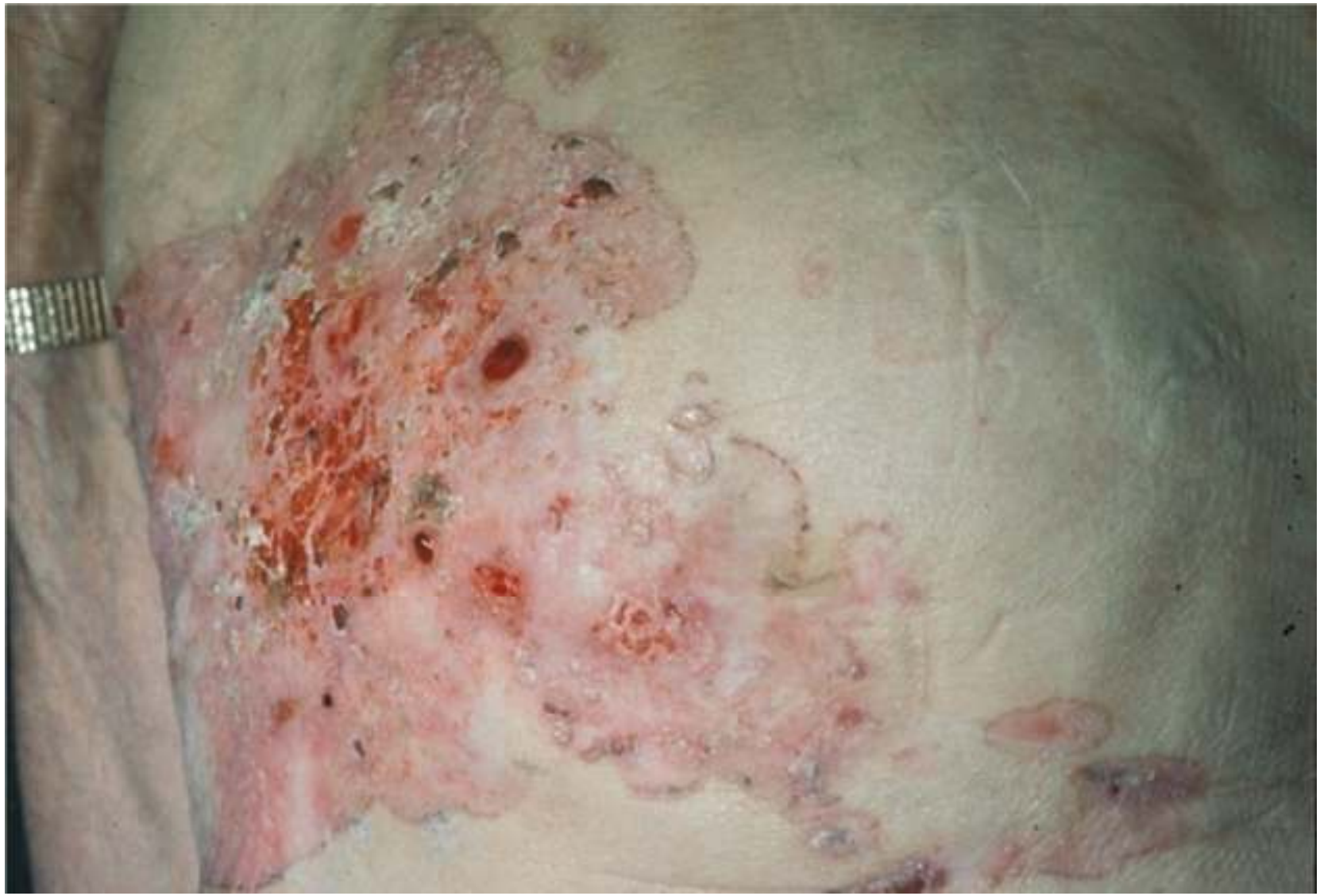
5. EBC pagetoid trunchi:



6. EBC sclerodermiform:



7. EBC superficiale multiple:



Genodermatoses associated with BCC

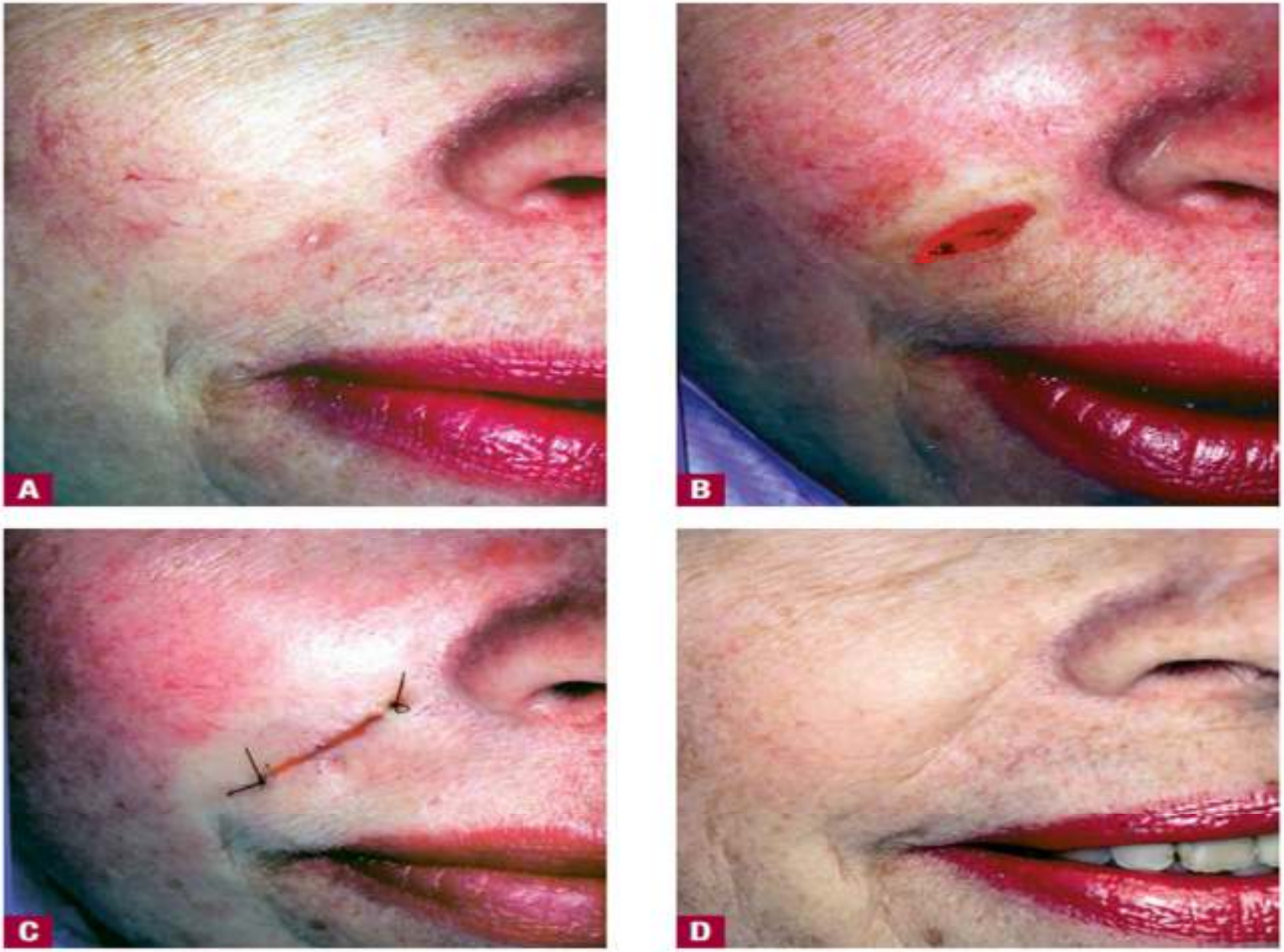
- **Nevoid Basal Cell Carcinoma Syndrome (NBCCS)**
- is an autosomal dominant disorder with complete penetrance and variable expression, characterized by numerous BCCs
- About 0,4% of all BCCs are NBCCS and 2% of patients under 45 years with BCCs have this syndrome
- NBCCS is caused by a mutated Patched gene on chromosome 9
- The most frequent locations for BCCs are on the face, back and chest; on the face, the BCCs appear around the eyes, on the eyelids, nose, and upper lips
- **Five features are characteristic of NBCCS:**
- numerous, usually aggressive, BCCs that appear at early stage;
- jaw (odontogenic) cysts;
- skeletal abnormalities including the ribs, spine, and skull;
- ectopic calcification;
- palmar and plantar pits.

Genodermatoses associated with BCC

- **Bazex – Dupre – Christol Syndrome**
- Bazex – Dupre – Christol syndrome was described by Bazex et al in 1966. This disorder has a dominant inheritance and is linked to Xq24-q27
- Characteristics of this syndrome are:
- congenital diffuse hypotrichosis;
- follicular atrophoderma;
- basocellular neoformations, including BCCs and basal nevi
- **Rombo syndrome**
- Rombo syndrome is hypothesized to be autosomal dominant and is characterized by peripheral vasodilatation with cyanosis and follicular atrophy in sun-exposed areas
- Manifestations tend to appear between the ages of 7 and 10 years
- Atrophic skin has a “worm-eaten” appearance termed atrophodermia vermiculatum
- Telangiectasias and milia-like papules appear later, and atrophic skin becomes more prominent
- Patients may also present with vellus hair cysts

Treatment - Surgical excision

- Surgical excision is a primary treatment option for NMSC
- This option is most appropriate for well-delineated tumors located in less cosmetically sensitive areas such as extremities
- Margins are generally 3 to 6 mm for small and well – delineated BCCs; however, large tumors, clinical extension, rate of growth, and local structures involved need to be considered to merit larger excision margins
- The overall goal of convectional excision is to resect the entire tumor until histologic margins show no residual neoplastic cells at the surgical borders
- Excision can produce good cosmetic result
- Potential drawbacks to conventional surgery include possible infection, scarring, longer procedural time than those of some nonsurgical methods, and more normal tissue removed than with Mohs' microsurgery
- Surgical excision cure rates range from 90 to 98%

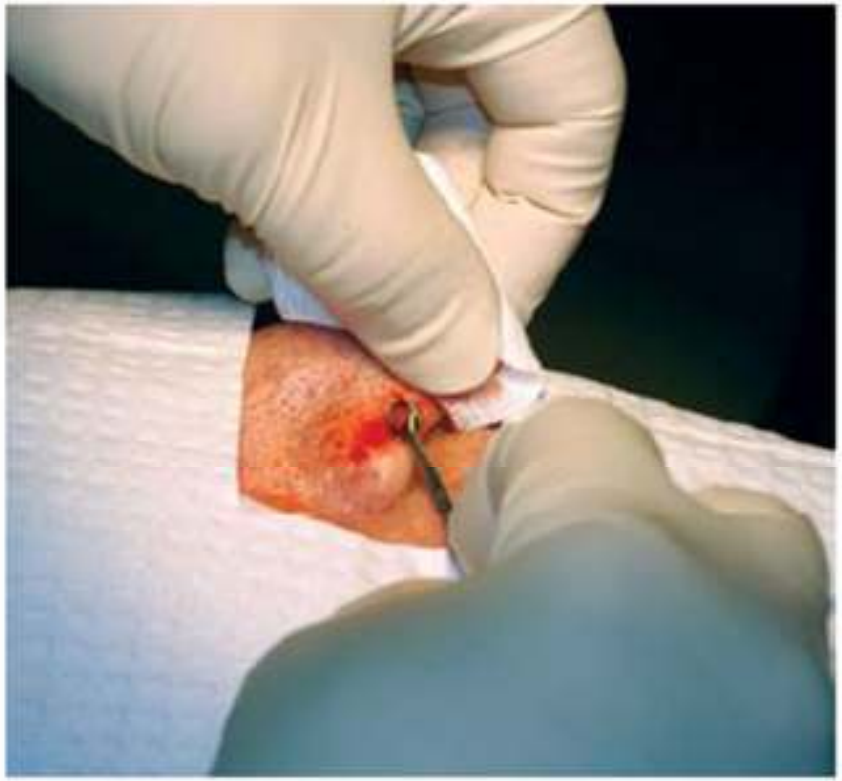


▲ **FIGURE 244-6** **A.** A primary basal cell carcinoma of the right nasolabial fold was previously biopsied by the shave technique. **B.** The excision with 5-mm margins is planned as an ellipse that lies in the nasolabial fold. **C.** Closure under minimal tension with buried subcutaneous sutures and a pullout suture. **D.** Ten years after surgery.

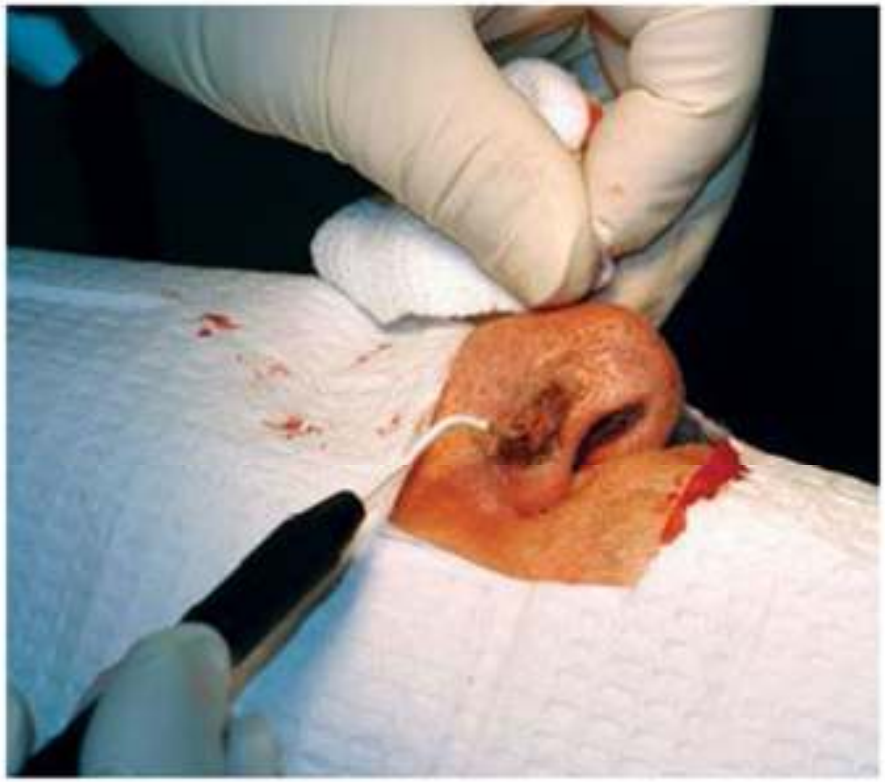
Treatment - Curretage and Electrodessication

- Curretage and electrodessication are one of the most commonly used treatment modalities for the removal of BCCs
- It's appropriate to use this treatment option for small well-demarcated cutaneous tumors
- However, this modality is not recommended for large-diameter BCCs, aggressive subtypes, or BCC involving high-skin risk anatomic areas because of the high recurrence rates in this types of situation
- A curretage and electrodessication wound doesn't usually require sutures; wounds usually have a satisfactory cosmetic result

Treatment - Curretage and Electrodessication



▲ **FIGURE 247-7** Curettage of skin tumor during curettage and electrodesiccation procedure.



▲ **FIGURE 247-8** Electrodesiccation of skin tumor during curettage and electrodesiccation procedure.

Treatment - Cryosurgery

- Cryosurgery employs the use of a cryogen to form an ice ball
- Different cryogens are available, including ethyl chloride, Freon, carbon dioxide, and nitrous oxide, but most procedures use liquid nitrogen
- This inexpensive cryogen has a boiling point of - 196°C and can be readily stored in an insulated container
- Cryosurgery has high cure rates and the overall recurrence rate for primary BCCs is approximately 4,3%
- Use caution when treating patients with a dark skin tone
- This mode of treatment may cause a hyperpigmentation, postinflammatory hypopigmentation, or even a white depigmentation
- Cryosurgery is a quick, low-cost, and safe treatment option that remains a viable nonsurgical option to treat BCCs

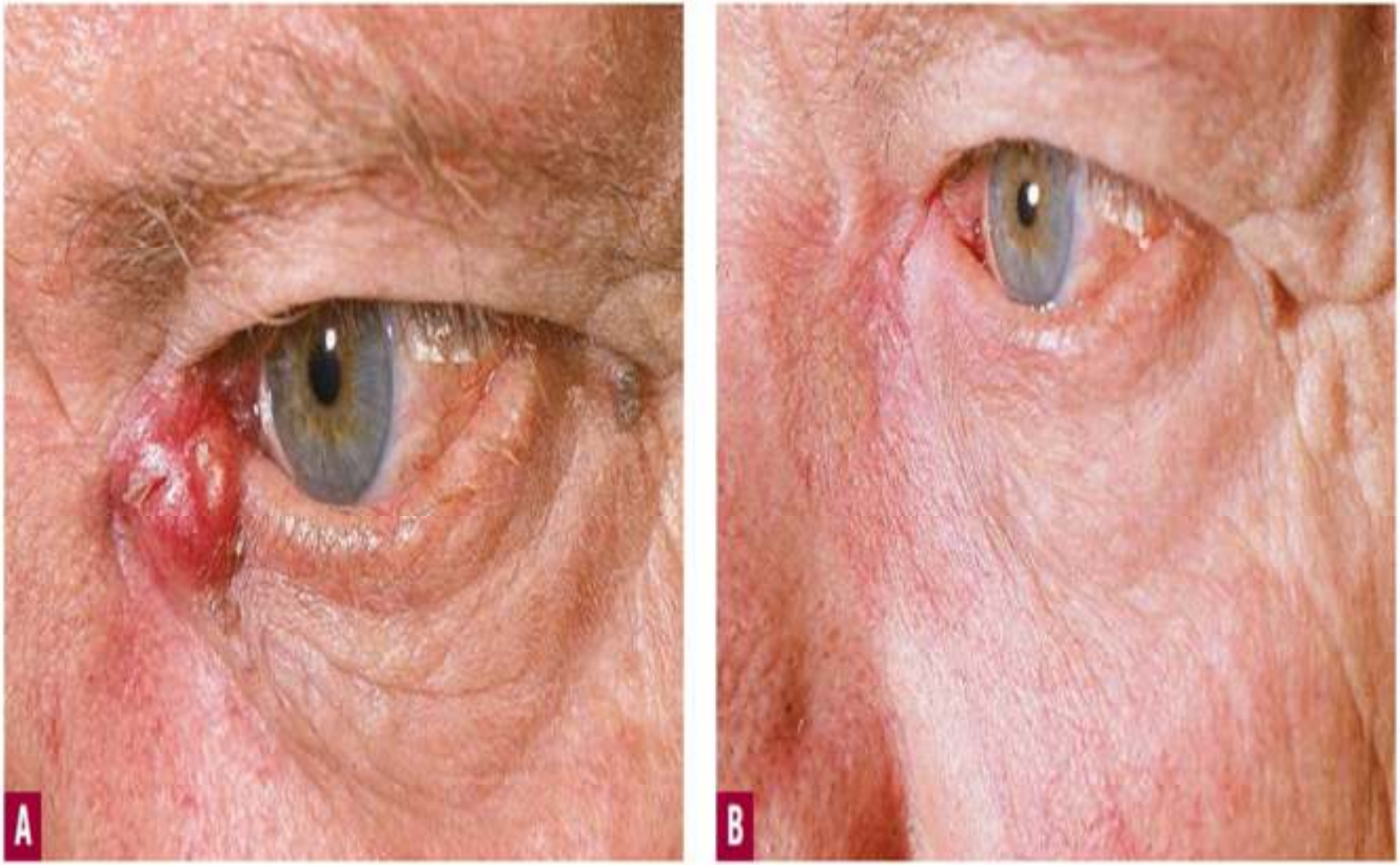
Treatment - Radiation therapy

- Radiation is an appropriate treatment option for patients that are not candidates for surgical procedures or if their skin carcinoma is considered unrespectable
- Recommended locations include facial structures and usually patients are greater than 60 years of age and have medium to large-sized tumors
- The most common types of radiation used in dermatologic practices include superficial X – rays, Grenz rays, contact therapy, supervolatge therapy, electron beam therapy, and radiation from implanted radioactive isotopes
- Chronic treatment can cause radiodermatitis and cutaneous atrophy
- Radiation postoperatively should be used in patients with advanced lesions, positive surgical margins, lymph node metastasis, and perineural invasion

TABLE 241-1
Radiation Qualities

TYPE	KV	FSD (CM)	HVL (MM)	$D_{1/2}$ (MM)
Grenz rays (ultrasoft, supersoft, Bucky therapy)	10–20	10–30	0.03 Al	0.2–1.0
Soft x-ray	20–100	10–30	0.1–2.0 Al	1–20
Contact therapy (Chaoul therapy)	50–60	1.5–3.0	2.0–4.0 Al	4–30
Superficial x-ray (low voltage)	60–150	15–30	0.7–2.0 Al	7–10
Orthovoltage therapy (deep x-ray therapy, conventional x-ray therapy)	150–400	50–80	2–4 Cu	50–80
Supervoltage therapy	400–800	50–80	5–10 Pb	80–110
Megavoltage therapy (betatron, particle accelerators)	> 1000	80	> 10 Pb	10–200

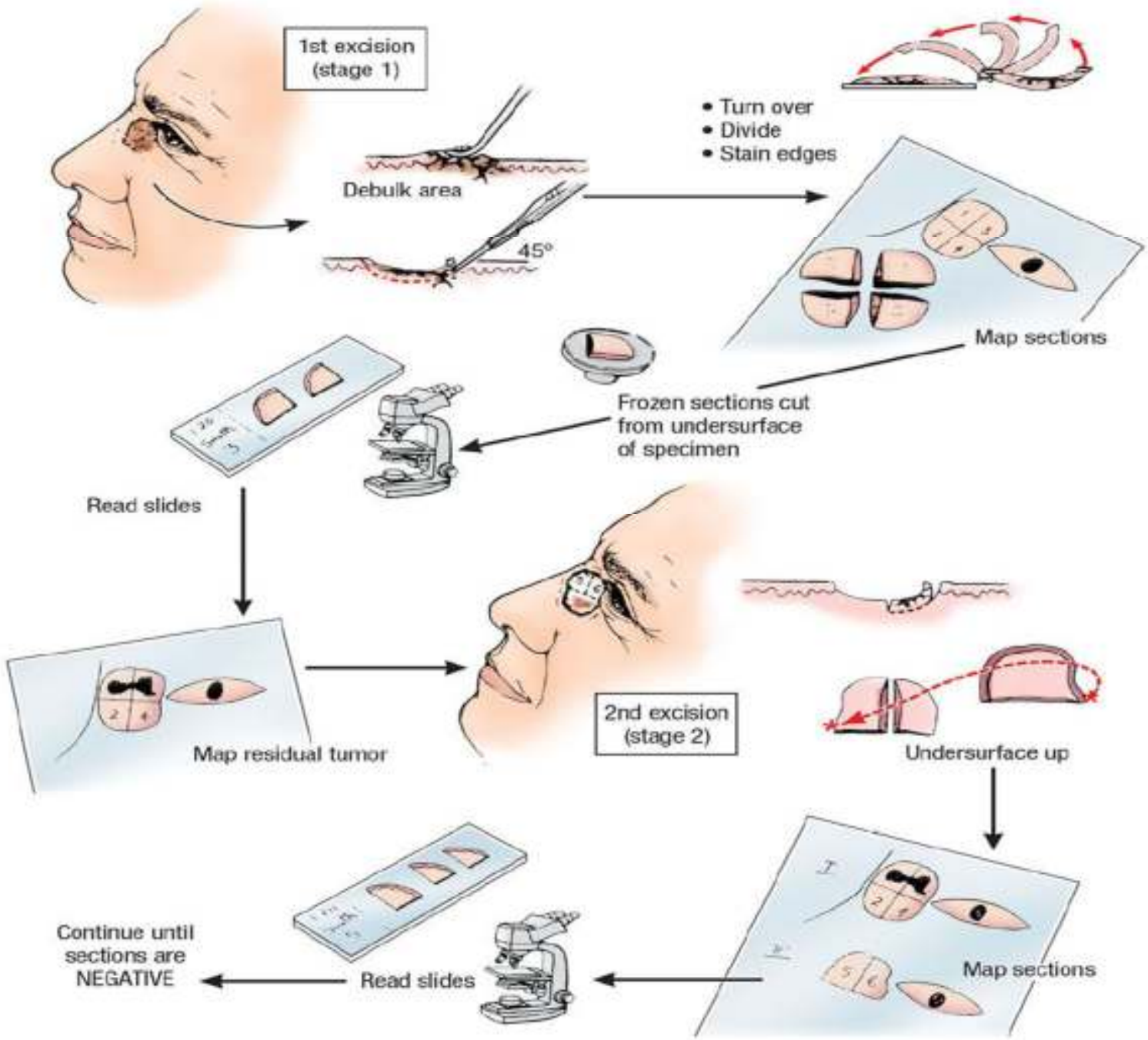
FSD = focus-skin distance; HVL = half-value layer; $D_{1/2}$ = half-value depth.



▲ **FIGURE 241-2** **A.** Basal cell carcinoma on the left inner canthus of a 64-year-old man before and (**B**) 6 months after soft x-ray treatment (40 kV) [12 × 4 Gy (48 Gy), twice per week].

Treatment - Mohs' micrographic surgery

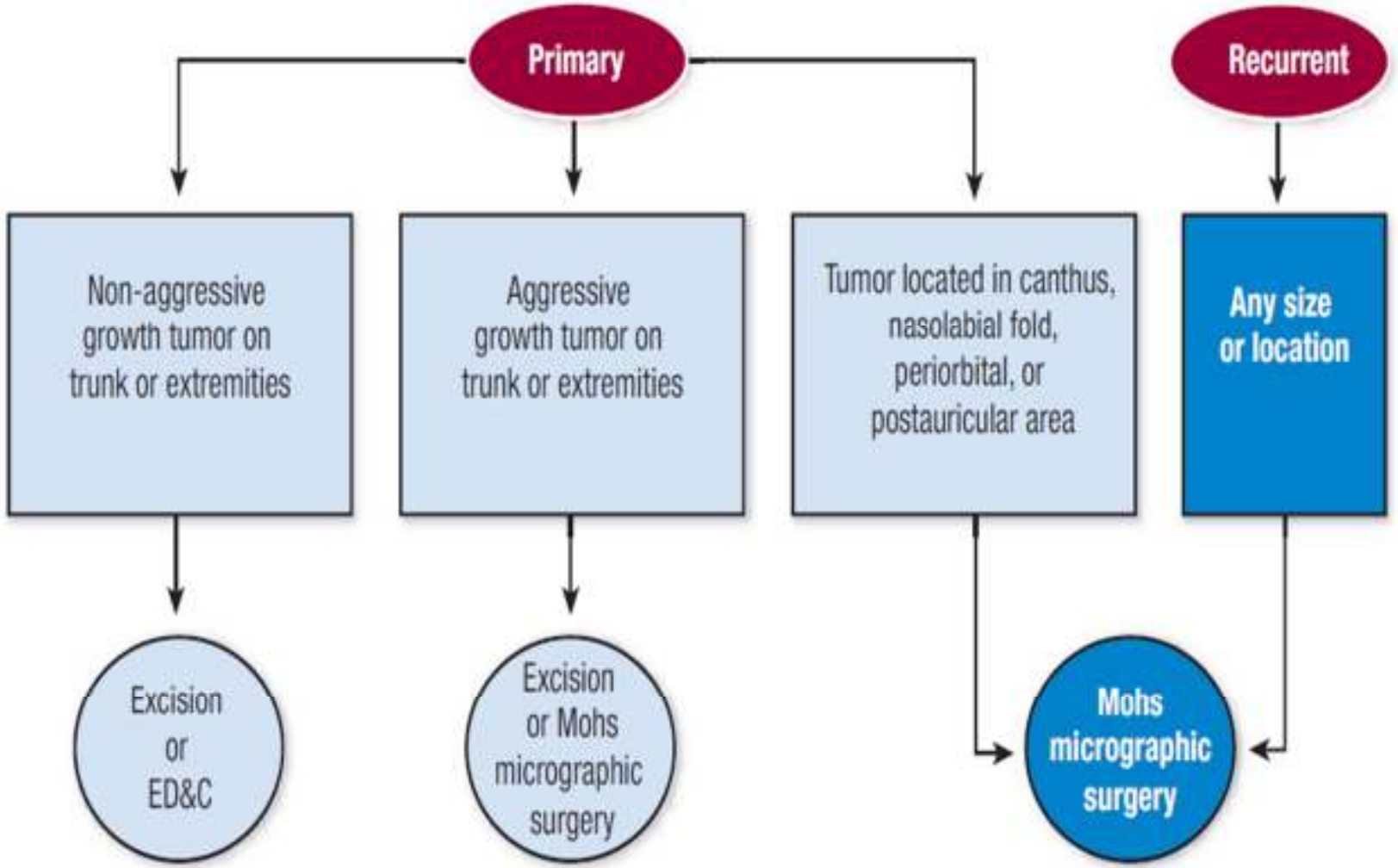
- Mohs' micrographic surgery is the treatment modality that has the highest cure rates along with the best tissue conservations and patient's satisfaction record
- Dr. Frederic E. Mohs developed this surgical technique that currently consists of a fresh-tissue technique with precise microscope-guided excision
- Mohs' micrographic surgery is indicated for NMSCs and a variety of other rare and aggressive skin lesions
- Overall Mohs' microsurgery 5 year cure rates are greater than 99% and 96% with primary BCC and recurrent BCC, respectively



▲ **FIGURE 245-1** Schematic of Mohs micrographic surgery technique. See text for detailed explanation.

Indications for Mohs Surgery for Basal Cell Carcinoma

- Location on a high-risk anatomic site including mask area of face, scalp, anatomic fusion planes, periorbital area/eyelid
- Tumor > 2 cm
- Aggressive histologic sub-type
- Recurrent tumor
- Incompletely excised basal cell carcinoma
- Location on previously irradiated skin
- Immunosuppression of patient after solid organ transplantation
- Indistinct clinical border
- Situation requiring conservation of normal tissue to preserve function and cosmesis
- Situation requiring highest achievable probability of cure to preserve function and cosmesis



▲ **FIGURE 115-9** Management of basal cell carcinoma is guided largely by anatomic site and histologic sub-type of the lesion. ED&C = electrodesiccation and curettage.

Treatment - Other types of treatment

- Laser surgery
- Photodynamic therapy
- Interferon
- Imiquimod
- 5-Fluouracil

Squamous cell carcinoma of the skin
Introduction

- Squamous cell carcinoma (SCC) is the malignant neoplasm of keratinocytes that constitutes the epidermis, mucosal epithelium, and the epithelium of adnexal structures
- SCC is the second most common malignant skin neoplasm, and can arise *de novo* in the skin, as well as preceded by natural or artificial UV damage, human papillomavirus infection, HIV infection, immunosuppression, radiation, scarring, adjacent chronic ulcer, sinus or fistula formation, and exposure to carcinogens
- SCC has many clinical and histopathological variants that show different biological behavior
- The term SCC *in situ* defines the malignant neoplasm that is only confined to the epidermis or the epithelium
- When the neoplasm extends through or presents beneath the basement membrane zone in the dermis or even deeper in the skin, then it's called *invasive* SCC

Squamous cell carcinoma of the skin Epidemiology

- The estimated incidence of SCC in the US is 100,000 to 200,000 cases per year
- Among all skin cancers, SCC seems to be the one, which is the most positively correlated with total and occupational UVR exposure
- SCCs are mostly located on body sites that have the highest cumulative UVR exposure such as the head and neck region
- UVB radiation is more associated with SCCs and the amount of UVB radiation is also dependent on the latitude
- SCCs in general are expected to be more frequent in individuals older than 45 to 50 and more common in males than in female, with the highest incidence among skin type I and II Caucasians
- SCCs in other ethic groups are usually non-UV related and associated with other risk factors
- SCC incidence is increased in transplant patients associated with HPV

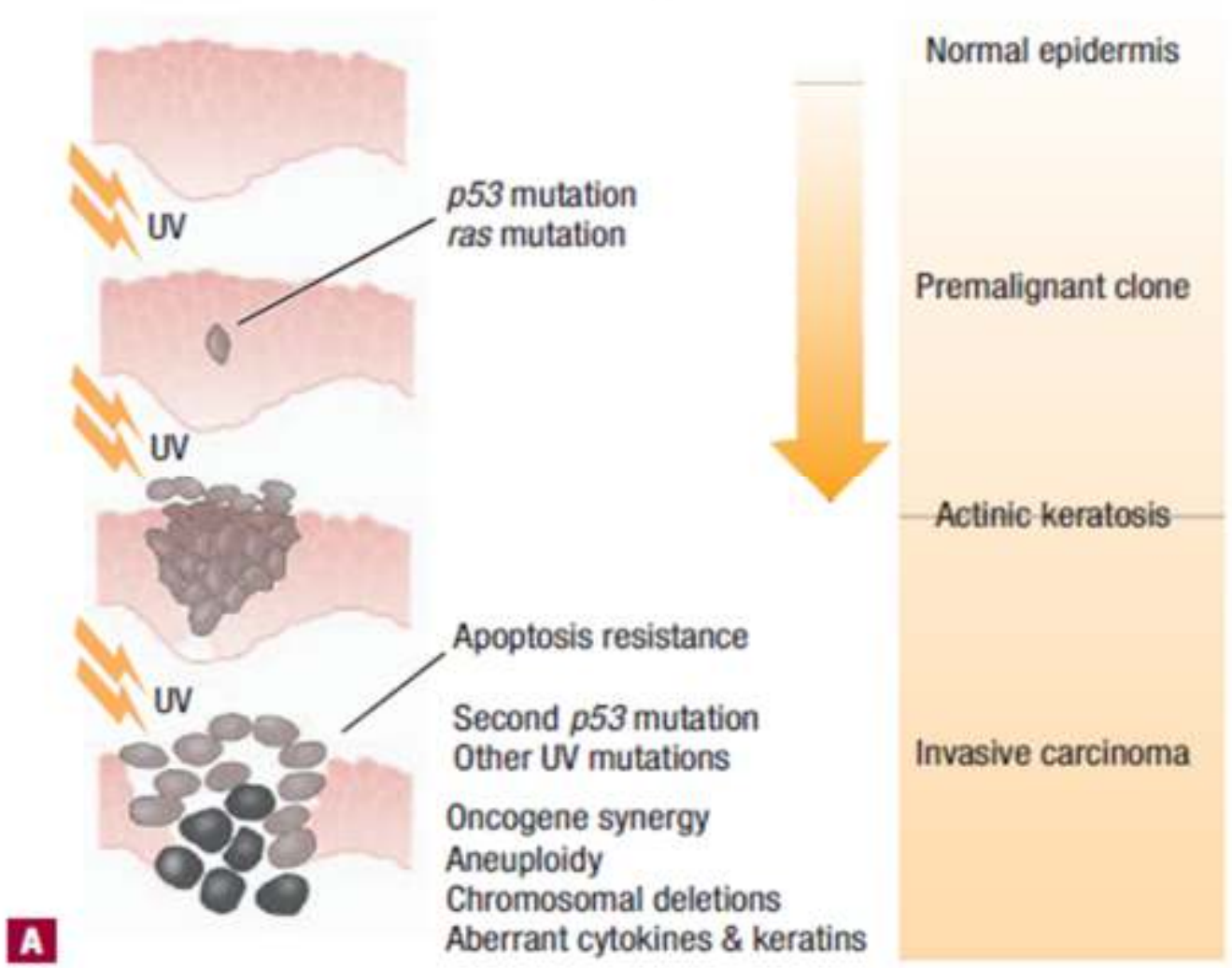
Squamous cell carcinoma of the skin
Pathogenesis

- SCC pathogenesis is a multistep process that involves both extrinsic and intrinsic factors that ultimately leads to carcinogenesis
- Mutations in protooncogenes and tumor suppressor genes (p53 and Ras) are important to the pathogenesis of SCC
- The most important extrinsic risk factor for the development of SCC is UV radiation
- UVA causes indirect damage through the production of reactive oxygen species (ROS), while UVB is responsible for more direct and destructive biological mutation
- UV exposure is known to induce inflammatory response within the skin. Specific inflammatory factors include Pg, TNF and IL-1α.

Squamous cell carcinoma of the skin
Pathogenesis

- Another important extrinsic factor is infectious diseases, mostly importantly the HPV
- Other extrinsic factors include chemical carcinogens, arsenic, polycyclic aromatic hydrocarbons, tobacco, and ionizing radiation; these agents are dose-dependent and the time period between exposure and carcinoma may be decades
- Important intrinsic risk factors include immune status and genetics of the host
- Organ transplant recipients, xeroderma pigmentosum patients and oculocutaneous albinism patients are more prone to SCC development

Squamous cell carcinoma of the skin
Pathogenesis



Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

- Cutaneous SCC arises from malignant proliferation of the keratinocytes in the epidermis and adnexa
- This neoplasm develops predominantly on sun-exposed areas of the skin and is considered the second most common skin cancer
- Cutaneous SCC manifests itself in two main forms:
  - SCC *in situ,* where the neoplasm is confined to the epidermis;
  - Invasive SCC, where the neoplasm extends beyond the epidermis
- These two forms have many clinical and histopathological variants that carry different clinical and prognostic features
- For SCC in situ and even locally invasive SCC, appropriate therapy is usually curative
- Nonetheless, SCC may metastasize to lymph nodes and organs, can cause significant morbidities and even death.

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

- **Prognostically, SCC variants can be divided into 4 categories:**
- Low-risk SCCs (metastatic rate < 2%);
- Intermediate-risk SCCs (metastatic rate 3 to 10%);
- High-risk SCCs (metastatic rate ≥ 10%);
- SCCs with intermediate risk
- **SCC uses the Broders grading system, which correlates biologic behavior of the tumor with the degree of histologic differentiation**
- *Broders grade 1* represents moderately differentiated cells that microscopically show abundant keratinization, little nuclear anaplasia, and less than 25% undifferentiated cells
- *Broders grade 2* represents moderately differentiated cells that are 50% keratinizing, with nuclear anaplasia and less than 50% undifferentiated cells.
- *Broders grade 3* represents moderately to poor differentiated cells, that are less 25% keratinizing, extensive nuclear anaplasia, and less than 75% undifferentiated cells.
- *Broders grade 4* represents poorly differentiated cells, extensive nuclear anaplasia, no keratinization and greater than 75% undifferentiated cells.

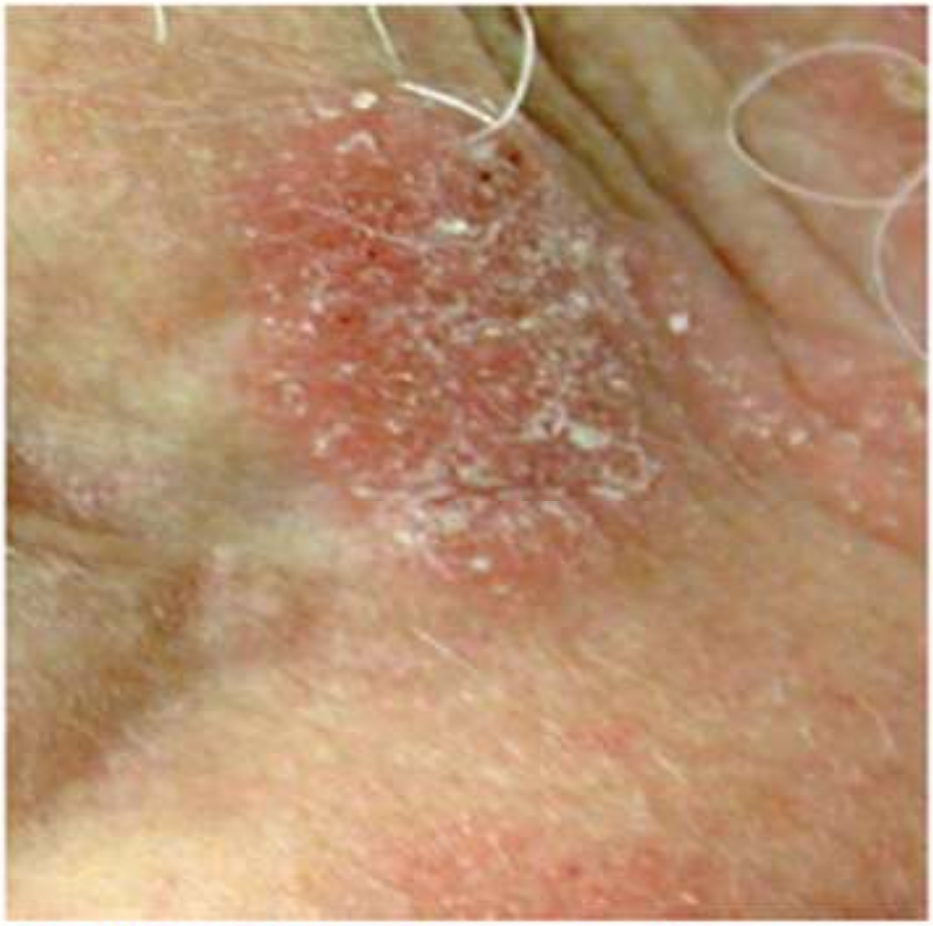
Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

- ***In situ* Squamous Cell Carcinomas - Actinic keratoses/actinic chelitis type**
- Actinic keratoses (AK) is the most common type of in situ SCC of the skin among light-skinned individuals
- Actinic keratoses is the initial manifestation of continuum of clinical and histopathologic abnormalities that progress into invasive SCC
- Clinical manifestations of AK are usually very subtle and asymptomatic
- In the most common form, AK appears as an ill-defined, subtle, erythematous macule with a slightly hyperkeratotic surface on sun exposed areas of the head, neck, forearms, hands and upper back
- Lesions can be multiple, usually less than 1 cm in diameter
- The key to clinical diagnosis on physical examination is sandpaper-like sensation felt on touching the surface of these persistent skin lesions on sun-damaged skin

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses



▲ **FIGURE 7-1** Solitary AK on the face of an elderly male.

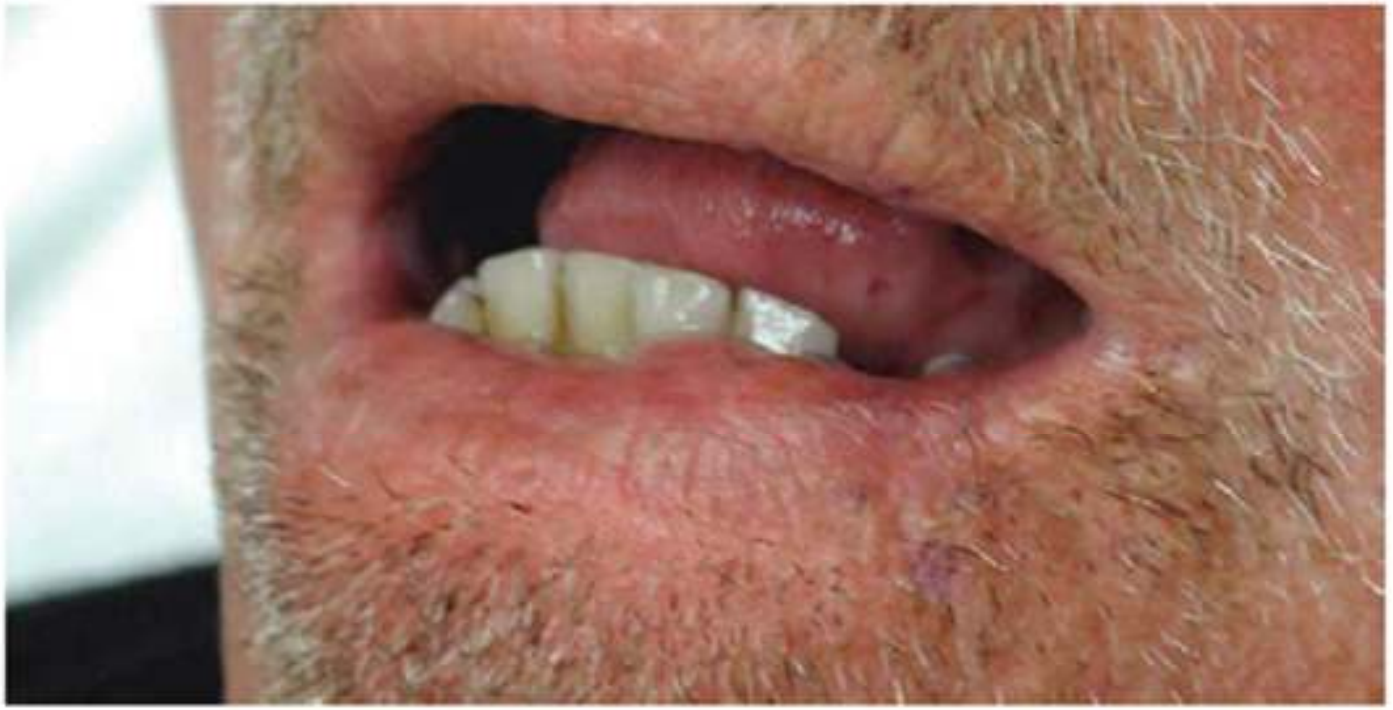
Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

- Actinic chelitis is the mucosal analog of actinic keratoses and is located primary on the lip, this lesion mostly occurs on the lower lip as slight scaling on an erythematous base
- Small wrinkles may also appear on the lip
- Surrounding skin and mucosa show other signs of sun damage, which include atrophy, solar lentigines, telangiectasias
- When actinic chelitis progress into invasive SCC of the lip, usually lesion becomes more circumscribed, associated with slight light infiltration and the border of the lip loses its usual plasticity
- Ulceration follows as a definitive sign of invasive SCC
- The gold standard in diagnosing AK/AC type of SCC in situ is histopathologic examination of the affected skin/mucosa biopsy specimen

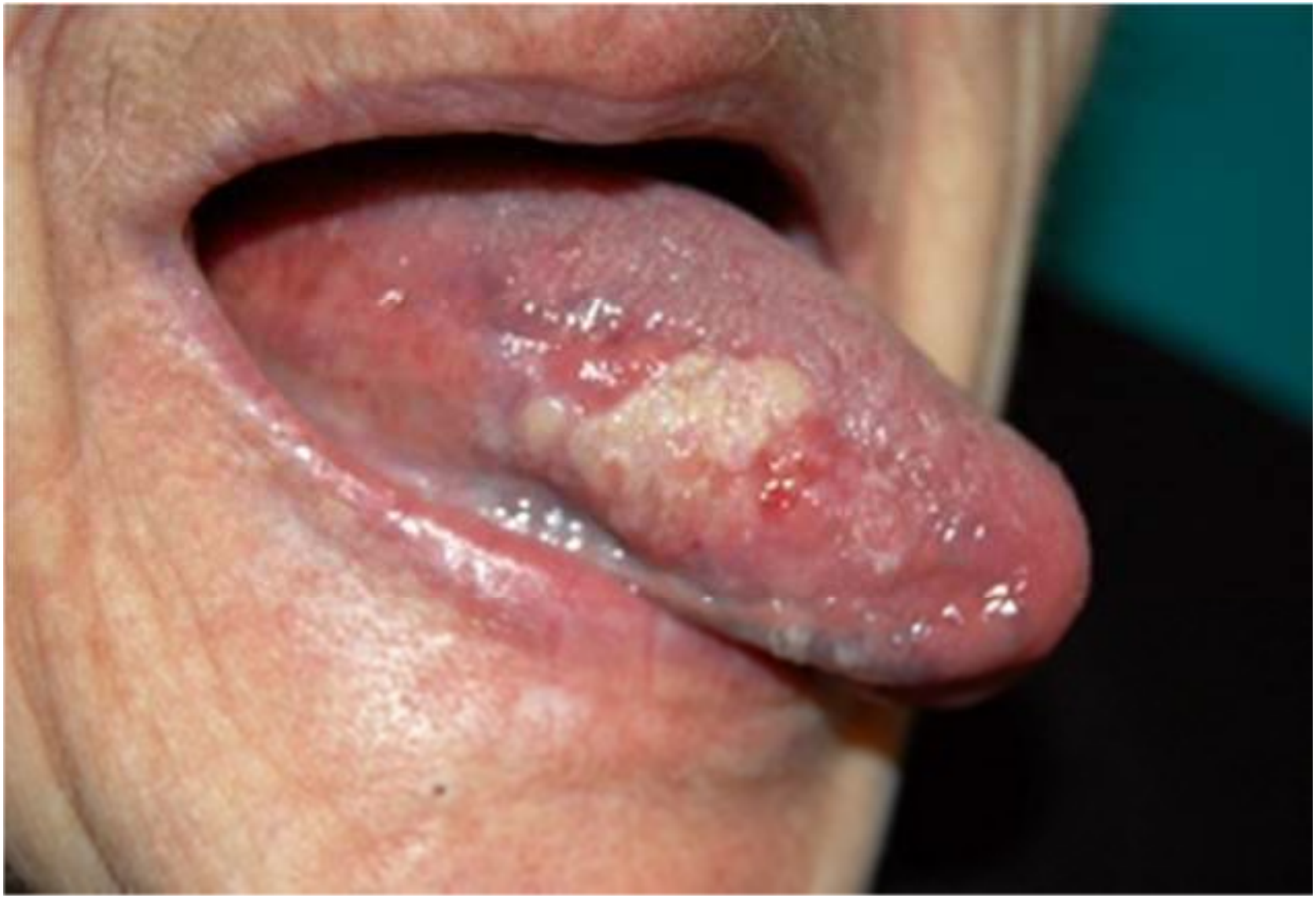
Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses



▲ **FIGURE 7-3** AC on the lower lip.

SCC



Squamous cell carcinoma of the skin

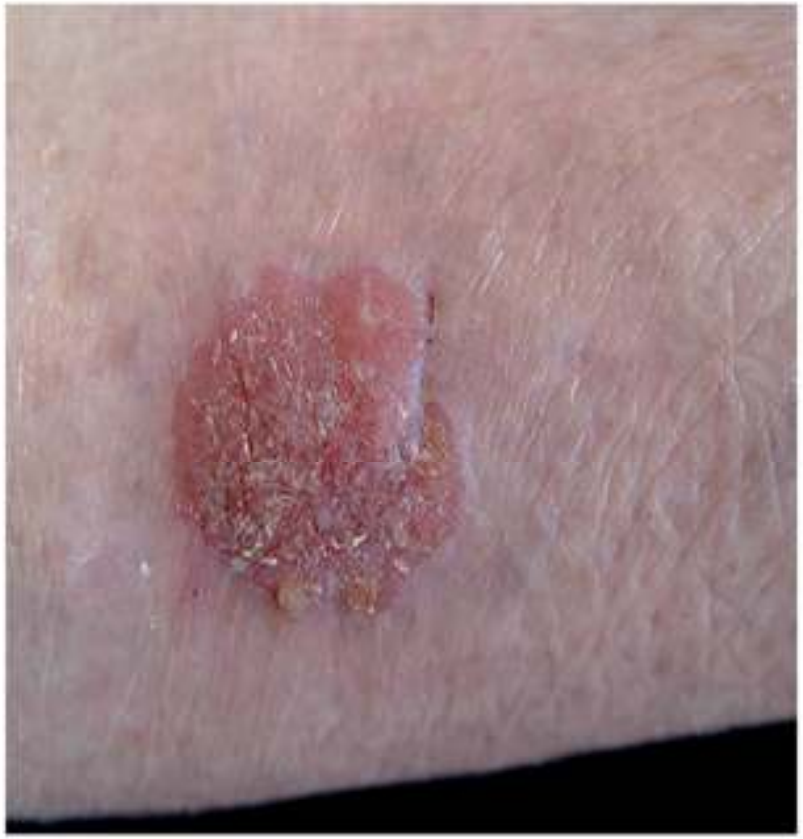
Clinical manifestations and diagnoses

Bowen disease

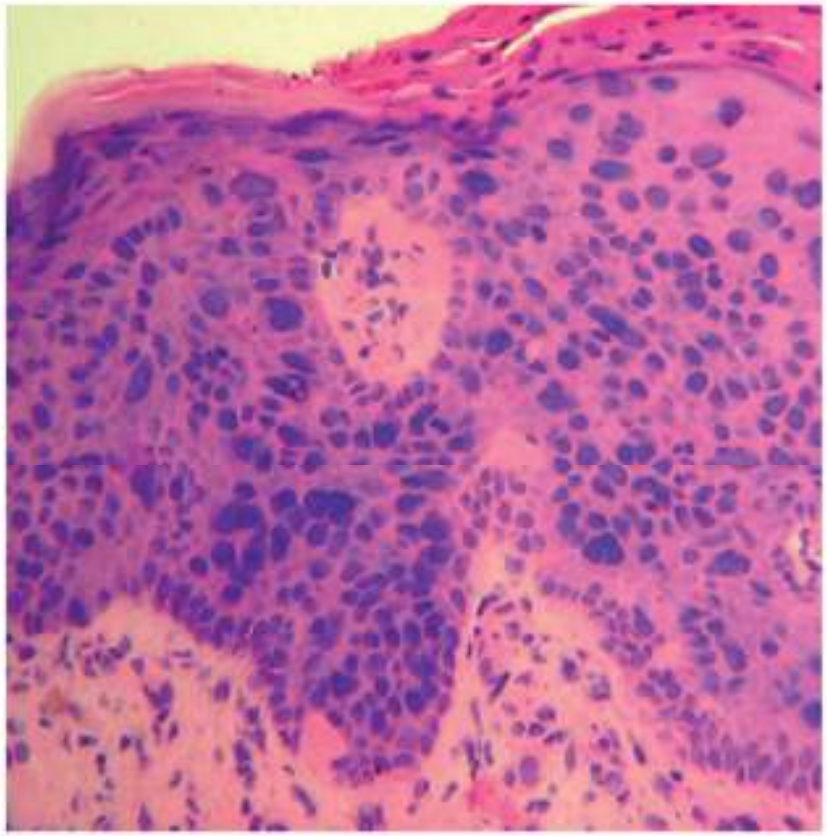
- Bowen disease (BD) is a type of SCC in situ with dysplasia at all levels of the epidermis
- Bowen disease occurs both on the skin and mucosal surfaces
- Bowen disease occurs mainly in the elderly and general, affects both sexes with a slight female predominance
- The lesions mostly occur both on sun exposed skin and mucosa, with the head and neck the most commonly affected anatomic locations, followed by he limbs
- Clinically, Bowen disease appears as an erythematous, scaly and crusty macule, patch, papule, or plaque with sharply defined borders
- Bowen disease can be found on the oral, anal, as well as both male and female genital mucosa
- Histopathologically, the lesions of Bowen disease on the skin and mucosa share many similar features of SCC in situ throughout all levels of epidermis
- On the skin hyperkeratosis is a prominent feature; the epidermis/epithelium shows acanthosis, which bears atypical keratinocytes that have large, hyperchromatic and pleomorphic nuclei.

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses



▲ **FIGURE 7-10** SCC *in situ* Bowen type, clinical.



▲ **FIGURE 7-12** SCC *in situ* Bowen type—atypical keratinocytes with prominent nuclear pleomorphism in all layers of the epidermis (H&E high magnification).

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

Erythroplasia of Queyrat

- Erythroplasia of Queyrat refers to penile carcinoma *in situ,* particularly on the glans and prepuce of the penis
- Erthroplasia of Queyrat usually manifests as solitary or multiple cutaneous lesions with minimally raised, erythematous plaques
- It is seen almost exclusively in uncircumcised men
- Presenting symptoms can vary and may include redness, crusting, scaling, ulceration, bleeding, pain, pruritis, dysuria, penile discharge, and difficulty retracting the foreskin

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

SCC *in situ* of the oral mucosa: leukoplakia type

- Leukoplakia is a white patch or plaque that cannot be scraped off and cannot be characterized clinically or pathologically as any other disease
- Leukoplakia manifests as a well-circumscribed white patch, the surface of the patches are slightly raised above surrounding mucosa, may be single or multiple lesions. Individuals of the oral leukoplakia are not symptomatic
- Clinically, oral leukoplakia can appear in two different forms: homogenous leukoplakia and verrucous leukoplakia
- Not all leukoplakia are in situ SCC and not all types of leukoplakia are associated with increased risk of invasive SCC of the oral mucosa
- The overall incidence of developing an invasive SCC from all forms of leukoplakia varies between 4.4 and 36% with an annual rate of 2.9 %
- Leukoplakia may or may not be associated with any physical, chemical or viral causative agent such as tobacco, HPV and EBV
- The current standard for diagnosis of leukoplakia is histopathologic observation of prominent cellular atypia and “dysplasia” within the epithelium

Squamous cell carcinoma of the skin
Clinical manifestations and diagnoses

Invasive Squamos Cell Carcinoma

- Invasive SCC of the skin is believed to occur both *de novo*, as well as preceded by any of earlier-mentioned *in situ* forms
- Approximately 60% of all invasive SCCs have been reported to be associated with SCC *in situ*
- Being an epithelial cancer itself, hypothetically all invasive SCCs must have gone through an *in situ* phase, except for metastatic SCCs

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

Common Invasive SCC

- Common invasive SCC that is associated with preexisting SCC in situ actinic keratosis/actinic chelitis type is the most common form of invasive SCC in the skin
- It represents the majority of the cases and lesions are located always on the sun exposed areas of the body, predominantly on the head and neck and distal extremities

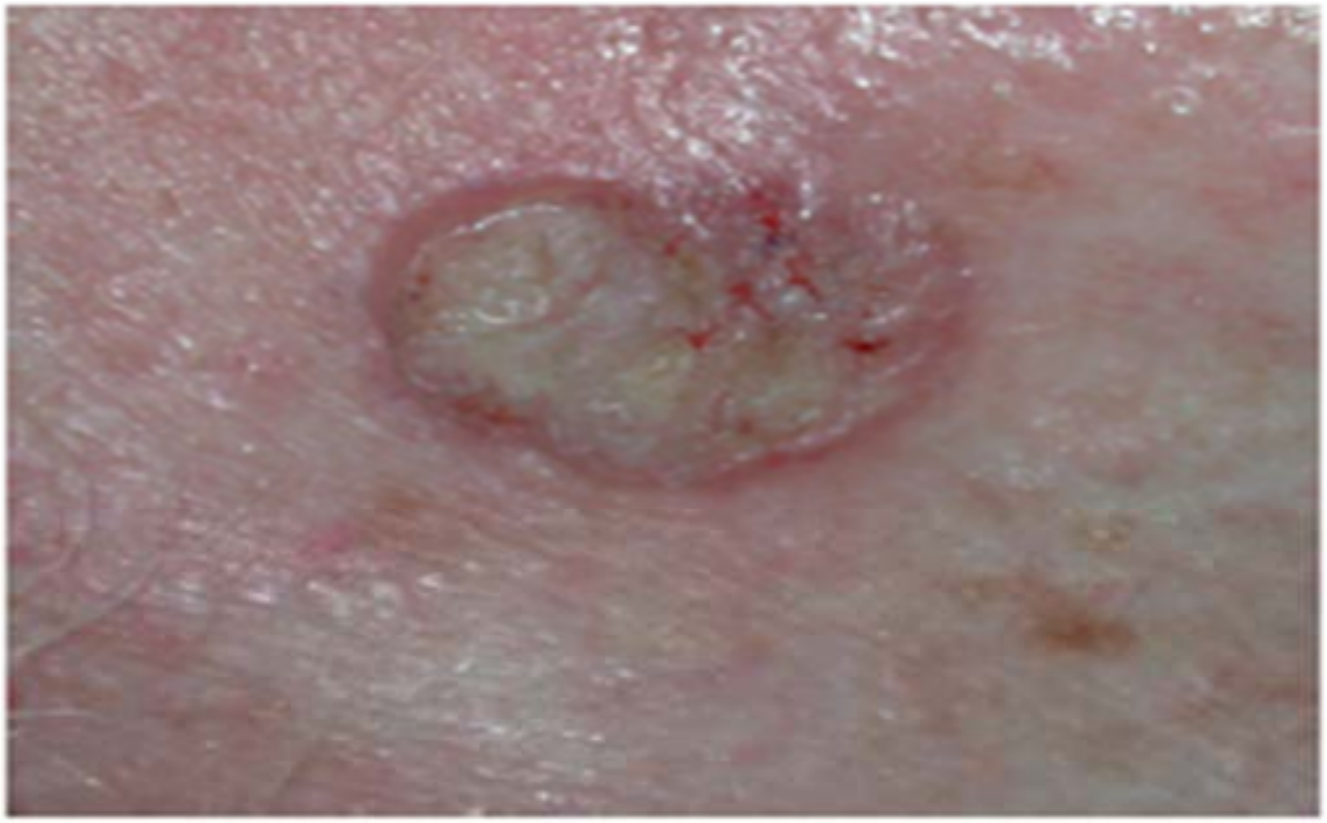
Clinically:

- Sharp circumscription
- Increase in size
- Thickness/infiltration
- Erosion/ulceration
- Prominent increase in scalling
- Hyperkeratosis or crusting
- Exophitic growth especially on a preexisting lesion on sun damaged skin

are the signs of invasive SCC

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

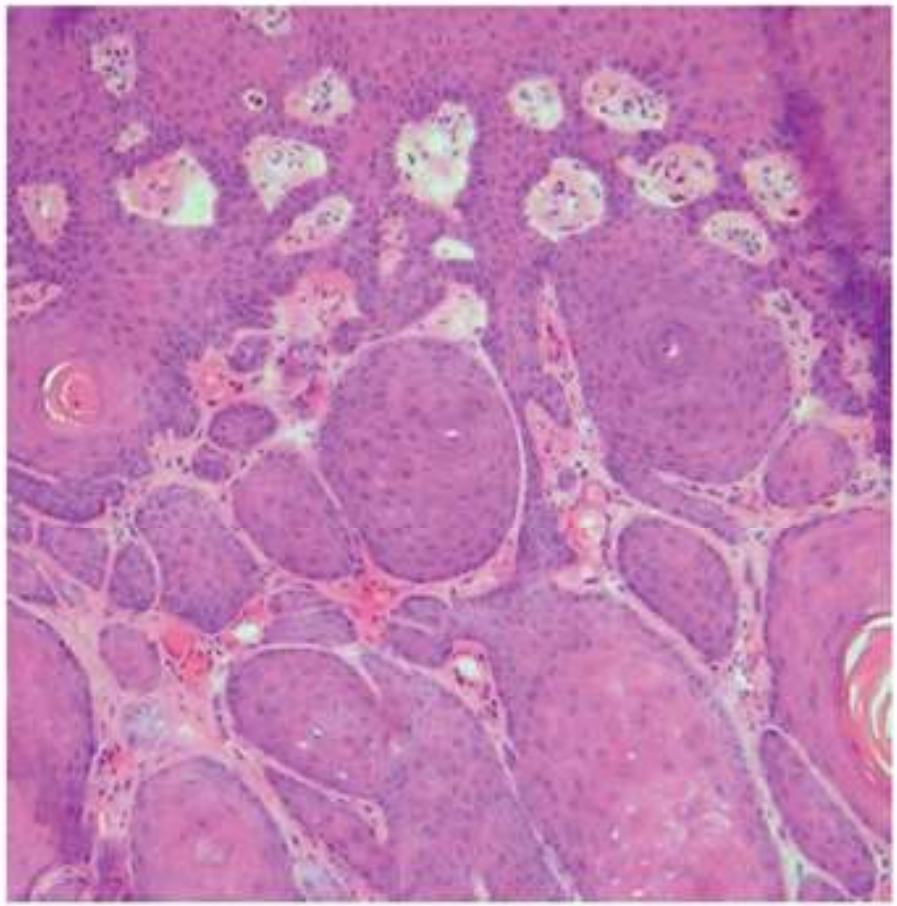


▲ **FIGURE 7-15** Common invasive SCC on sun-damaged skin.

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

- **Histopathologically**, the common invasive SCC is characterized by the malignant proliferation of keratinocytes in the form of large buds extending from or in conjunction with the surface epidermis, or islands, and/or sheets of neoplastic cells infiltrating the dermis and the deeper tissue
- **Prognostically**, the common invasive SCC of the skin is reported to be generally associated with low risk of metastases and favorable prognosis



▲ **FIGURE 7-19** Well-differentiated SCC—islands of highly keratinized neoplastic keratinocytes are capable of complete keratinization in the form of eosinophilic horn pearls (H&E low magnification).

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

De novo invasive SCC

- *De novo* invasive SCC is an invasive SCC of the skin, mucosa and adnexal epithelium that is not associated with or preceded by an *in situ* component
- *De novo* malignancies, including de novo SCC of the skin and mucosa, are reported to be increasingly associated with organ transplant and immunosuppressed patients
- *De novo* invasive SCC is reported to be a high-risk lesions as they tend to be more aggressive and associated with poor prognosis
- The incidence of local and/or distant metastases in this type of invasive SCC is approximately 8 to 14%

Squamous cell carcinoma of the skin

Clinical manifestations and diagnoses

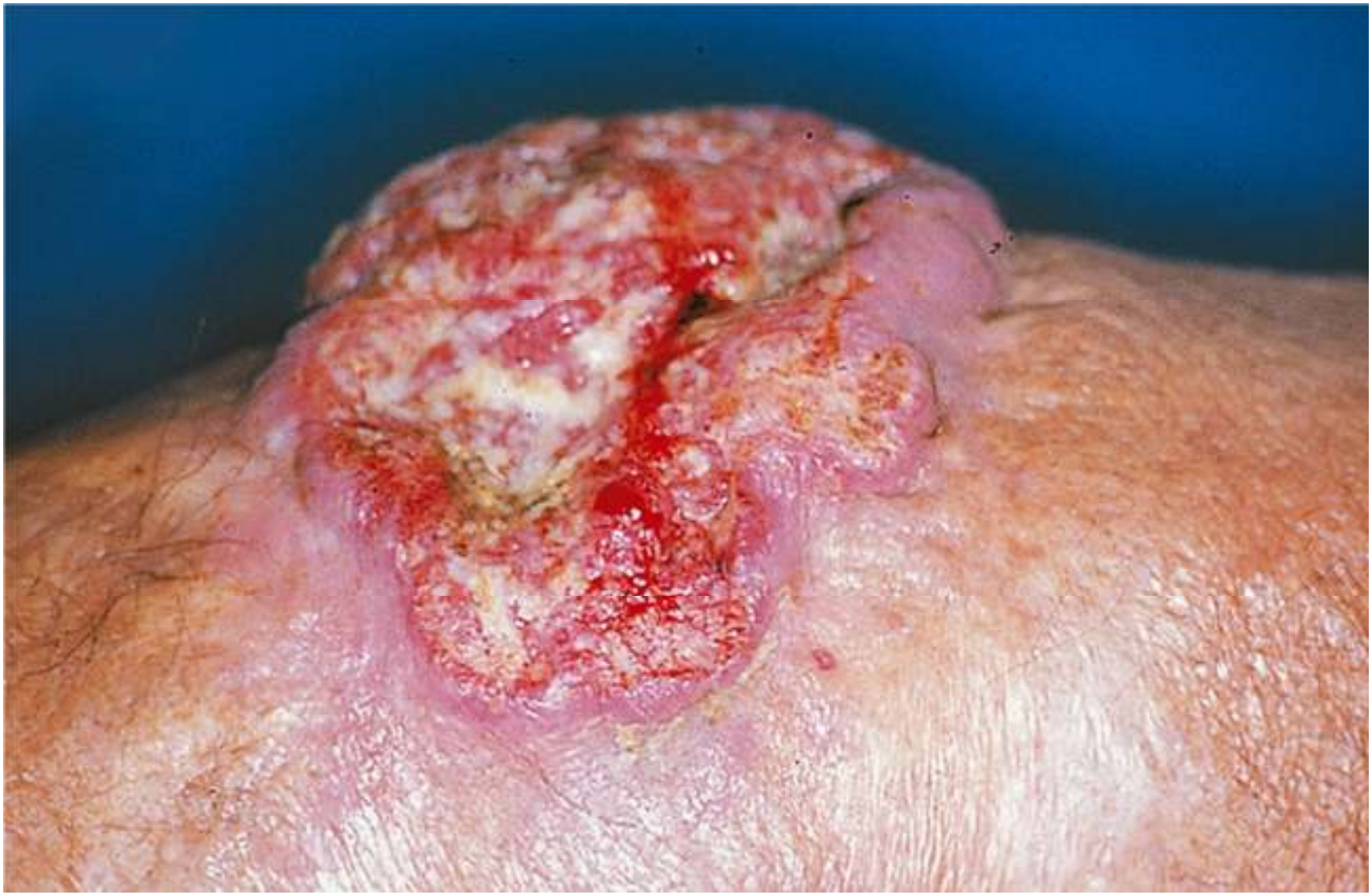
Other clinical forms of invasive SCC:

- Solitary keratoacantoma;
- Bowen type;
- Verrucous carcinoma type;
- Epithelioma cuniculatum;
- Verrucous carcinoma of the oral mucosa;
- Acantholytic type;
- Spindle cell type;
- Papillary type;
- Signet ring type;
- Pigmented type;
- Desmoplastic type;
- Clear cell type

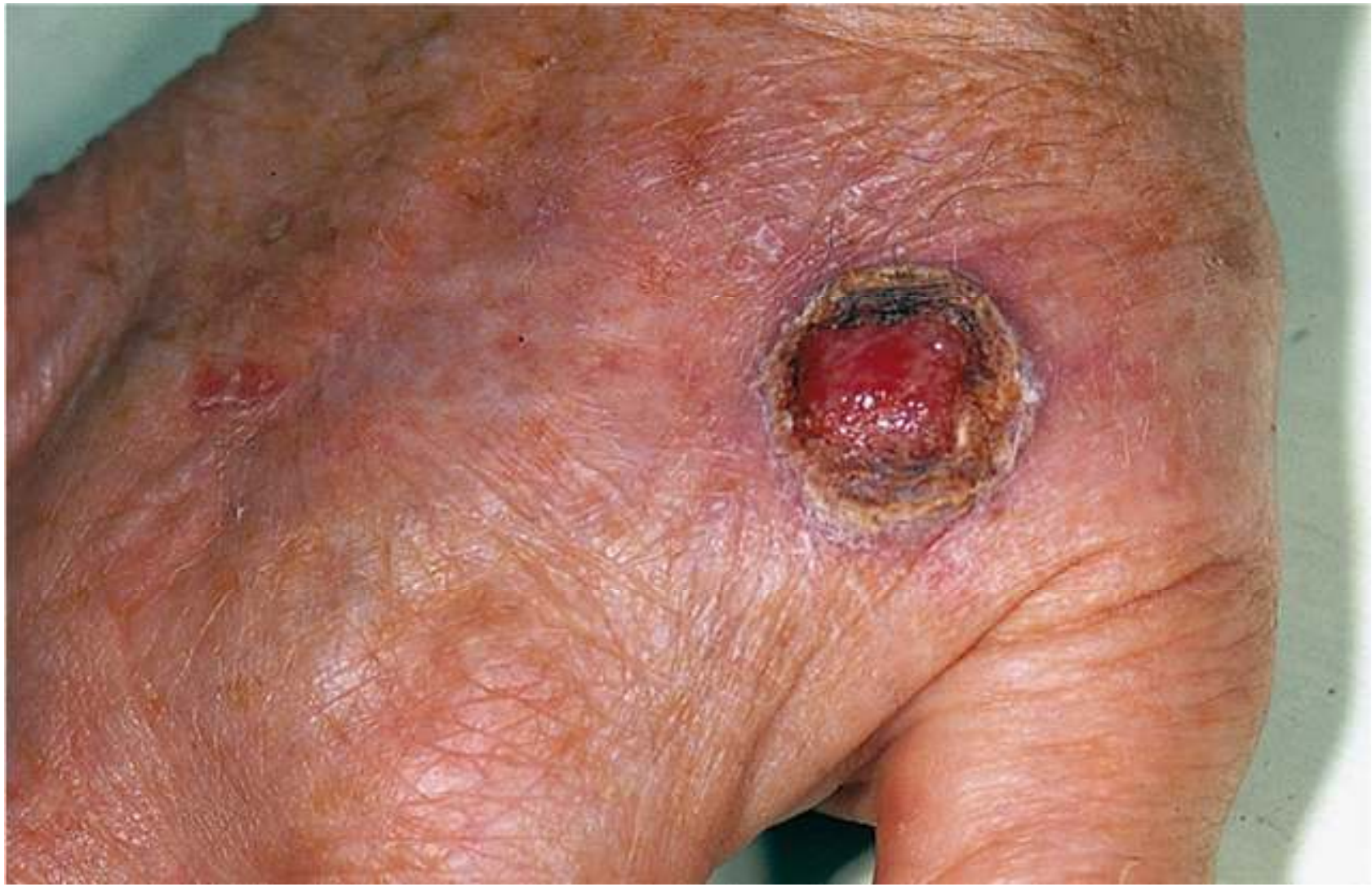
Squamous cell carcinoma of the skin
Diagnoses in SCC

- The diagnosis of SCC is based on patient history, clinical manifestations, and most importantly histopathologic examination of the lesions.
- SCC is a common malignant neoplasm that can be cured by adequate and complete removal of the tumor.
- **The clinical features that are associated with high risk in SCC are:**
- High risk clinical types of SCC;
- Patients with preexisting conditions;
- Radiation or burn scars;
- Chronic ulcers;
- Other scarring skin diseases;
- Immunosuppression;
- Organ transplantation;
- HIV infection.

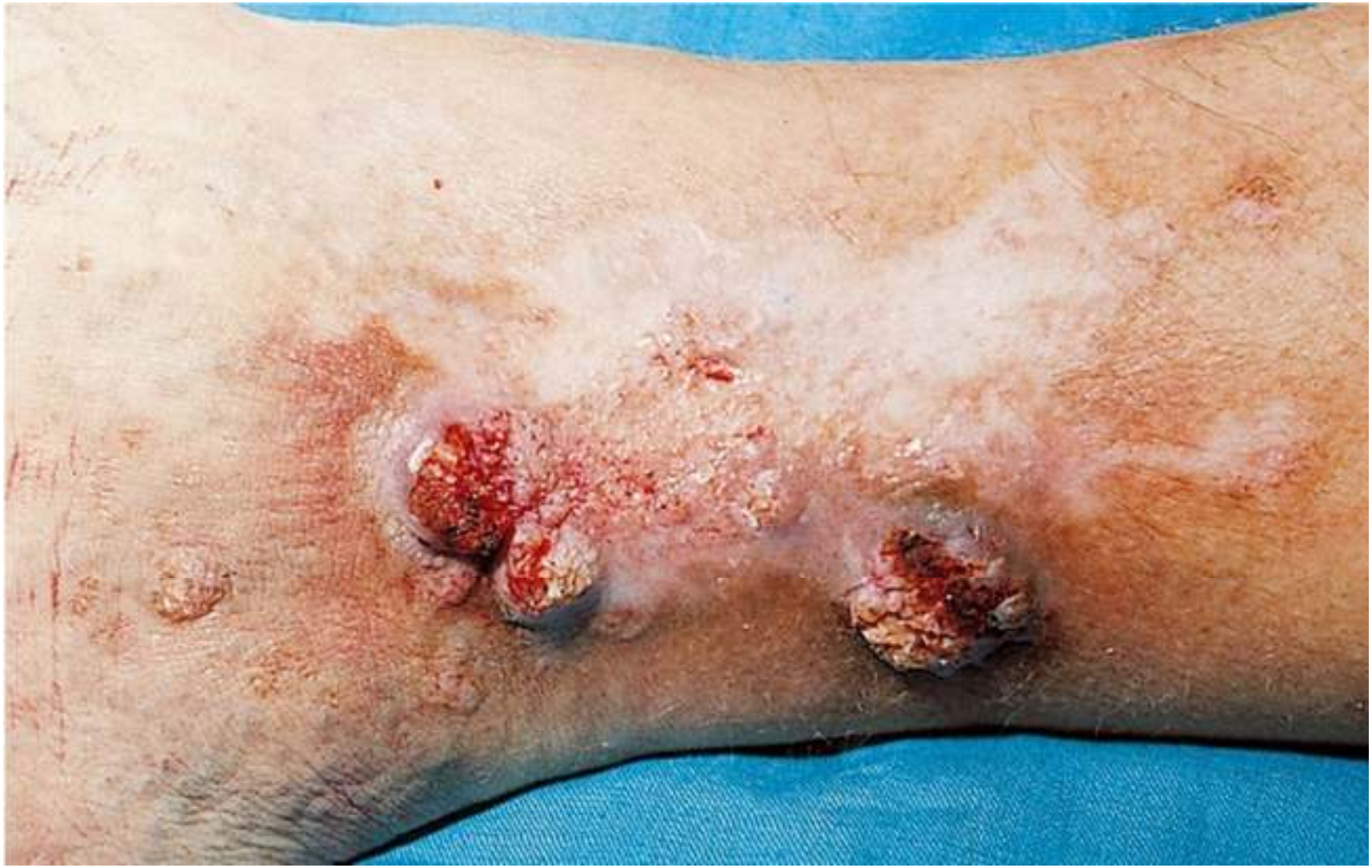
1. ESC ulcero-vegetant:



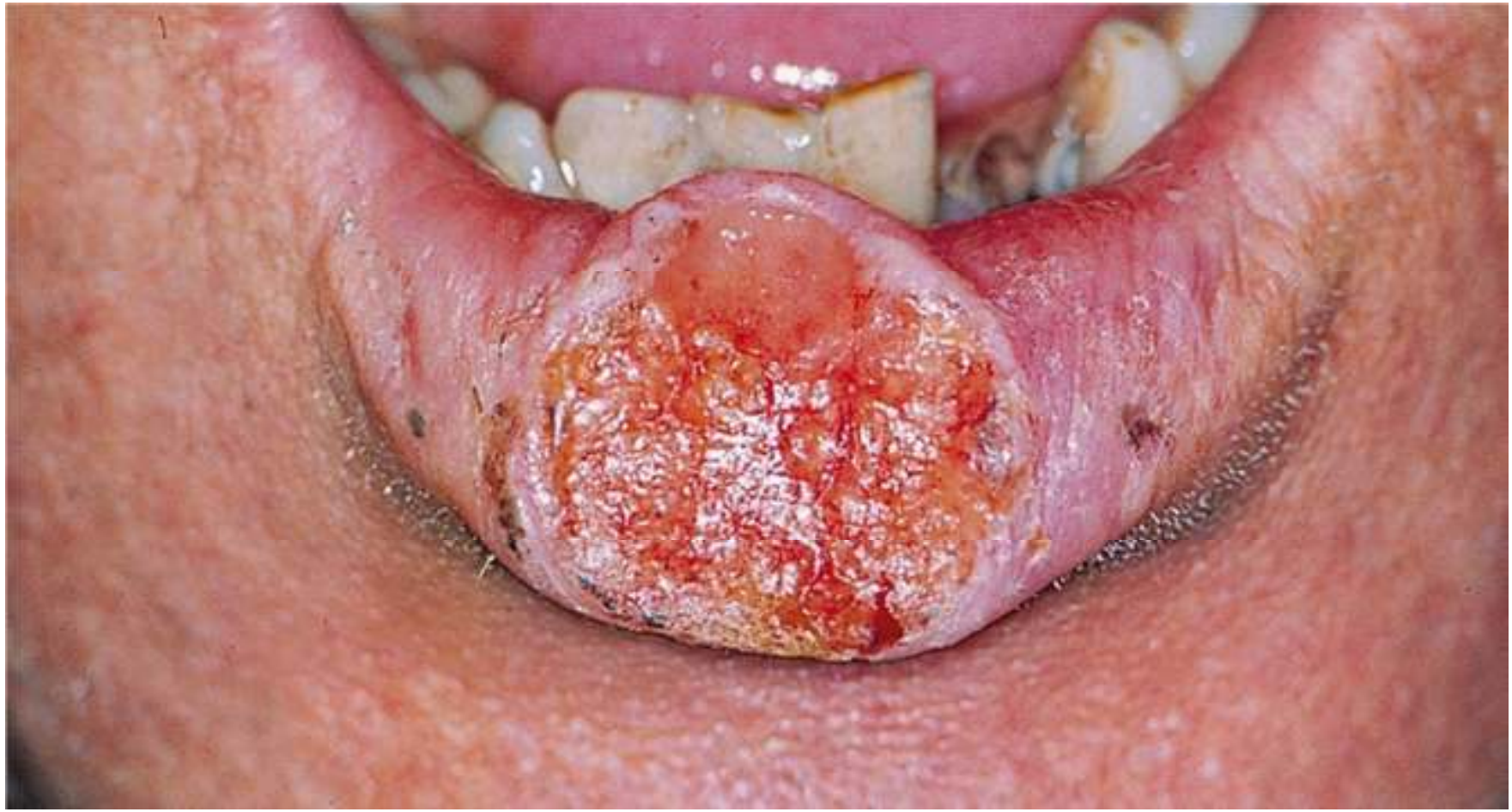
2. ESC nodular:



3. ESC verucos:



4. ESC ulceros (buza inferioară):



Treatment of Squamous Cell Carcinoma

- The type of treatment should be based on histology of lesions and its size, location and degree of metastasis
- Mohs' micrographic surgery offers the highest 5 year cure rate for SCC, and may be treatment of choice for the considered high risk tumors
- Surgical excision is the treatment of choice for lower risk SCC tumors and provides the second-highest cure rate
- Cryosurgery offers good short-term cure rates for low-risk tumors; however, the treatment doesn't provide histologic control which may lead to recurrence
- Laser therapy, in particular the carbon dioxide laser and diode laser, is useful in treating Bowen disease at certain locations
- Radiation therapy can be primary or adjuvant treatment ideal for lower-staged SCC tumors

Treatment of Squamous Cell Carcinoma

- Chemotherapy with topical 5 – fluorouracil, photodynamic therapy, or immunomodulators such as interferon or imiquimod has been proven beneficial in the prevention and treatment of Bowen disease and superficial SCC
- Retinoids, specifically oral isotretinoin, have proven effective in the prevention of SCC; they can also be used in combination with other therapies for the treatment of advanced SCC
- NSAIDS, specifically topical 3% diclofenac, have been effective in the prevention and treatment of AK
- Follow up evaluations are recommended after any treatment because SCC has a high metastatic potential and may recur at a local or distant site

CUTANEOUS MELANOMA
INTRODUCTION

- The incidence of melanoma has increased significantly worldwide over the last several decades
- The American Cancer Society estimates that in 2006 111,900new cases of melanoma were diagnosed
- Invasive melanoma of the skin is the fifth most frequent site for cancer to occur in men and the sixth most frequent site in women, representing approximately 5% of all newly diagnosed cancers
- Mortality rate have also risen over last several decades but not as quickly as incidence rate
- Melanoma accounts for 79% of all skin cancer death
- Although mortality rates have increased, survival for those diagnosed with melanoma have also increased
- The mean age of diagnosis is relatively young at 52 years, which is 10 to 15 years earlier than the mean age of diagnosis in the more common tumors of the breast, lung, colon, and prostate

CUTANEOUS MELANOMA
ETIOLOGY AND PATHOGENESIS

Risk Factors for Cutaneous Melanoma:

1. Ultraviolet radiation exposure:
   - Blistering sunburns at any time in life; intermittent or sporadic high levels of exposure
   - Excessive chronic exposure to sunlight
2. Phenotypic characteristics :
   - Fair skin, inability to tan, tendency to sunburn or freckle (SPT I and II)
   - Blue or green eyes
   - Red or blond hair
   - Numerous or typical nevi and/or more than one atypical nevus
   - Large congenital nevus
3. History of prior melanoma
4. Family history of melanoma
5. Mutation in p16, BRAF and MC1r
6. Xeroderma pigmentosum
7. Immune suppression (debatable)

CUTANEOUS MELANOMA
ETIOLOGY AND PATHOGENESIS

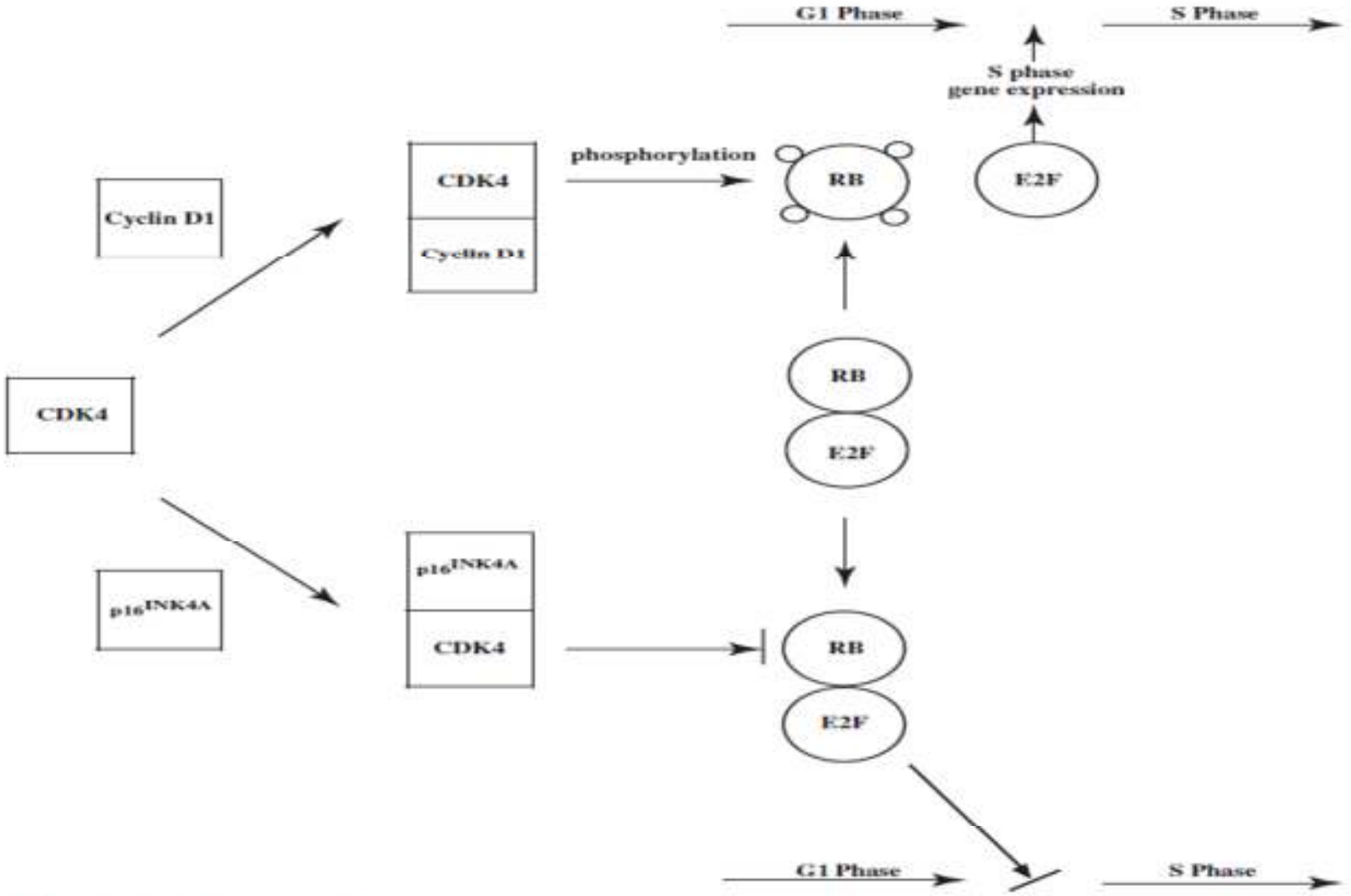
Risk factors:

- **Sun exposure:** epidemiologic studies suggest that periodic, intense sun exposure (particularly during the critical time period of childhood and adolescence) rather than long, continued, heavy sun exposure is most important in melanoma causation, termed the intermittent exposure hypothesis
- **NB!** One blistering sunburn in childhood more than doubles a person's chances of developing melanoma later in life
- **Skin phenotype:** Tendency to sun burn with Fitzpatrick skin phototype I –II are phenotypic features associated with an increased risk of melanoma; melanoma occurs infrequently in type V-VI skin, suggesting that skin pigment plays a protective role
- **Melanocytic nevi:** nevi more often serve as a genetic marker of increased risk rather than a pre-malignant lesion, as most melanomas arise de novo; large congenital nevi are recognized potential precursors of melanoma. Although the degree of risk varies depending on the size of the lesion
- **Family history:** patients with familial melanoma are estimated to account for 10% to 15% of all patients with melanoma: having one first-degree relative with melanoma doubles the risk of melanoma, whereas having three or more first-degree relatives increases the risk 35 to 70 fold
- **Personal history:** a previous history of melanoma increases the risk for primary melanoma with 5% to 15% of individuals developing multiple primary melanomas
- **Immunosuppression:** two to fivefold increase incidence reported post-transplantation in a few studies

CUTANEOUS MELANOMA
ETIOLOGY AND PATHOGENESIS

Genetics pathways:

- **Genetics CDKN2A- CDKN4-p53 Pathway**
- Germline mutations in the chromosome 9p21 tumor suppressor gene , cyclin-dependent kinase inhibitor 2A (CDKN2A), account for approximately 40% of hereditary melanoma cases
- CDKN2A encodes two gene products: p16 and p14ARF (alternative reading frame)
- P16 is a cell cycle regulator that binds and inhibits cyclin-dependent kinases CDK4 and CDK6, thereby inhibiting progression of cells through the G1 phase of the cell cycle
- If p16 function is absent or inactivated by the mutation, unrestrained CDK4 activity phosphorylates the retinoblastoma protein thereby releasing the transcription factor E2-F and inducing S-phase entry
- This culminates in enhanced cellular proliferation which, in the absence of check-point regulation results in unrestrained growth and neoplasia
- The binding partner of the p16 protein is CDK4; functional studies suggest that mutations in CDK4 render the cyclin-dependent protein kinase resistant to p16 inhibition, resulting in a phenotype identical to that from p16 loss
- The p14ARF protein from CDKN2A inhibits cellular oncogene MDM2, which in turn accelerates the destruction of the p53 tumor suppressor gene, which lead to cell proliferation and neoplasia

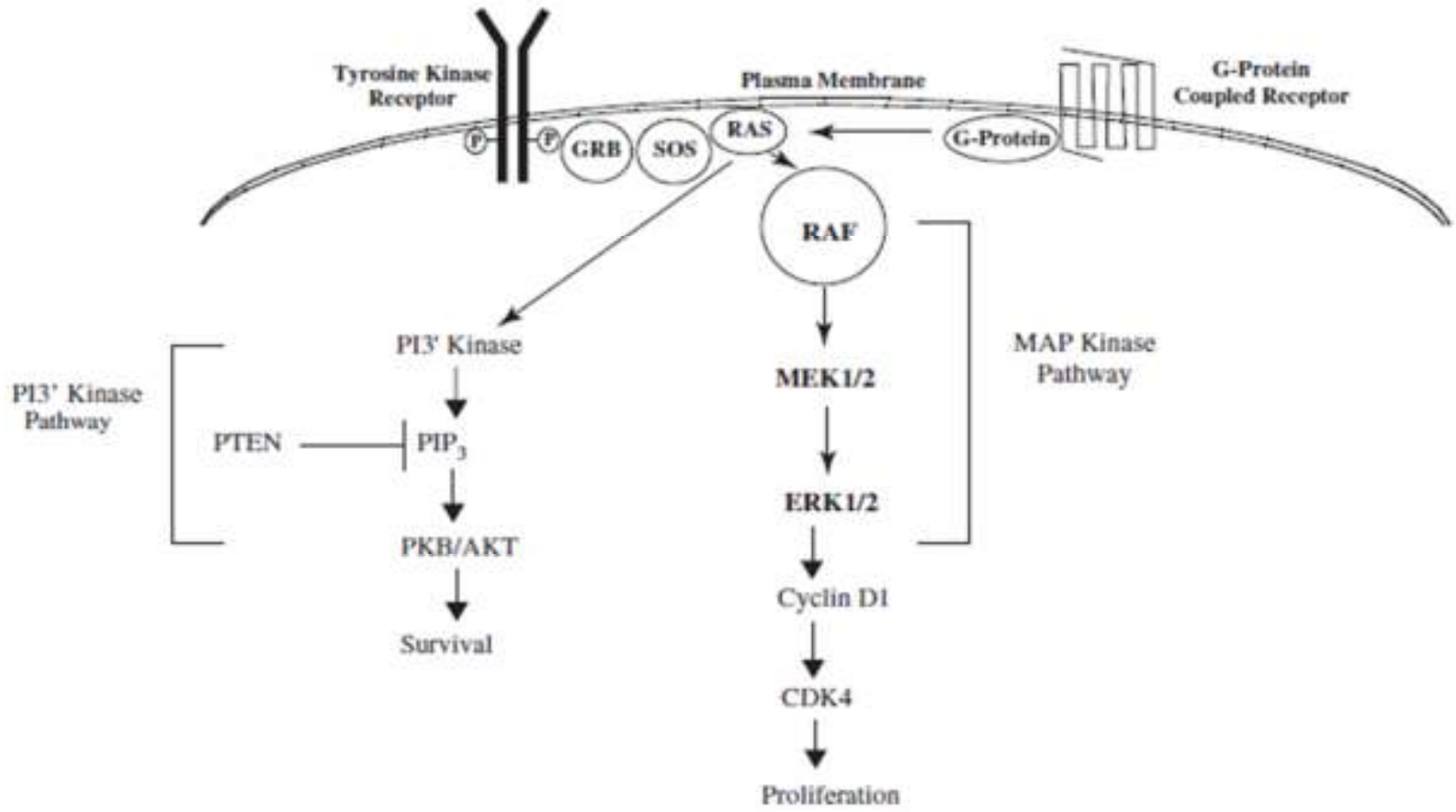


▲ **FIGURE 5-2** CDK4 and $p16^{INK4A}$ regulation of the cell cycle. (upper panel) CDK4 and cyclin D1 bind each other to form a complex that phosphorylates RB through the kinase activity of CDK4. After it becomes phosphorylated, RB releases E2F transcription factors, which induce expression of various genes needed for progressing from G1 to S phase of the cell cycle. (lower panel) $p16^{INK4A}$ binds CDK4 and inhibits its kinase activity. This leads to hypophosphorylation of RB, which prevents release of E2F transcription factors and inhibits progression to S phase.

CUTANEOUS MELANOMA ETIOLOGY AND PATHOGENESIS

Ras signaling pathway:

- B-raf is a serine/threonine kinase, which is a major player in the Ras-Raf-Mek-Erk mitogen-activated protein kinase (MAPK) signaling transduction pathway that regulates cell growth, proliferation and differentiation response to various growth factors, cytokines and hormons
- The stimuli activate the G-protein Ras by inducing the exchange of guanosine 5'-diphosphate for guanosine 5'-triphosphate, which than binds and activate Raf
- Raf phosphorylates and activates Mek, which in turn phosphorylates and activates MAPK
- This signaling cascade serves to intracellularly amplify the extracelullar signals mediated by growth factors
- There are three functional Raf proteins in humans A-raf, B-raf and C-raf; B-raf has a much higher basal kinase activity than either A-raf or C-raf
- BRAF mutations are significantly more common in melanomas occuring on skin subject to intermittent sun exposure



▲ **FIGURE 5-3** RAS signaling pathway. RAS-mediated signaling may be activated by tyrosine kinase or G-protein-coupled cell surface receptors. RAS activates the MAP kinase and PI3′ kinase effector pathways. RAF serine/threonine kinases function immediately downstream of RAS and activate signaling through the MAP kinase pathway, resulting in cell proliferation. PI3′ kinase activity produces PIP_3, leading to phosphorylation of PKB/AKT and promoting survival. The PI3′ kinase pathway may be inhibited by PTEN, which dephosphorylates PIP_3.

CUTANEOUS MELANOMA ETIOLOGY AND PATHOGENESIS

Tumorigenesis and Tumor Progression

- Five stages of malignant transformation and tumor progression in melanocytes have been suggested, based on clinical, histopathologic, immunopathologic, cytogenetic and *in vitro* properties:

1. Benign melanocytic nevi
2. Atypical nevi
3. Primary malignant melanoma, radial growth phase
4. Primary malignant melanoma, vertical growth phase
5. Metastatic malignant melanoma

- It's believed that with each successive step of tumorogenesis, a new clone of cells emerges with growth advantages over the surrounding tissue, resulting in "clonal expansion"
- It has been postulated that a critical step in tumor progression of melanoma may be transition from radial to vertical growth phases

CUTANEOUS MELANOMA ETIOLOGY AND PATHOGENESIS

The radial growth phase:

- Consist of primarily intraepidermal proliferation of melanoma cells, but also invasion of the papillary dermis by small numbers of cells that have gained a growth advantage
- These cell are thought o have capacity for autonomous proliferation in this location, but not for aggregative growth
- Radial growth phase cells are characterized by the presence of E-cadherin, an adhesion molecule that interacts with keratinocytes and impedes migration of the cells from their intraepidermal location
- Melanoma in this phase are probably incapable of metastasis

CUTANEOUS MELANOMA ETIOLOGY AND PATHOGENESIS

The vertical growth phase:

- Is signaled by the property of aggregative growth, resulting in the formation of expansile nests or nodules of cells
- Among other characteristics, vertical growth phase cells lose E-cadherin and express N-cadherin, a molecule that interacts with fibroblasts, macrophages and endothelial cells
- This latter interaction may facilitate intravasation of the malignant cells

CUTANEOUS MELANOMA
CLINICAL FINDINGS

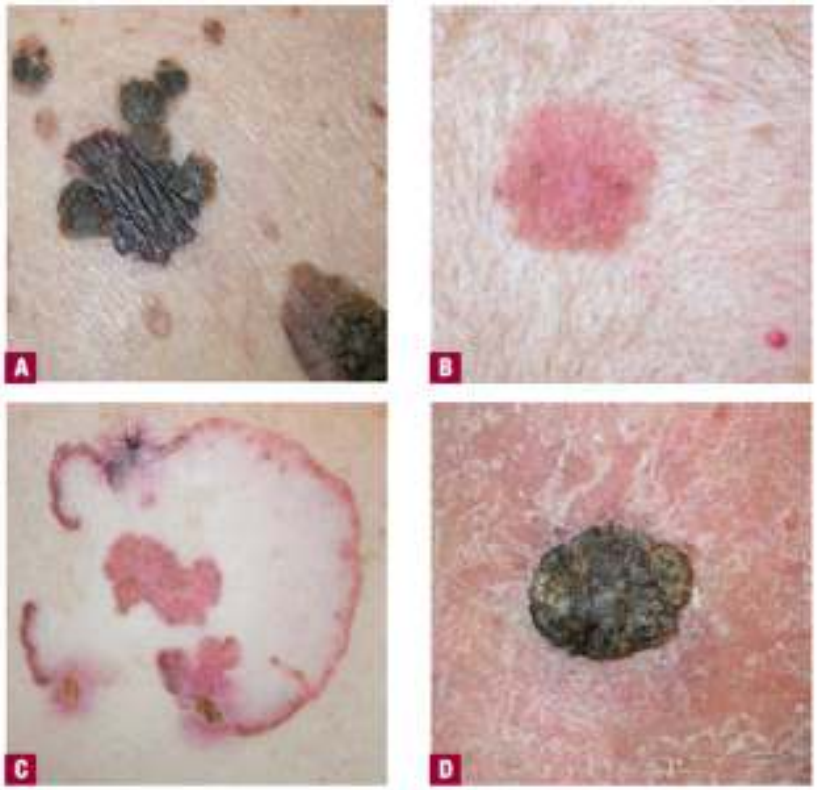
Sub-types of Melanoma

Superficial spreading melanoma:

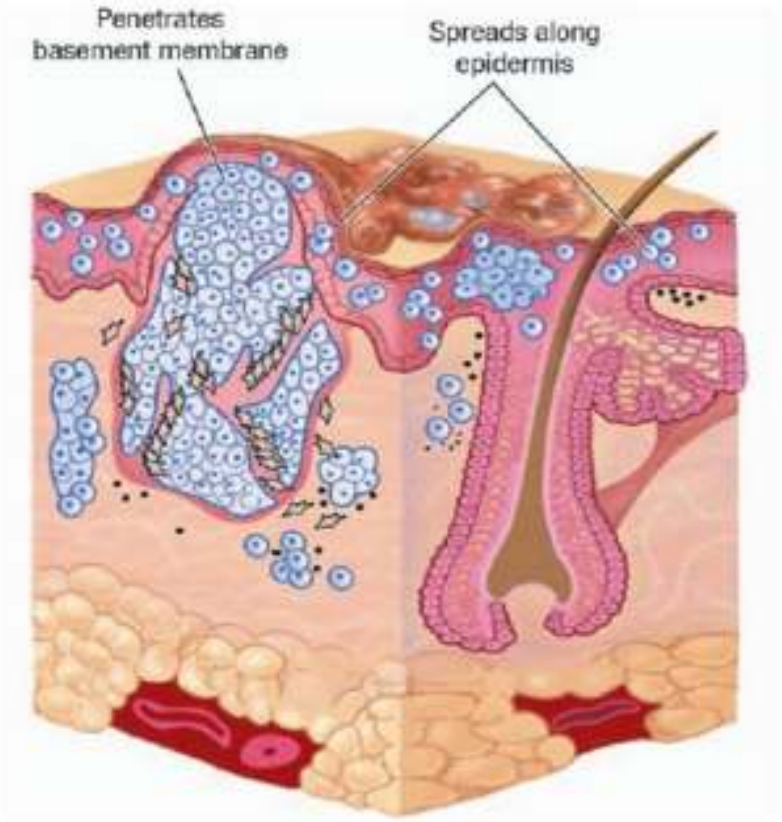
- Is the most common subtype, accounting for approximately 70% of all cutaneous melanomas
- Its diagnosed most commonly in the fourth and fifth decades on intermittently sun-exposed areas; most frequently the lower extremities of women and upper back of men
- Pain, pruritis
- Size often > 1cm (range 2mm to 15 cm)
- Initially macular, later stages may be papular and nodular
- Asymmetrical
- Irregular and often notched borders
- Variation of color with admixture of tan, brown, black, blue, gray, white, red
- May be entirely skin-colored (amelanotic) or black
- Ulceration and bleeding can be present
- **Differential diagnosis:** atypical nevus, common nevus, seborrheic keratosis, basal cell carcinoma

CUTANEOUS MELANOMA CLINICAL FINDINGS

Superficial spreading melanoma shows a broad range of appearance



Histolopathological architecture



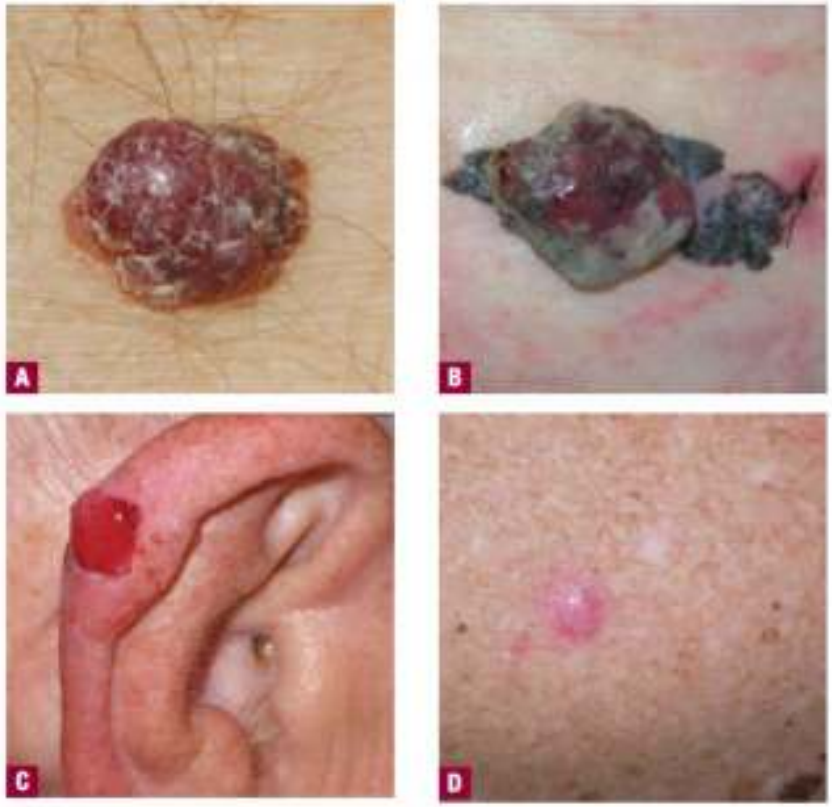
CUTANEOUS MELANOMA CLINICAL FINDINGS

Nodular melanoma

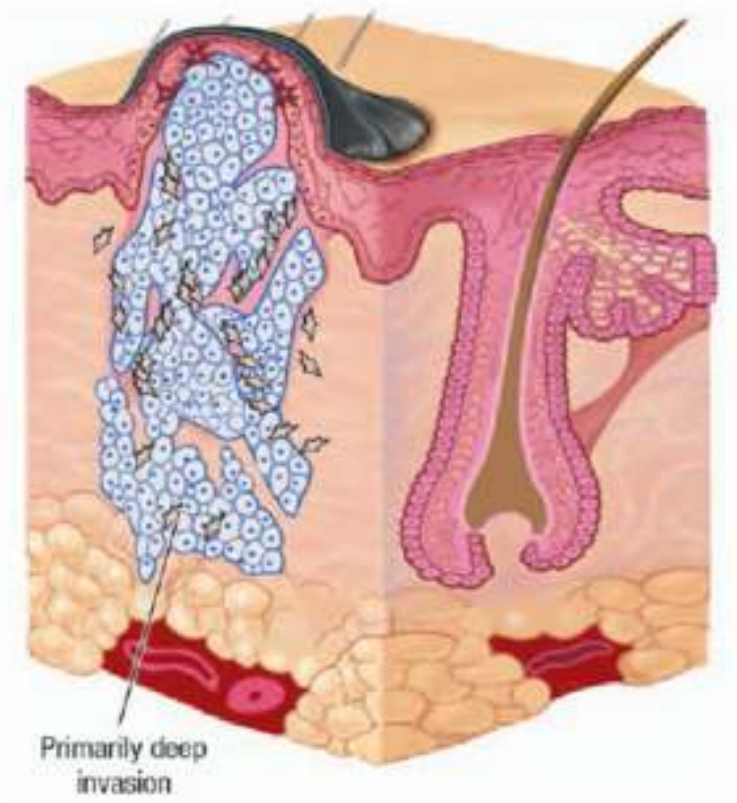
- Nodular melanoma is the second most common melanoma sub-type and accounts for approximately 15 – 30 % of all melanomas;
- the median age of onset is 53 years, and the trunk is the most common site\is remarkable for rapid evolution, often arising over several weeks to months
- Papule or nodule, pigmented or amelanotic
- Often protuberant, polypoid
- Black, blue-black, pink
- Ulceration bleeding
- Asymmetry but symmetry may be present
- Often well-defined borders

CUTANEOUS MELANOMA CLINICAL FINDINGS

Nodular melanoma



Histolopathological architecture



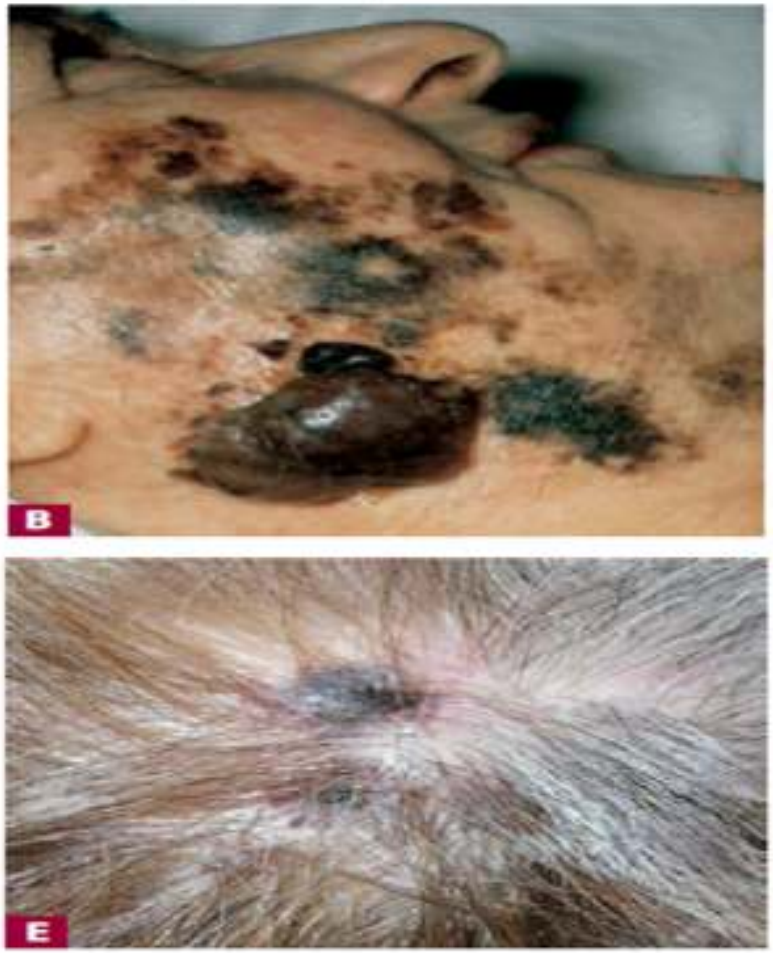
CUTANEOUS MELANOMA CLINICAL FINDINGS

Lentigo maligna (Solar) melanoma

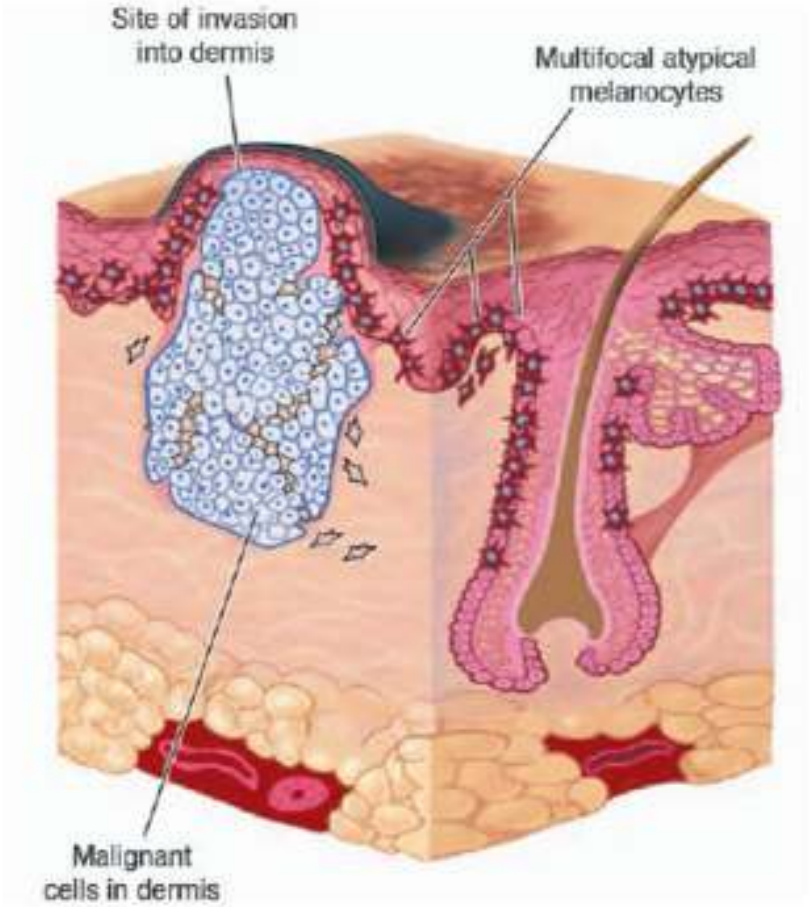
- Age 60-70 years
- Men = Women
- Sun-exposed surfaces: cheek (most common), nose, forehead, ears, neck
- Dorsal surfaces of the hands
- 0,2 – 20 cm in diameter
- Tan, brown, black, macule or patch early lesions
- Pink, gray, white with progression and ares of regression
- Papule or nodule, pigmented or amelanotic (advanced)
- Ulceration and bleeding
- Asymmetry
- Irregular, notched borders

CUTANEOUS MELANOMA CLINICAL FINDINGS

Lentigo maligna melanoma



Histolopathological architecture



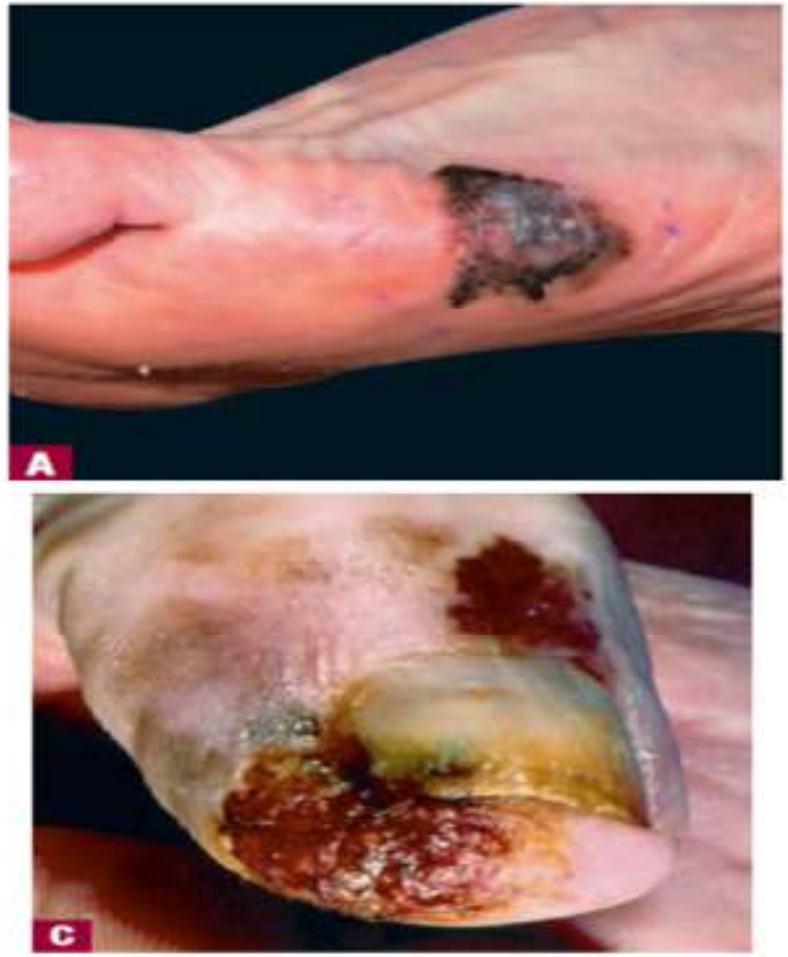
CUTANEOUS MELANOMA CLINICAL FINDINGS

Acral lentiginous melanoma

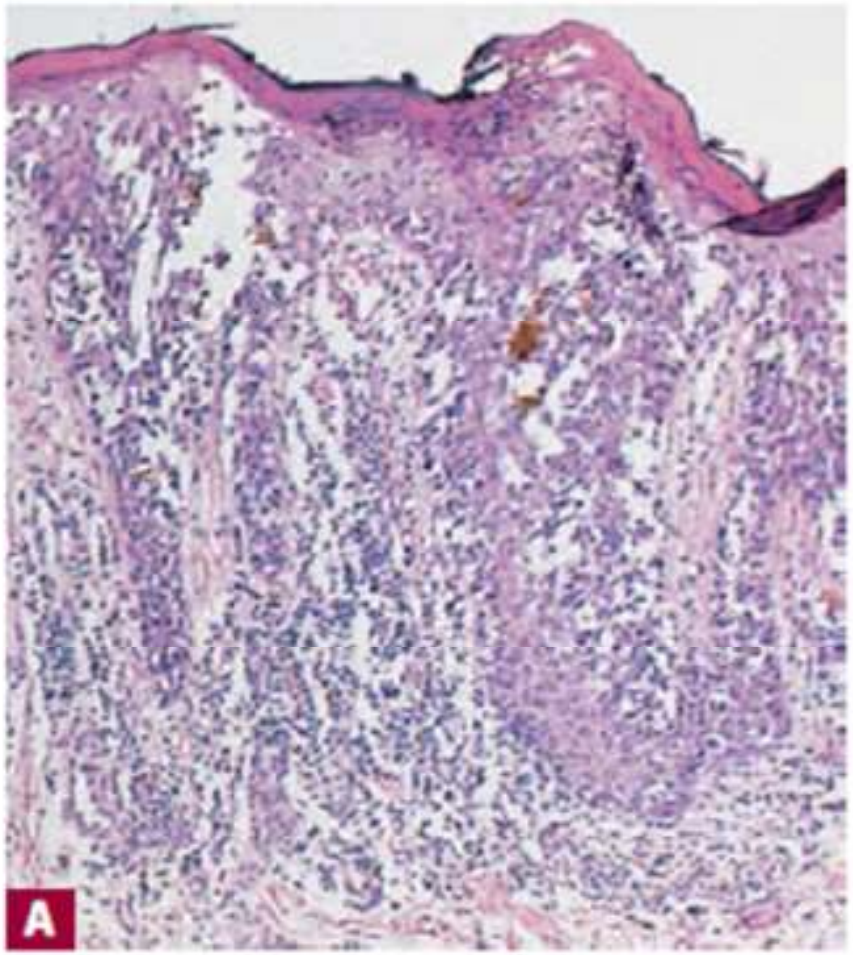
- Age 60-70 years
- Men=Women
- Equal incidence in all racial groups
- **Localization:**
- Glabrous (volar) skin and nail unit:
  - Palms, digits 85% of acral melanoma
  - Nail unit 15%
- Feet 90% of cases:
  - ✓ Soles 68 to 71%
  - ✓ Toes 11%
  - ✓ Nail units 16 to 20%
- **NB!** Hutchinson sign, the finding of pigmentation of the posterior nail fold, has been considered an ominous finding associated with advanced subungual melanoma
- 0,3 – 12 cm in diameter
- Often jet-black macule early but also tan, brown, gray, blue, pink, white
- Pigmented or amelanotic papule, nodule (advanced) with ulceration, bleeding, eschar
- Irregular borders, notching

CUTANEOUS MELANOMA CLINICAL FINDINGS

Acral melanoma



Histolopathological architecture



CUTANEOUS MELANOMA
CLINICAL FINDINGS

- **Other variants:**
- Desmoplastic melanoma
- Mucosal melanoma
- Nevoid melanoma
- Spitzoid melanoma

CUTANEOUS MELANOMA
MAKING A DIAGNOSIS

- Early detection is the key to improving prognosis in melanoma
- Although melanoma may have a characteristic appearance, there is no single clinical feature that ensures or excludes a diagnosis of melanoma
- The well-known ABCD acronym for melanoma detection was developed in 1985 and continues to be useful tool for the physicians

ABCD checklist:

- **A** stands for **asymmetry** (one half is not identical to the other half);
- **B** for **border** (irregular, notched, poorly defined borders as opposed to smooth and straight edges);
- **C** for **color** (having varying shades from one area to another);
- **D** for **diameter** (greater than 6 mm, approximately the size of a pencil eraser)
- Lesions having this characteristics may potentially represent melanoma
- Another diagnostic aid that is useful in detecting melanoma is the “ugly duckling” sign: a pigmented lesion that is different from other pigmented lesions on a particular individual should be approached with a high index of suspicion; this is based on the premise that within the individual, nevi should globally share a common apearance or family resemblance, even in the individual with atypical nev, the nevi should be morphologically similar

CUTANEOUS MELANOMA MAKING A DIAGNOSIS

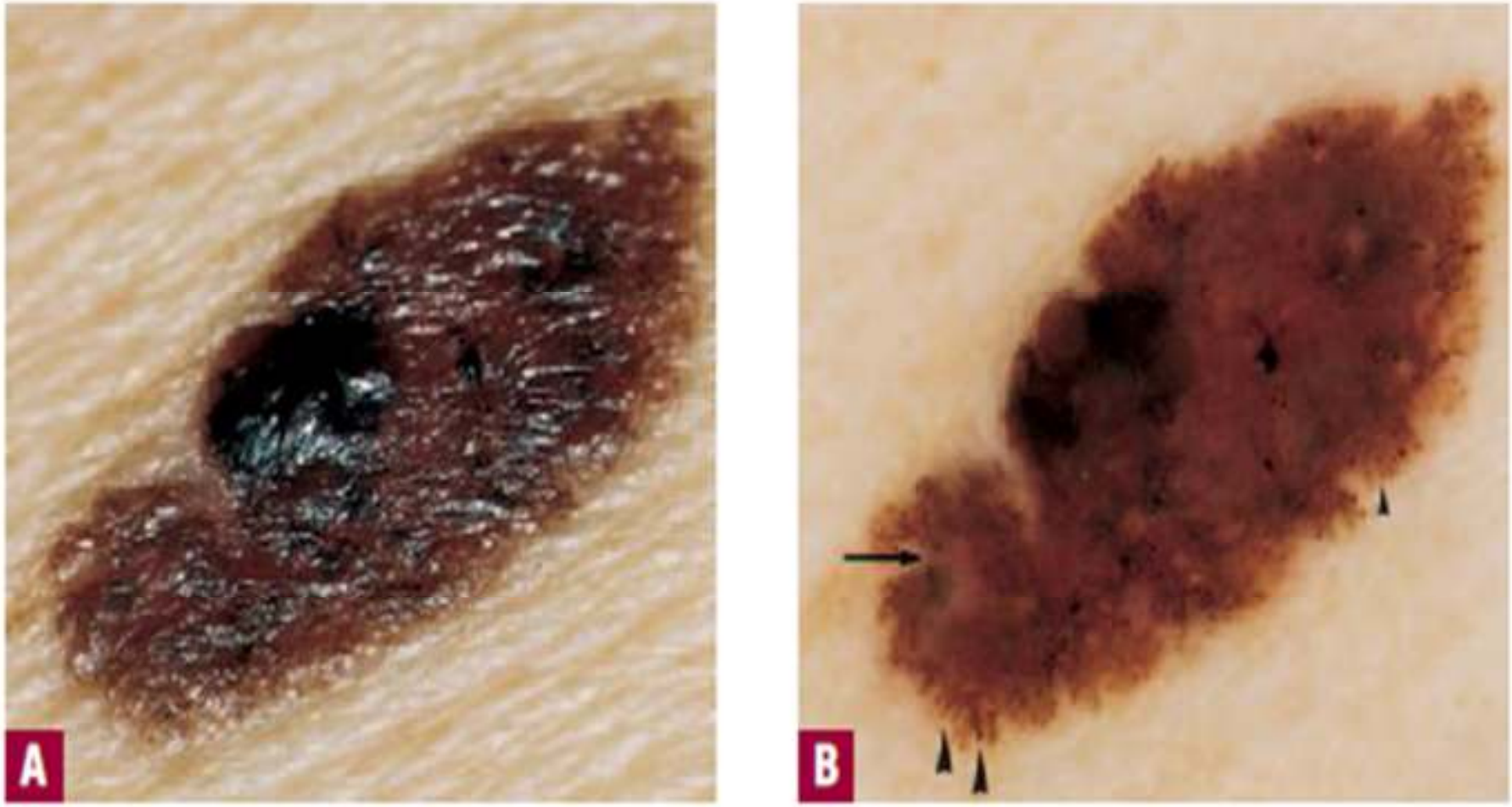
- **History** is vary important in the evaluation of the lesion
- Change in color and increase in size (or a new lesion) are the two most common early characteristics noticed by the patients that may be useful in discriminating between melanoma and other benign lesions
- In addition to change in color, size, or shape/elevation, persistent lesional itching I also an earlier symptom
- Ulceration, bleeding and tenderness generally sinify a more advanced primary lesion
- Therefore, it is important to ask patients if lesions have changed overtime and to pay particular attention to changing or symptomatic lesion

CUTANEOUS MELANOMA MAKING A DIAGNOSIS

- **Physical examination**
- The skin examination should be conducted under optimal lighting and encompass the entire skin surface, including the scalp, external ocular/conjunctivae, oral mucosa, genitalia, buttocks, and palms, soles
- Melanomas in hidden anatomic sites are associated with thicker tumors at diagnosis, often due to latter detection
- Total body and lesional photography may be useful, especially in high-risk patients with numerous nevi
- The use of photo to document the appearance of skin lesions or the absence of a skin lesion can allow for better and earlier detection of a changing or new lesion
- If a lesion suspicious for melanoma is found on skin examination, palpation of the regional lymph nodes should be performed to evaluate for lymphadenopathy

CUTANEOUS MELANOMA MAKING A DIAGNOSIS

- **Dermoscopy**
- Dermoscopy is a simple, non-invasive technique in whicih a liquid, usually immersion oil, is applied to the lesion, which is than examined with a hand-held lens (magnification usually 10x) or a commercially available device
- **Dermoscopy signs in melanoma:**
- ***The pigment network*** seen as aseries of pigmented lines, identifies a pigmented lesion as being melanocytic; it correlates to pigment along rete ridges, both in basal layer and nests along the dermal-epidermal junction
- ***Brown globules*** correlate with pigmented nests of melanocytes in the papillary dermis
- ***Black dots*** are focal collections of melanocytes and clumps of melanin in the stratum corneum
- ***A blue grey veil*** represents regression in melanoma

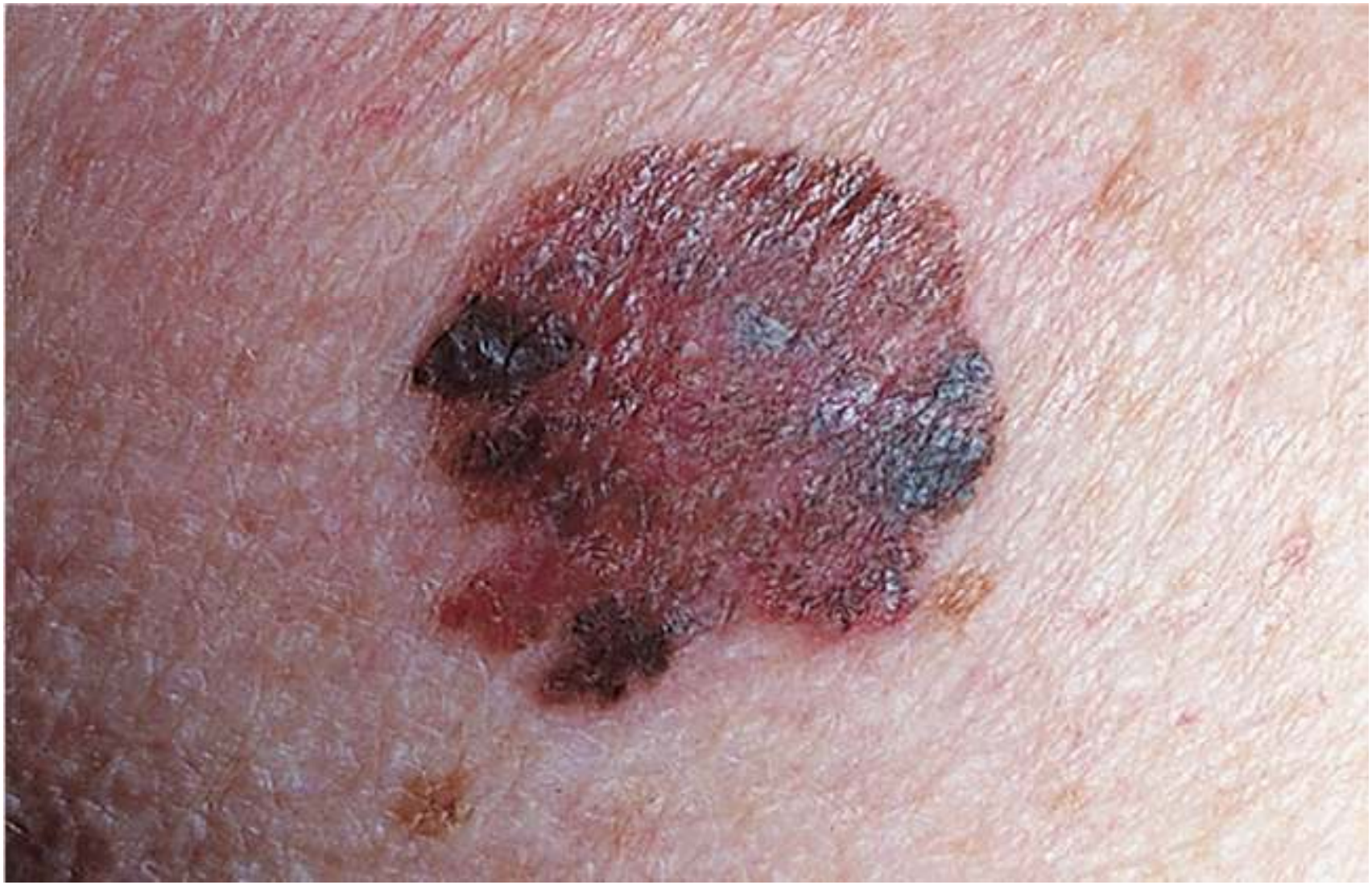


▲ **FIGURE 124-8** **A.** Superficial spreading melanoma as viewed by close inspection with a hand-held lens or a dermoscope without oil immersion. **B.** With oil immersion, new features become apparent, such as the pigment network, brown globules (*small arrowhead*), pseudopods (*large arrowheads*), and depigmentation, extending irregularly to the periphery of the lesion (*arrow*). (Used with permission from Michael Binder, MD.)

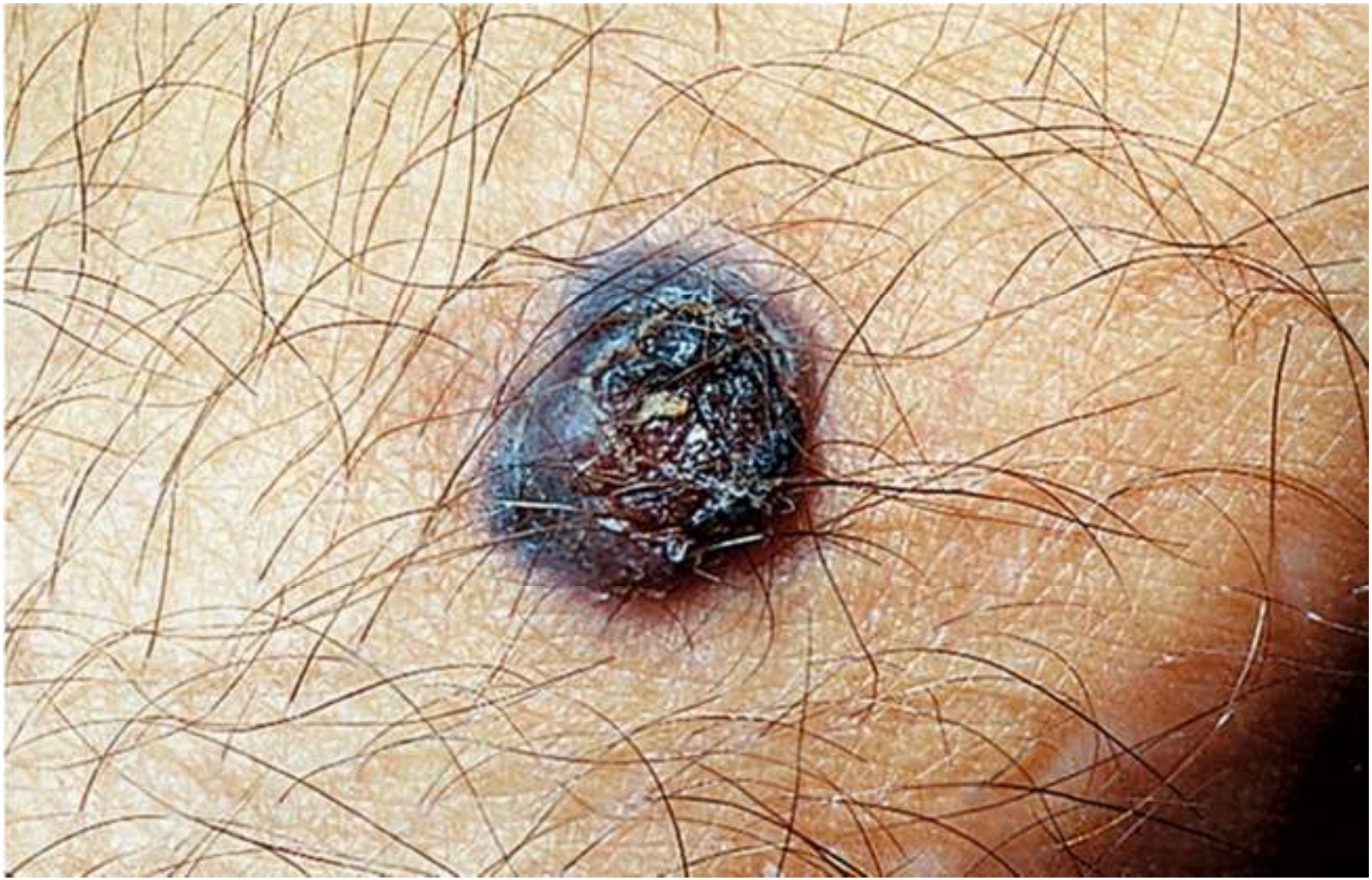
CUTANEOUS MELANOMA MAKING A DIAGNOSIS

- **Histopathology**
- The gold standard for diagnosing melanoma is based on histopathologic evaluation of the biopsy specimen, preferably by adermatopathologist or pathologist experienced with pigmented lesions
- The histopathologic diagnosis of melanoma is based on the assessment of a constellation of findings, including both architectural and cytologic features; no single feature is diagnostic
- **Cytologic atypia:** cellular enlargement, nuclear enlargement, nuclear pleomorphism, hyperchromasia of nuclei, the presence of mitoses especially in the dermis, is considered necessary for a diagnosis of melanoma
- **The major architectural features of melanoma include:**
  - Asymmetry
  - Poor circumscription
  - Large size > 5 to 6 mm
- Nests of melanocytes in the lower epidermis and dermis vary in size, shape, with lack of maturation
- Pagetoid spread of melanocytes
- The different sub-types of melanoma have histopathologic differences as well
- **Immunohistochemistry** may be useful for the diagnosis of melanoma, especially in poorly differentiated neoplasms

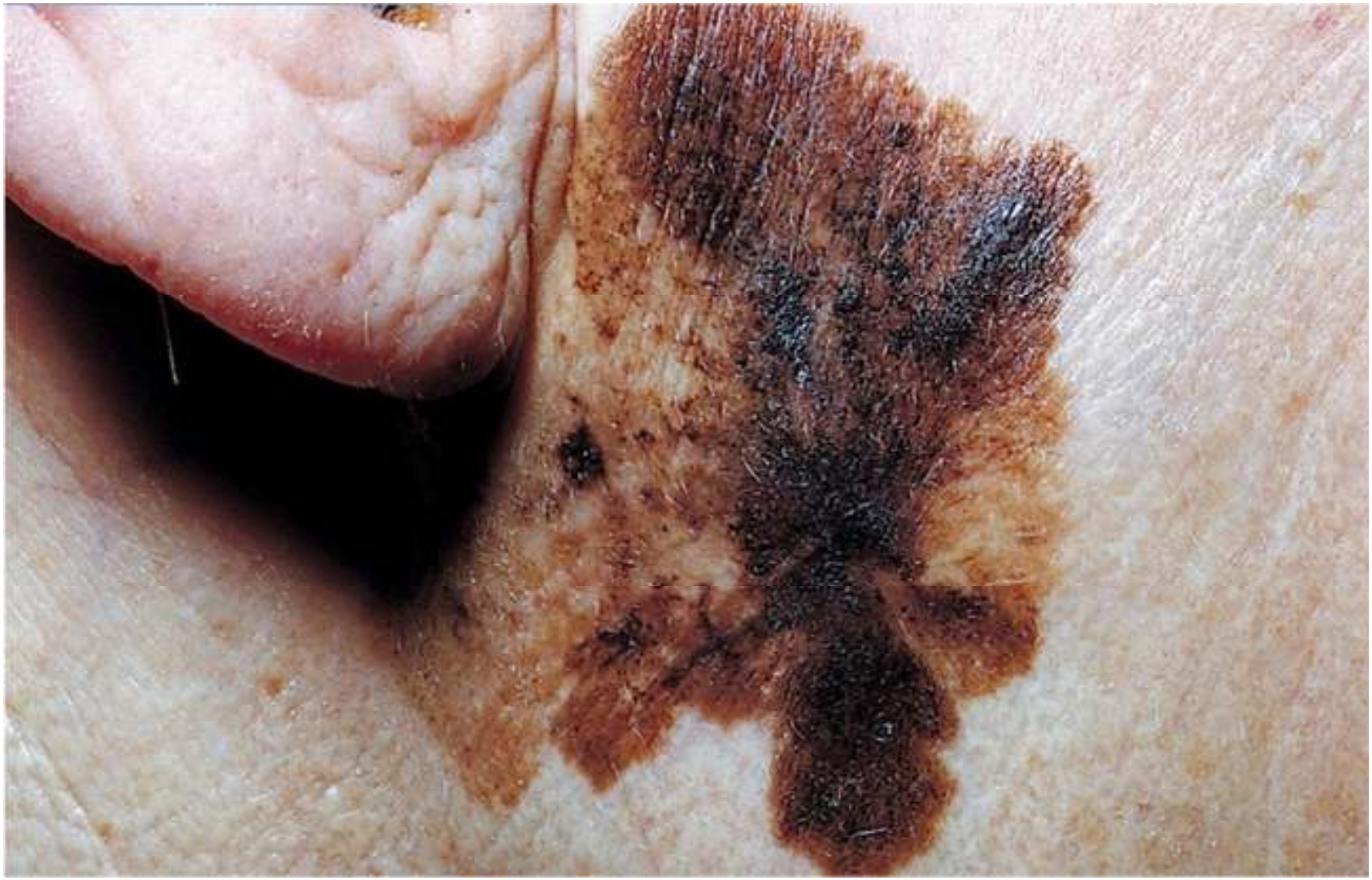
1. Melanom superficial extensiv:



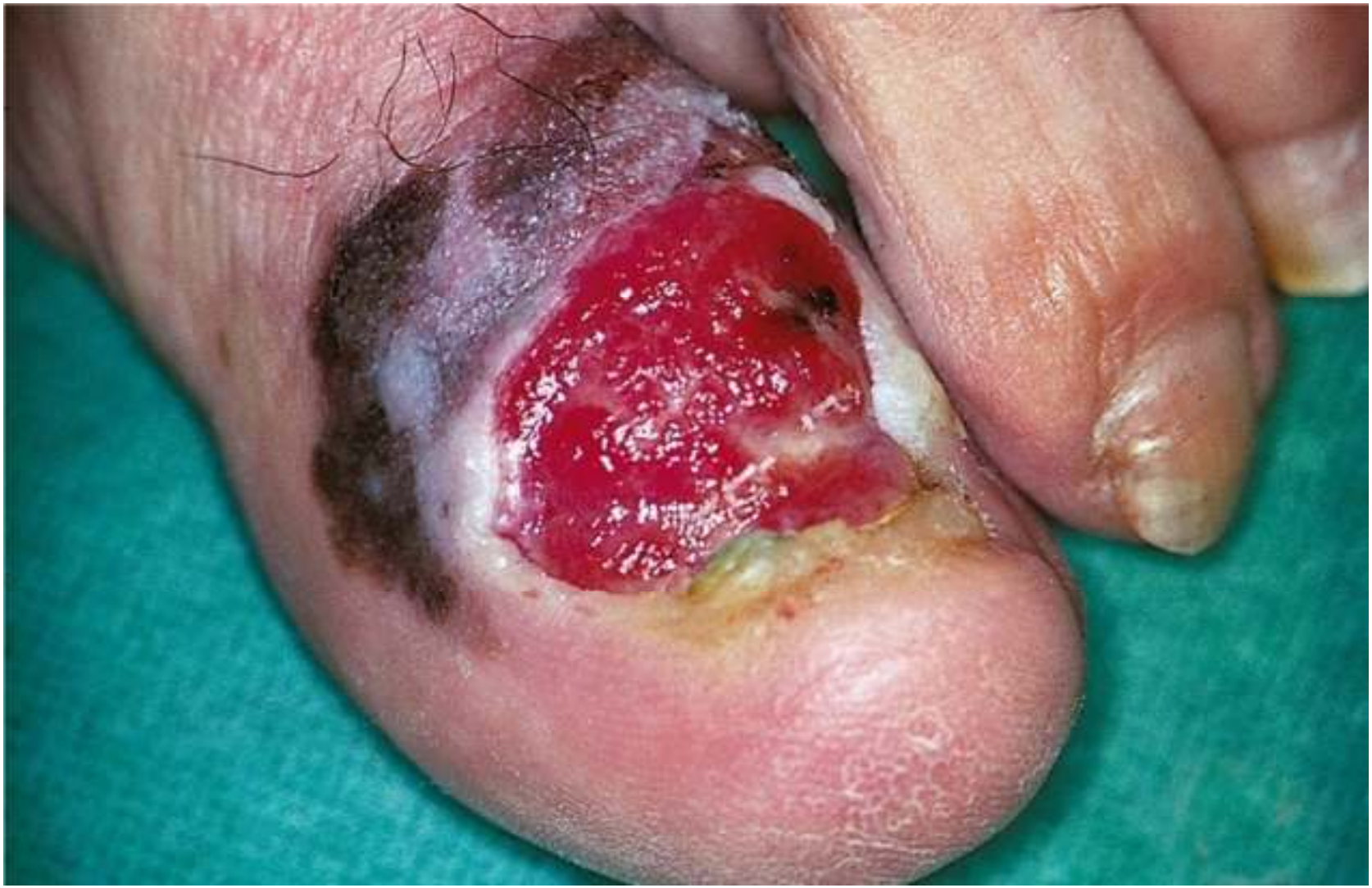
2. Melanom nodular:



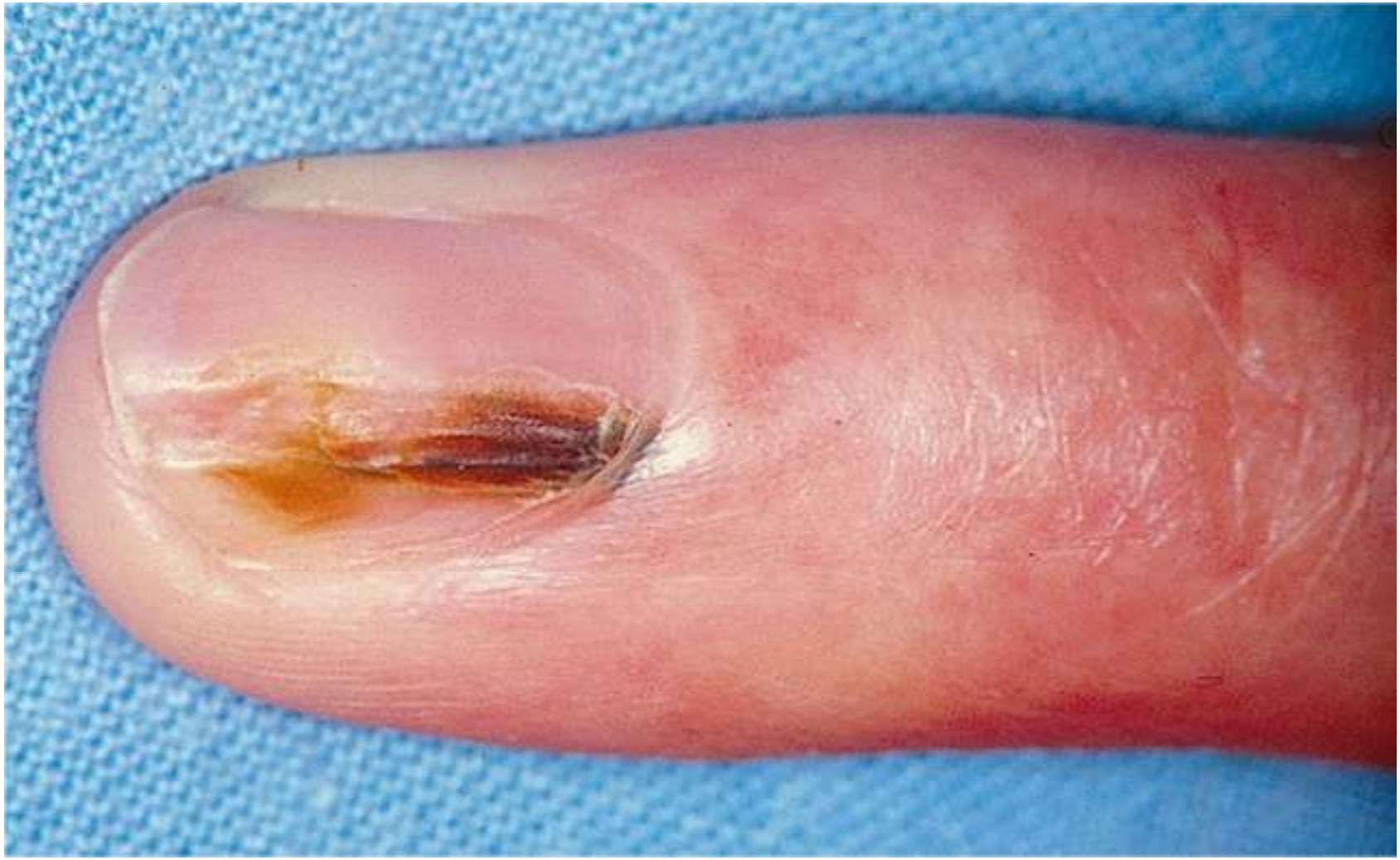
3. Lentigo malign al bătrânilor:



4. Melanom acral ulcerat:



5. Melanom acral unghial:



CUTANEOUS MELANOMA
PROGNOSIS AND CLINICAL COURSE

- **Prognostic factors in microstaging**
- *Tumor thickness* is the single most important prognostic factor for survival and clinical management in localized stage I and II cutaneous melanoma
- as originally described by Breslow, thickness is measured from the top of granular layer of the epidermis to the greatest depth of tumor invasion using an ocular micrometer and measured in mm
- Survival decreases with increasing Breslow depth
- *Ulceration* represents an independent prognostic factor for localized melanoma and is highly correlated with survival
- The presence of ulceration in the primary confers a higher risk of developing advanced disease and lower survival rate
- Ulceration correlates with the thickness it frequently occurs in thick melanomas
- *Mitotic rate* measured as the number of mitoses per square mm, is usually counted as the number of mitosis seen in five high-power microscope fields (the equivalent of a 1 mm^2 area), starting in the field with the most mitoses
- Patients with a mitotic rate 0 mitosis/mm^2 have a significantly better survival than those with ≥1mitosis/ mm^2
- *Angiolymphatic invasion* : vascular involvement denotes the invasion of tumor cells into the microvasculature in the dermis; vascular invasion significantly increases the risk of relapse, lymph node involvement, distant metastases and death

CUTANEOUS MELANOMA
PROGNOSIS AND CLINICAL COURSE

- **Clinical prognostic factors:**
  - **Age** increasing patient age portends a worse prognosis with respect to overall survival rates
  - **Gender** women have better survival rates, than men, even after adjustment for tumor thickness and anatomic site
  - **Anatomic location** melanomas located on the trunk and head and neck were correlated with worse prognosis than melanomas on the extremities

CUTANEOUS MELANOMA
PROGNOSIS AND CLINICAL COURSE

- **Prognostic Factors in Regional Metastases**
- The status of the regional lymph nodes is the most powerful prognostic factor for survival in melanoma
- The presence of regional lymph node metastasis portends a worse prognosis
- The second most important risk factor is tumor burden stratified into micrometastatic disease as determined by **Satellite lymph node (SLN) biopsy:** in clinically node-negative stage I or II patients, SLN status was the most signoficant prognostic fact with respect to disease-free and disease-specific survival
- SLN biopsy is a staging technique used to detected occult nonpalpable micrometastses in regional lymph nodes, this SLN is most likely o contain any tumor cellss that may have metastasized from the primary
- Blue dye or techetium-99 injected intradermally at the primary site was identified in the SLNs 90% of the time and 15 % of the SLN contained melanoma
- Satellite, both clinical and microscopic metastasis around a primary melanoma and in – transit metastasis between the primary melanoma and its nodal basin represent intralymphatic metastases and portend the worst prognosis for regional metastasis

CUTANEOUS MELANOMA
PROGNOSIS AND CLINICAL COURSE

- **Prognostic Factors in the distant metastasis:**
- The presence of distant metastases portends the worst prognosis, with mean survival rates measured in month rather than years
- The most common visceral sites for melanoma metastasis are: the lungs, liver, brain, bone and gastrointestinal tract
- Once metastasis to distant sites have been detected, median survival is approximately 6 to 8 months, and a minority live beyond 1 year

TABLE 124-2
Melanoma TNM Classifications[a]

T CLASSIFICATION	THICKNESS (MM)	ULCERATION STATUS
T1	≤ 1.0	a: without ulceration and level II/III b: with ulceration or level IV/V T2
T2	1.01–2.0	a: without ulceration b: with ulceration
T3	2.01–4.0	a: without ulceration b: with ulceration
T4	> 4.0	a: without ulceration b: with ulceration
N CLASSIFICATION	**NUMBER OF METASTATIC NODES**	**NODAL METASTATIC MASS**
N1	1	a: micrometastasis[b] b: macrometastasis[c]
N2	2–3	a: micrometastasis[b] b: macrometastasis[c] c: in-transit met(s)/satellite(s) without metastatic nodes
N3	4 or more nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic node(s)	
M CLASSIFICATION	**SITE**	**SERUM LACTATE DEHYDROGENASE**
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

TNM = tumor size, node status, metastasis classification.
[a]Six major changes are included in the 2002 version of American Joint Committee on Cancer melanoma staging system:

1. Anatomic level is used only in the staging of thin tumors. Thickness and ulceration are primarily used in the T category. The anatomic level of invasion (Clark levels) is currently understood to be an independent prognostic feature only for thin melanomas. As a result, Clark levels are incorporated only into staging of thin melanomas (≤ 1.0 mm or category T1).
2. Ulceration of the tumor has been added to the staging system. Ulceration is an independent risk factor and portends a higher risk of developing advanced disease. The presence of ulceration "upstages" all patients with stages I to III disease. In a given T grouping, the new system subclassifies patients as "a" for tumors without ulceration, and "b" for tumors with ulceration.
3. The number of metastatic nodes, rather than the size of nodes, is used as a primary criterion in the N staging.
4. The system incorporates a new convention for categorizing patients both clinically and pathologically. This system incorporates date from lymphatic mapping and sentinel node biopsy.
5. In-transit and satellite metastases have been grouped in the same subclassification (N2c). Patients with intralymphatic metastases but no nodal metastases are recognized as having a similar prognosis and are thus grouped together.
6. Distant metastatic melanoma is classified by site(s) of metastases and levels of lactic dehydrogenase detected in serum.

[b]Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

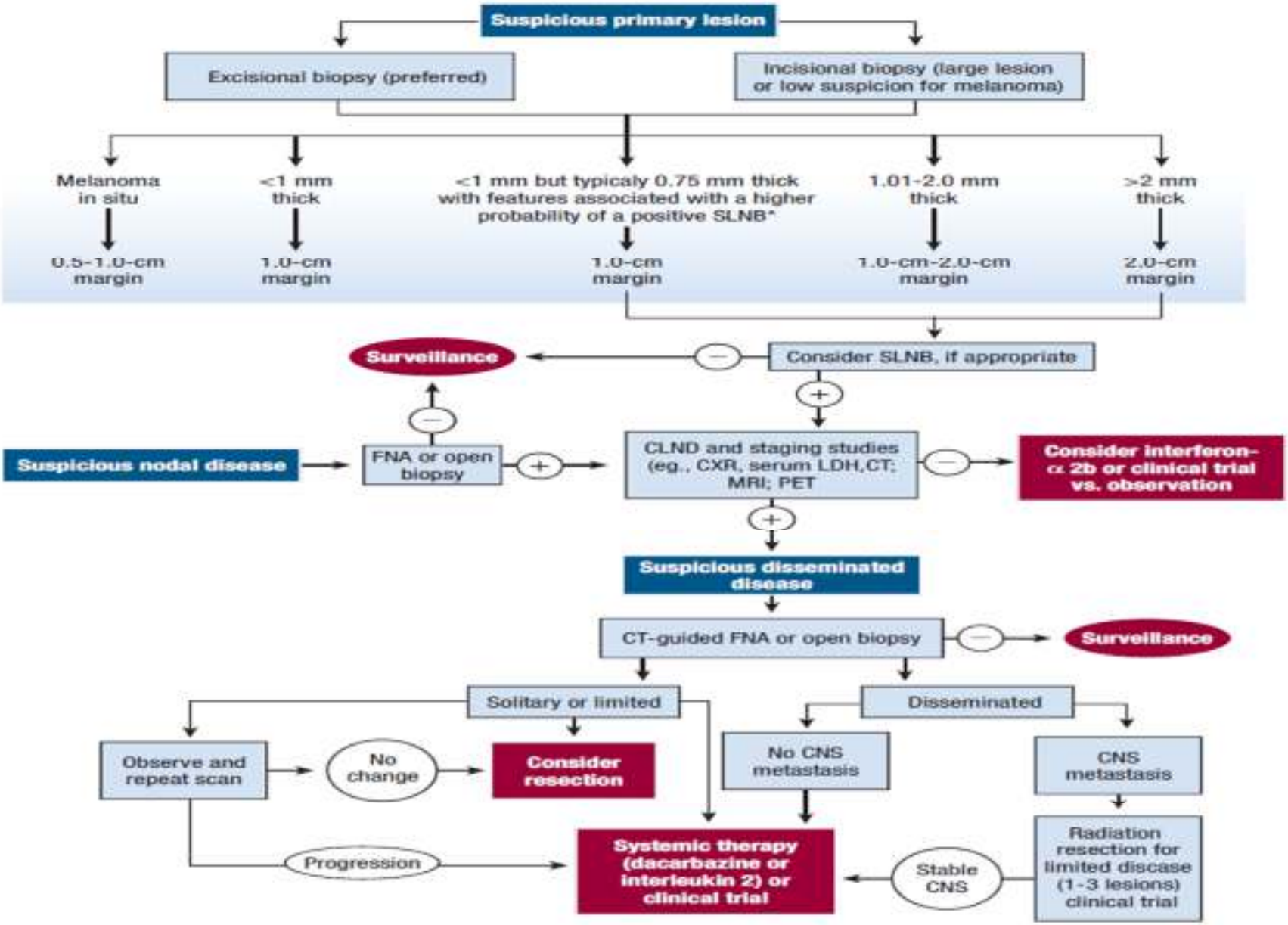
TABLE 124-3
Proposed Stage Groupings for Cutaneous Melanoma

	Clinical Staging[a]			Pathologic Staging[b]		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III[c]	Any T	N1	M0			
		N2				
		N3				
IIIA				T1-4a	N1a	M0
				T1-4a	N2a	M0
IIIB				T1-4b	N1a	M0
				T1-4b	N2a	M0
				T1-4a	N1b	M0
				T1-4a	N2b	M0
				T1-4a/b	N2c	M0
IIIC				T1-4b	N1b	M0
				T1-4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

T = tumor size; N = node status; M = metastasis classification.
[a]Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.
[c]There are no stage III subgroups for clinical staging.
From Balch CM et al: Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* **19**:3635, 2001, with permission.

CUTANEOUS MELANOMA
MANAGEMENT CONSIDERATIONS

- Optimal biopsy for exam of entire lesion is possible
- Elliptical excision or incision for lesions suspicious for melanoma
- Complete skin and physical examination; scanning visceral organs if specifically indicated
- Sentinel lymph node biopsy may be considered for melanomas > 1.00 mm in thickness
- Surgical margins:
  - Melanoma in situ: 0.5 cm margins
  - Melanomas ≤ 2 mm in thickness: 1cm margins
  - Melanomas ≥ 2 mm in thickness: 2 cm margins
- Follow-up examinations related to Breslow thickness, stage etc.
- Every 3-6 months for first 5 years
- Every 6-12 months for the remaining 5 to 10 years
- Treatment of distant and disseminated metastases:
  - Dacarbazine, Temozolomide
  - High-dose bolus interleukin-2 as immunotherapy
  - Novel therapies: Oblimersen sodium (Genasense) degradate a apoptotic suppressor protein and Sorafenib a RAF pathway inhibitor



▲ **FIGURE 124-20** General guideline algorithm for the treatment of cutaneous melanoma. *Ulceration, extensive vertical regression to at least 1 mm thick, young patient age, high mitotic rate, especially in younger persons, shave biopsy with positive deep margin, presence of angiolymphatic invasion, and Clark level IV. CLND = completion lymph-node dissection; CNS = central nervous system; CT = computed tomography; CXR = chest x-ray; FNA = fine-needle aspiration; LDH = serum lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; SLNB = sentinel-lymph-node biopsy. A minus sign indicates no evidence of disease, and a plus sign evidence of metastasis. Patients who are candidates for sentinel-lymph-node biopsy should be referred to a surgeon experienced in performing the procedure so that the benefits and complications can be fully discussed. (From Tsao H, Atkins MB, Sober AJ: Management of cutaneous melanoma. *N Engl J Med* **351**:998, 2004; with permission.)

Prevention

- **Prevention is the most critical measure one can take to decrease the risk of developing skin cancer:**
- avoid sun exposure between the hours of 10 a.m and 4 p.m.;
- sunscreens that protects against UVA and UVB rays should be applied liberally everyday;
- wearing sunscreen, with a protective factor index of at least 30 or higher, may decrease the risk of NMSCs;
- protective clothing is essential such as long-sleeved shirts, long pants, and wide-brimmed hats;
- preventative education must be implemented to encourage patients to be proactive against skin cancer;
- physicians must insist on a follow-up every 3 to 6 months for first year after treatment.

KAPOSI SARCOMA
Background

- Kaposi sarcoma (Kaposi's sarcoma, KS) was described initially in 1872 by a Hungarian dermatologist, Moritz Kaposi
- Kaposi sarcoma is a spindle-cell tumor thought to be derived from endothelial cell lineage
- This condition carries a variable clinical course ranging from minimal mucocutaneous disease to extensive organ involvement
- Kaposi sarcoma can be primarily categorized into four types:
  - epidemic of AIDS-related
  - immunocompromised
  - classic or sporadic
  - endemic (African)

KAPOSI SARCOMA

- **Epidemic AIDS-related Kaposi sarcoma**
- This entity occurs in patients with advanced HIV infection and is the most common presentation of Kaposi sarcoma. It is the most common malignancy seen in HIV-infected patients, especially where access to HAART (highly active antiretroviral therapy) is limited.[1]
- **Immunocompromised Kaposi sarcoma**
- This entity can occur following solid-organ transplantation or in patients receiving immunosuppressive therapy. The incidence of Kaposi sarcoma is increased 100-fold in transplant patients[6, 7] However, individuals with congenital immunodeficient states are not at increased risk for developing Kaposi sarcoma.
- **Classic (sporadic) Kaposi sarcoma**
- This entity typically occurs primarily in elderly men of Mediterranean and Eastern European background. It has a male predominance with a male-to-female ratio of 10-15:1. The age of onset is between 50 and 70 years.
- **Endemic African Kaposi sarcoma**
- This entity occurs primarily in men but also in women and children who are HIV seronegative in Africa and may carry an indolent or aggressive course. It was relatively common before the AIDS epidemic. Since the advent of AIDS, it has increased about 20-fold. In the African countries of Malawi, Swaziland, Uganda, Zambia, and Zimbabwe.[21, 8]

KAPOSI SARCOMA
PATHOPHYSIOLOGY

- Kaposi sarcoma is caused by an excessive proliferation of spindle cells thought to have an endothelial cell origin
- Despite their heterogeneity, the tumors are predominantly composed of KSHV genomic material with immunohistochemical markers of both lymphoid, spindle, and endothelial cells
- Although the cell of origin is still unknown, increased endothelial factor VIIIa antigen, spindle cell markers such as smooth muscle alpha-actin, and macrophage markers such as PAM-1, CD68, and CD14 expressed by these spindlecells have been observed
- This suggests a pluripotent mesenchymal progenitor
- The spindle cells proliferate in a background of reticular fibers, collagen and mononuclear cells including macrophages, lymphocytes and plasma cells
- They tend to be vascular involving in the either the reticular dermis (patch stage) or the entire thickness of the dermis (plaque or nodular stage)

KAPOSI SARCOMA
PATHOPHYSIOLOGY

- Human herpes virus8 (HHV-8) genomic sequences have been identified by polymerase chain reaction in more than 90% of all types of Kaposi sarcoma lesions (including epidemic and endemic forms), suggesting a causative role for this DNA virus. The current working hypothesis is that HHV-8 must be present for the disease to develop. It is transmitted in saliva. Blood-borne transmission has yet to be proved. HIV significantly increases the risk of immune suppression.
- Factors that are thought to contribute to the development of Kaposi sarcoma in individuals infected with HHV-8 and HIV include an abnormal cytokine milieu associated with HIV infection with angiogenic cytokines—IL-1 beta, basic fibroblast growth factor (bFGF), acidic fibroblast growth factor, endothelial growth factor, and vascular endothelial growth factor.
- Other cytokines include IL-6, granulocyte-monocyte colony stimulating factor (GM-CSF), transforming growth factor beta (TGF-beta), tumor necrosis factor (TNF), and platelet-derived growth factor alpha (PDGF-alpha from interstitial and mononuclear cells. Oncostatin M, IL-1, IL-6, fibroblast growth factor, tumor necrosis factor (TNF), and the HIV-tat protein all of which originate from HIV-infected T cells act as costimulants for Kaposi sarcoma cells.

KAPOSI SARCOMA
PATHOPHYSIOLOGY

- Thus, Kaposi sarcoma may be caused by HHV-8 (KSHV) with stimulation by autocrine and paracrine growth factors secreted by the spindle cells themselves as well as the supporting network of mononuclear and endothelial cells
- Coinfection with HIV may create a more aggressive course, which is mitigated by effective antiretroviral therapies
- Indeed, the risk of Kaposi sarcoma development is amplified 500-10,000 times in patients coinfected with KSHV and HIV
- **Transmission**
- KSHV is now thought to be largely transmitted by saliva.
- Although associated with sexual risk factors, these may just be a surrogate for close contact
- Heterosexual risk factors largely do not play a role here. Transmission by blood or blood products can occur but use of leukopoor stored blood is likely to significant reduce this risk
- Transmission of KSHV may occur during solid organ donation, but it does not appear to affect clinical outcome in terms of survival or graft loss
- There may be an increase of incidence of KS in patients in solid organ recipients that are seropositive versus those that seronegative.[42]

KAPOSI SARCOMA EPIDEMIOLOGY

- Prior to the advent of HIV, Kaposi sarcoma was common in central Africa and prevalent in Mediterranean countries and the Middle East
- In Africa, the incidence of Kaposi sarcoma is very high at 37.7 per 100,000 in men and 20.5 per 100,000 in women
- In Europe, the highest rates of classic Kaposi sarcoma are in Sicily (Ragusa, 30.1 cases per million in men/5.4 cases per million in women) and Sardinia (24.3 cases per million in men/7.7 cases per million in women)
- **Mortality/Morbidity**
- AIDS-related Kaposi sarcoma, unlike other forms of Kaposi sarcoma, tends to have an aggressive clinical course
- Morbidity may occur from extensive cutaneous, mucosal, or visceral involvement. In patients receiving HAART, the disease often has a more indolent clinical course or may regress spontaneouslyt
- The most common causes of morbidity include cosmetically disfiguring cutaneous lesions, lymphedema, gastrointestinal involvement, or pulmonary involvement (see History and Physical)
- Pulmonary involvement is the most common cause of mortality with uncontrolled pulmonary hemorrhage

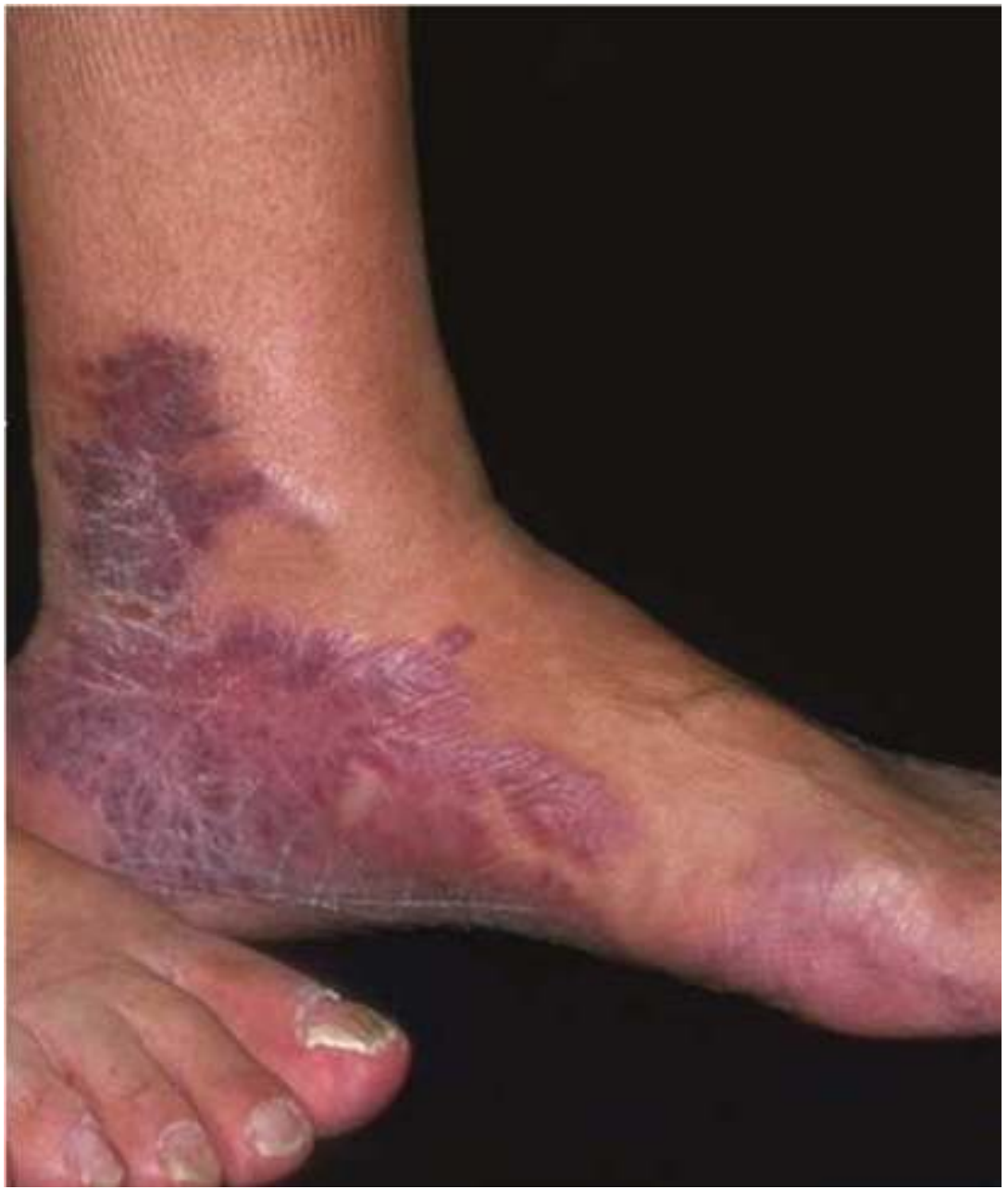
KAPOSI SARCOMA EPIDEMIOLOGY

- **Sex**
- AIDS-related Kaposi sarcoma: In the United States, this condition occurs primarily in homosexual males, bisexual men, and in the female sexual partners of bisexual men
- African Kaposi sarcoma occurs in heterosexual men and women with equal frequency
- Classic Kaposi sarcoma occurs primarily in males, with a male-to-female ratio of 10-15:1
- **Age**
- AIDS-related Kaposi sarcoma generally occurs in young to middle aged adults aged 20-54 years
- Classic Kaposi sarcoma typically occurs in patients aged 50-70 years
- African Kaposi sarcoma occurs in people of a younger age (35-40 y)

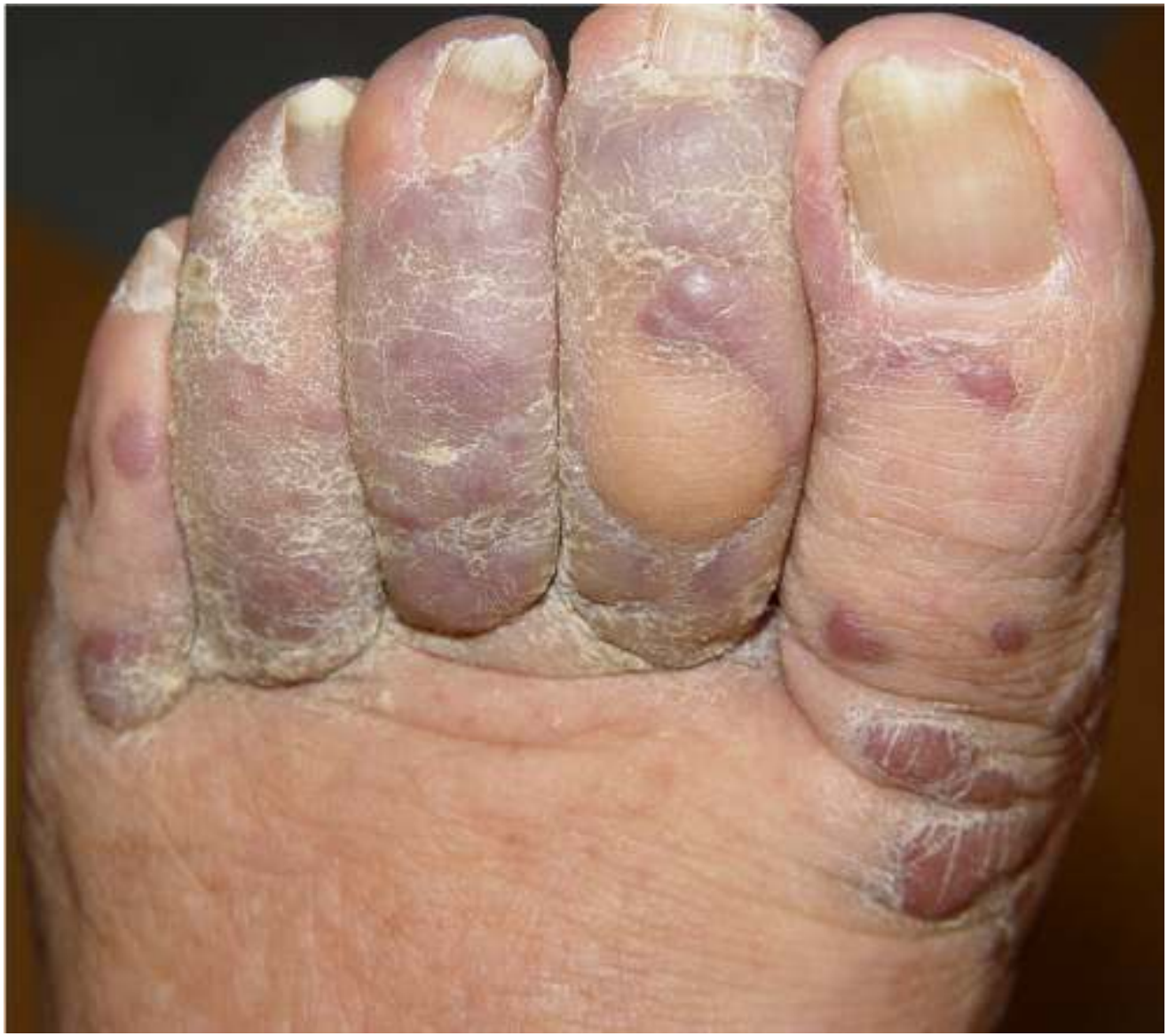
KAPOSI SARCOMA
CLINICAL FEATURES

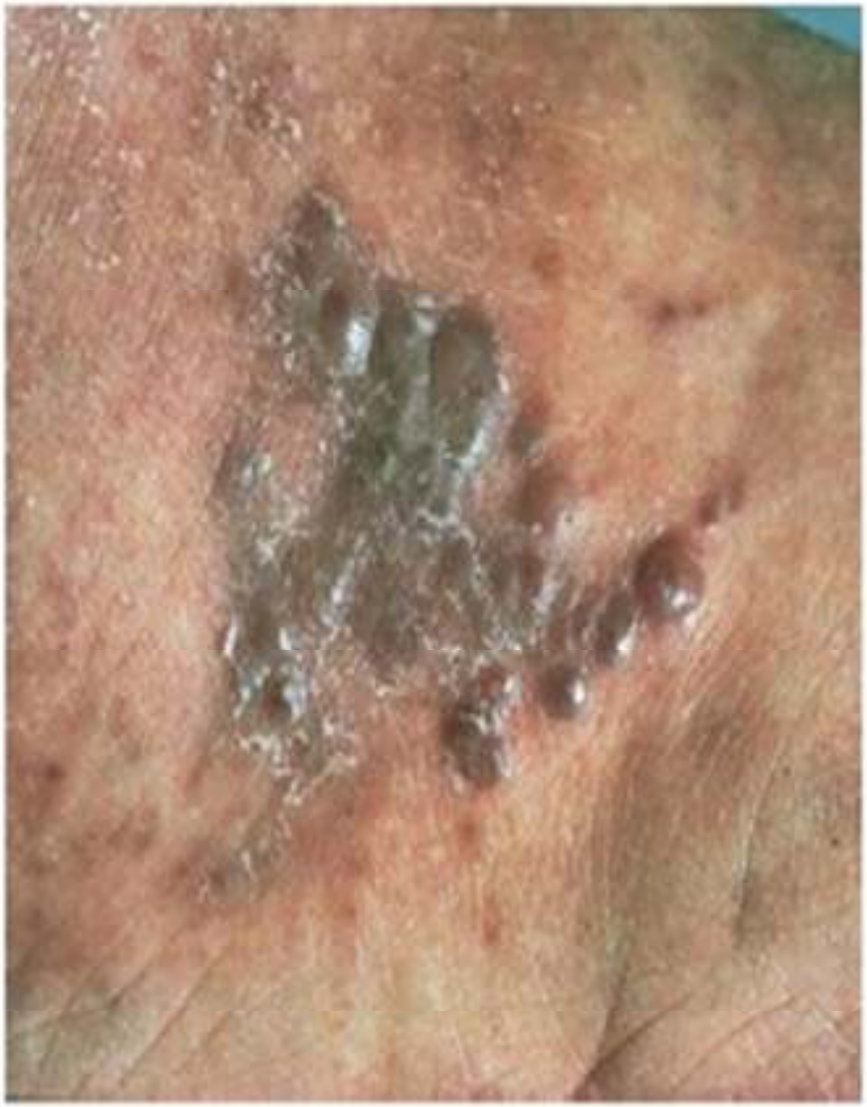
- AIDS-related Kaposi sarcoma (Kaposi's sarcoma, KS) carries a variable clinical course ranging from minimal mucocutaneous disease to widespread organ involvement.
- The lesions may involve the skin, oral mucosa, lymph nodes, and visceral organs
- Most patients present with cutaneous disease.
- Visceral disease may occasionally precede cutaneous manifestations
- Lesions have been reported in autopsy series involving virtually every organ.
- Cutaneous lesions occur in virtually all patients
- Cutaneous lesions may occur at any location but typically are concentrated on the lower extremities and the head and neck region
- Lesions may have macular, papular, nodular, or plaquelike appearances
- Nearly all lesions are palpable and nonpruritic
- Lesions may range in size from several millimeters to several centimeters in diameter
- Lesions may assume a brown, pink, red, or violaceous color and may be difficult to distinguish in dark-skinned individuals
- Lesions may be discrete or confluent and typically appear in a linear, symmetric distribution, following Langer lines
- Mucous membrane involvement is common (palate, gingiva, conjunctiva)
- Ulcerated or bulky tumor involvement may interfere with speech or mastication

Caz clinic – sarcom Kaposi:

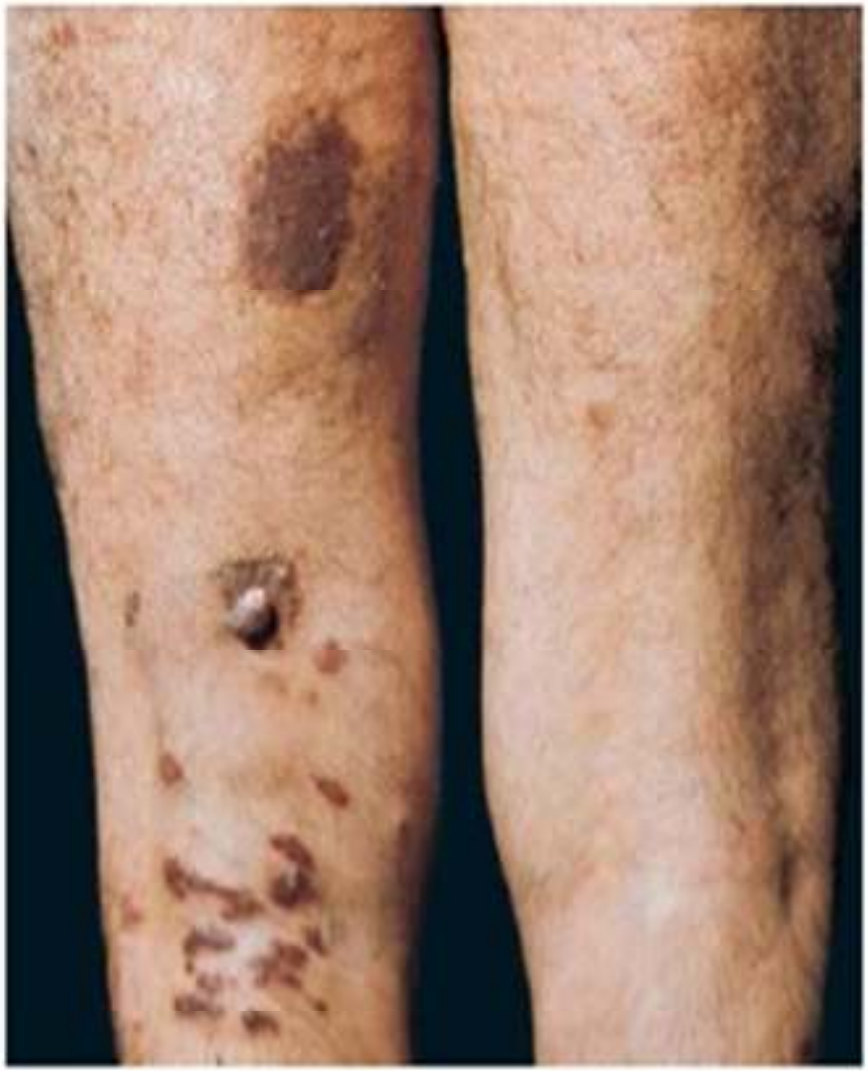


Caz clinic – sarcom Kaposi:

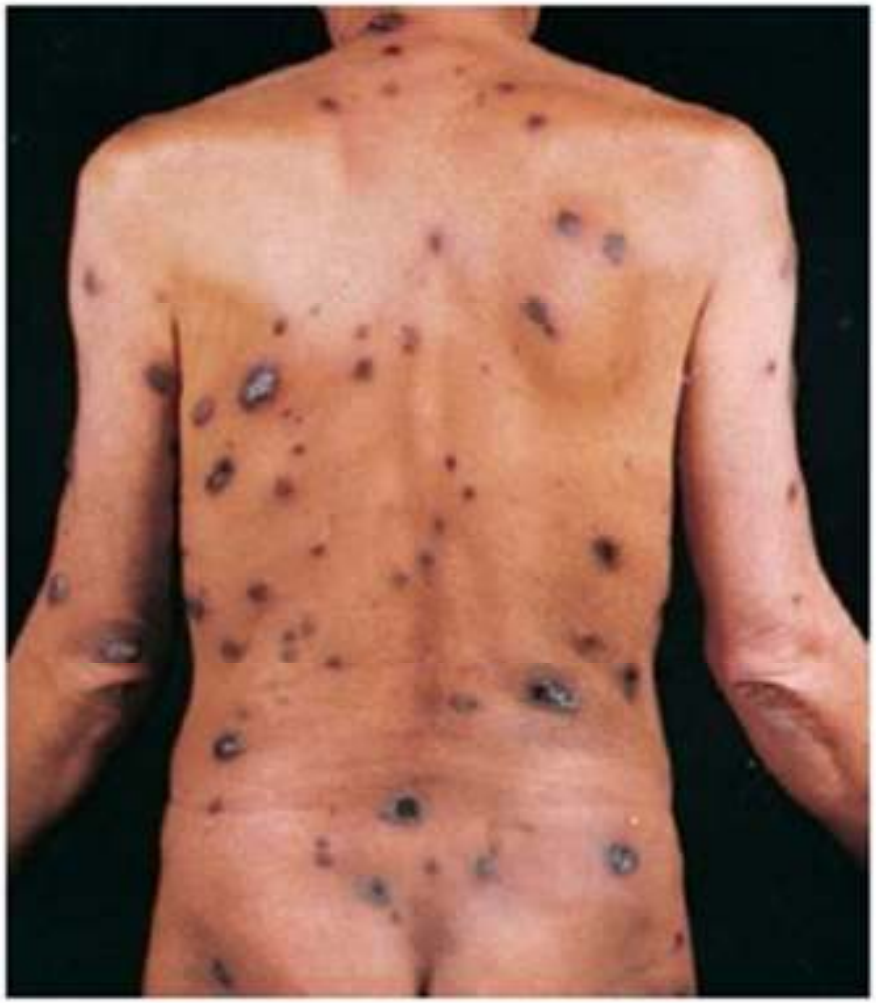




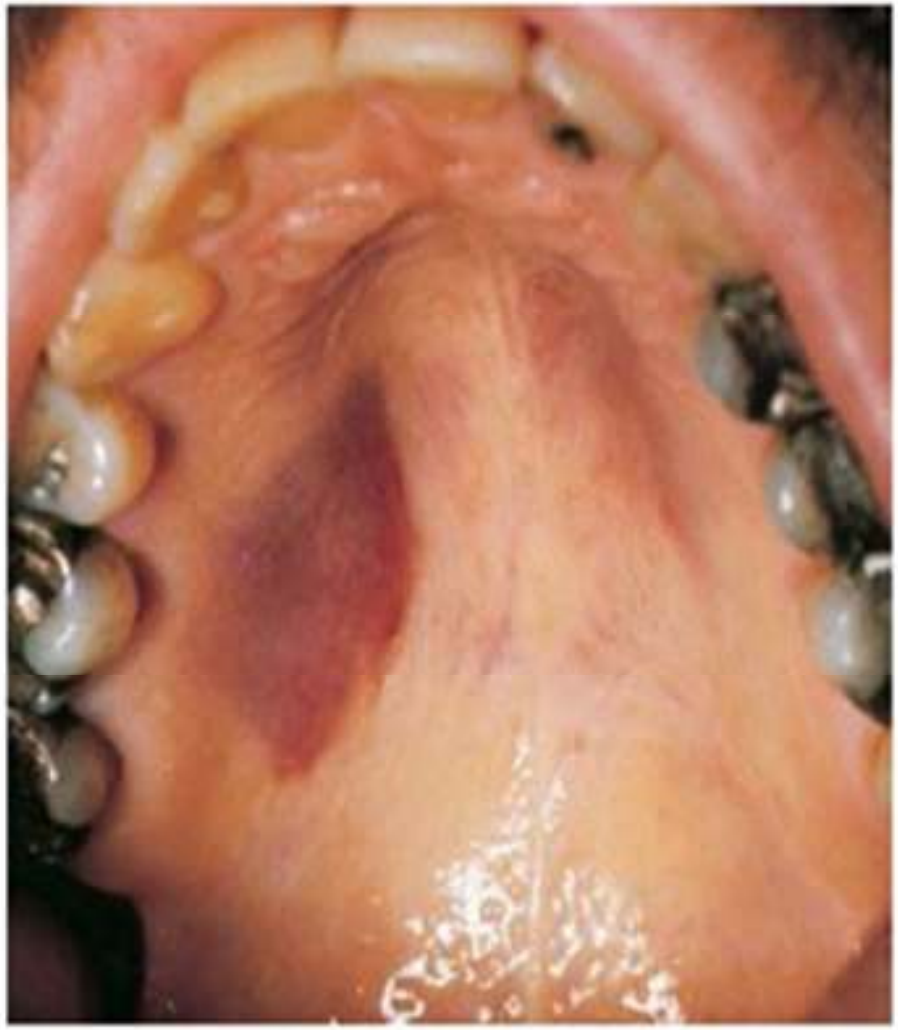
▲ **FIGURE 128-1** Classic variant. Plaques and papules localized on the dorsum of the foot, a site of predilection of classic Kaposi sarcoma.



▲ **FIGURE 128-2** Tumor nodules of more advanced classic Kaposi sarcoma (Mediterranean variant) with severe involvement of extremities.



▲ **FIGURE 128-3** Acquired immunodeficiency syndrome–associated Kaposi sarcoma. Multiple lesions at all stages of development (macules, papules, nodules) are present on the trunk. Note that the lesions follow the skin's relaxed tension lines.



▲ **FIGURE 128-4** Kaposi sarcoma lesions on the hard palate are typical manifestations of acquired immunodeficiency syndrome–associated Kaposi sarcoma.

KAPOSI SARCOMA
CLINICAL FEATURES

- ***Tumor-associated lymphedema*** - Typically manifested by lower extremity or facial involvement, thought to occur secondary to obstruction of lymphatic channels
- ***Pain*** associated with ambulation - Due to lesions involving the soles of the feet
- ***Gastrointestinal lesions*** can occur anywhere within the gastrointestinal tract. Lesions are often asymptomatic and clinically indolent.
- Gastrointestinal disease is usually an indicator of more advanced HIV infection.
- ***Pulmonary lesions*** may be an asymptomatic radiographic finding.
- ***Pleural effusions*** are often exudative and bloody.
- ***Lymphadenopathy*** may be the only site of disease requiring a lymph node biopsy. It may lead to significant lymphedema.
- **Classic Kaposi sarcoma** has a more indolent course of 10-15 years or more with very gradual enlargement of cutaneous lesions and development over years of new ones
- These lesions result in venous stasis and lymphedema of the lower extremities. Visceral lesions occur in the GI tract, lymph nodes, and other organs but are usually incidental findings at autopsy
- As many as one third of patients develop a second neoplasm, most often a non-Hodgkin lymphoma
- The brain is spared

KAPOSI SARCOMA - TREATMENT

I. Localized disease:

- ***Local therapy:***
  - surgical excision
  - cryotherapy
  - Topical 9-cis retinoid acid
- ***Radiation therapy***

II. Disseminated disease / internal organ involvement

- **Systemic therapy:**
- For patients with AIDS – initiate highly active antiretroviral therapy
- For patients on immunosuppressive therapy – re - evaluate drug regimen
- For patients with classical Kaposi Sarcoma:
  - Liposomal anthracyclines – liposomal doxorubicin 20-40 mg/m² every 2-4 weeks
  - Vinblastine 6 mg IV once a week
  - Doxorubicin/Bleomicin/Vincristin – 30mg/m²//10mg/m²//2mg every 2-4 weeks
  - Interferon α – 3 million - 30million units daily 3 weeks
- **Investigational treatments:**
- Thalidomide
- Vascular endothelial growth factor antisense
- COL-3 matrix metalloproteinase inhibitor

Cutaneous T-Cell Lymphoma

- Cutaneous T-cell lymphomas (CTCLs) are the largest group of cutaneous lymphomas, representing 65% of all cutaneous lymphomas
- The World Health Organization (WHO)/European Organization for Research and Treatment of Cancer (EORTC) classification (WHO-EORTC classification) is used to categorize CTCLs
- However, a substantial subset of T-cell primary cutaneous lymphomas remains that cannot be classified beyond the unspecified peripheral T-cell category, some of which may have an aggressive course

Cutaneous T-Cell Lymphoma

- **Mature T-cell and natural killer (NK) cell neoplasms according to the WHO-EORTC classification are as follows:**
- **Mycosis fungoides (MF):** - Variants of MF (pagetoid reticulosis [localized disease], follicular, syringotropic, granulomatous variant), subtype of MF (ie, granulomatous slack skin (GSS) syndrome)
- **Sézary syndrome**
- **$CD30^+$ T-cell lymphoproliferative disorders of the skin** - Lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma
- **Subcutaneous panniculitislike T-cell lymphom**a
- **Primary cutaneous peripheral T-cell lymphoma** (PTL), unspecified - Subtypes of PTL (primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma [provisional], cutaneous gamma/delta-positive T-cell lymphoma (CGD-TCL) [provisional], primary cutaneous $CD4^+$small/medium-sized pleomorphic T-cell lymphoma [provisional])
- **Extranodal NK/T-cell lymphoma**, nasal type - variant (hydroa vacciniformialike lymphoma)
- **Adult T-cell leukemia/lymphoma**
- **Angioimmunoblastic T-cell lymphoma**

Cutaneous T-Cell Lymphoma
CAUSATIVE AGENTS

- Chemical, physical, and microbial irritants have been discussed as causes for cutaneous T-cell lymphoma (CTCL) or mycosis fungoides (MF), but evidence related to an etiology is not convincing
- They may play the role of a persistent antigen, which, in a stepwise process, leads to an accumulation of mutations in oncogenes, suppressor genes, and signal-transducing genes

Cutaneous T-Cell Lymphoma

PATHOPHYSIOLOGY

- The primary pathophysiologic mechanisms for the development of cutaneous T-cell lymphoma (CTCL) (ie, mycosis fungoides [MF]) have not been elucidated
- MF may be preceded by a T-cell–mediated chronic inflammatory skin disease, which may occasionally progress to a fatal lymphoma
- A genotraumatic T cell is one with a tendency to develop numerous clonal chromosomal aberrations
- Normal T lymphocytes show apoptosis during in vitro culturing, whereas genotraumatic ones have the ability to develop clonal chromosomal aberrations to become immortalized
- This concept implies genetic instability followed by T-cell proliferation
- Successive cell divisions of a genotraumatic T-cell clone may produce multiple and complex chromosomal aberrations
- Some may reprogram the genotraumatic cells to apoptosis, whereas one or more may produce the phenotypic alterations of malignancy if not eliminated *in vivo*
- Thus, one hypothesis is that the development of genotraumatic T lymphocytes is involved in the etiopathogenesis and the progression of MF
- It would also predict that each patient would likely have a unique malignant clone, which, in fact, has been found to be the case

Cutaneous T-Cell Lymphoma Epidemiology

- The incidence of cutaneous T-cell lymphoma in the US is approximately 5 cases per million population per year
- **Sex**
- Cutaneous T-cell lymphoma (CTCL) is more common in men in a ratio of approximately 2:1
- **Age**
- Most patients with cutaneous T-cell lymphoma (CTCL) are middle-aged or elderly
- Many patients have had a poorly defined form of dermatitis for many years prior to the onset of CTCL

Cutaneous T-Cell Lymphoma
MICOSIS FUNGOIDES

- **Classic Micoses Fungoides**
- Classic cutaneous T-cell lymphoma (CTCL) or mycosis fungoides (MF) is divided into 3 stages: patch (atrophic or nonatrophic), plaque, and tumor.
- Often, the first stage goes on for many years and is characterized by a nonspecific dermatitis usually consisting of patches, often on the lower trunk and buttocks
- Sometimes, these patches have a thin, wrinkled quality, often with reticulated pigmentation. In this stage, pruritus is usually minimal or absent
- Classic MF is usually preceded by a nonspecific indolent inflammatory process, manifesting as atopic dermatitis, nonspecific chronic dermatitis, or parapsoriasis, most commonly large-plaque parapsoriasis, which may progress over years to decades to early plaque-stage MF
- Some authorities regard large-plaque parapsoriasis as patch-stage MF
- In many cases, the disease never progresses beyond this stage, and the diagnosis of MF is never confirmed
- In other cases, the disease appears from the beginning as rather well-defined superficial plaques that range from 2 cm to more than 20 cm in greatest diameter.

Cutaneous T-Cell Lymphoma

MICOSIS FUNGOIDES

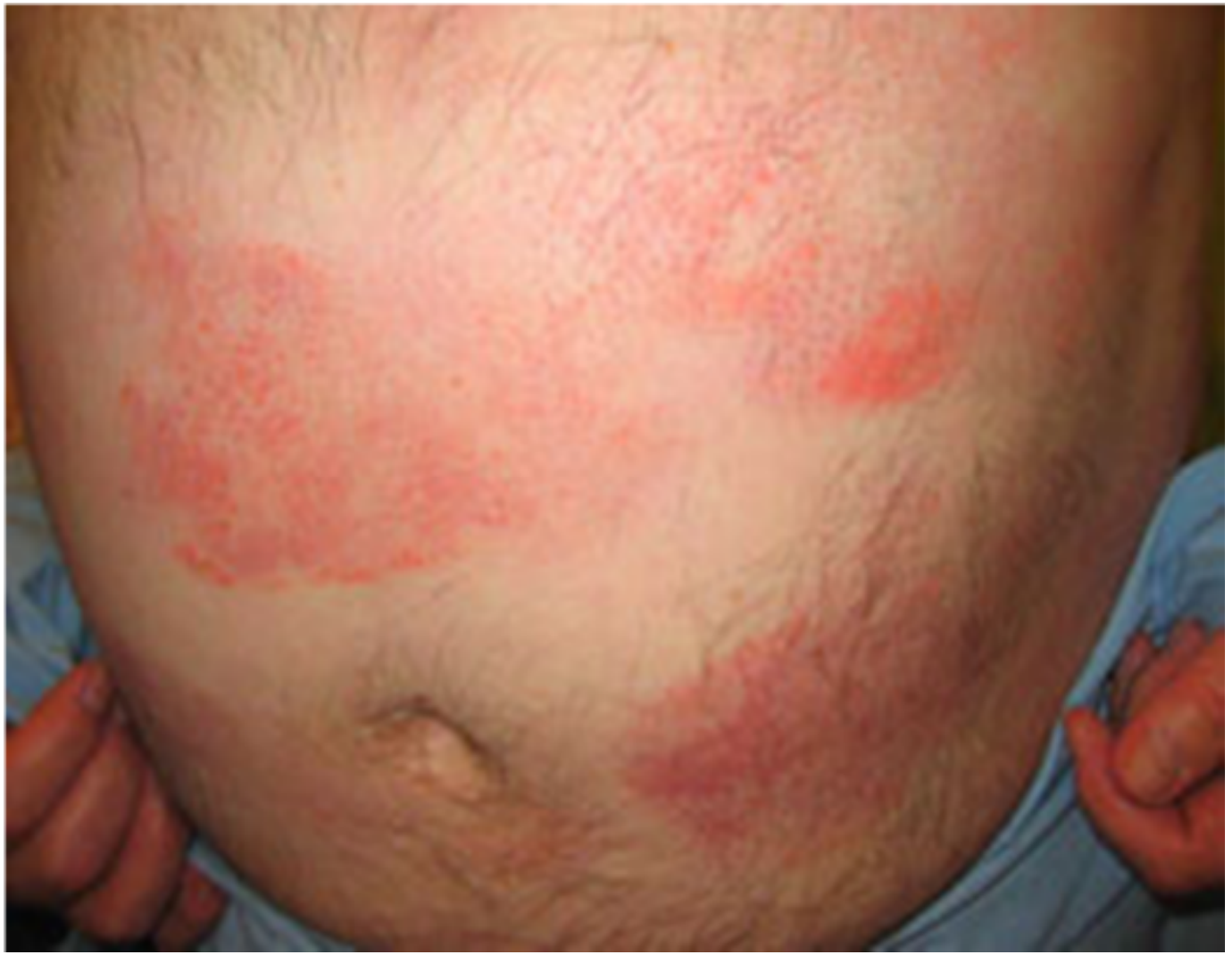
- **Erythrodermic MF**
- MF evident as an erythroderma but with too few circulating lymphocytes to warrant a diagnosis of SS is designated erythrodermic MF
- Dermatopathic lymphadenopathy is present in these cases
- Rarely, such patients may present with a nodulotumorous eruption
- **D'emblee MF**
- The sudden multifocal development tumors of apparent MF may rarely occur without preceding patches or plaques
- Most, if not all, such cases probably represent primary cutaneous $CD30^{+}$ pleomorphic, medium or large cell T-cell lymphomas

Cutaneous T-Cell Lymphoma

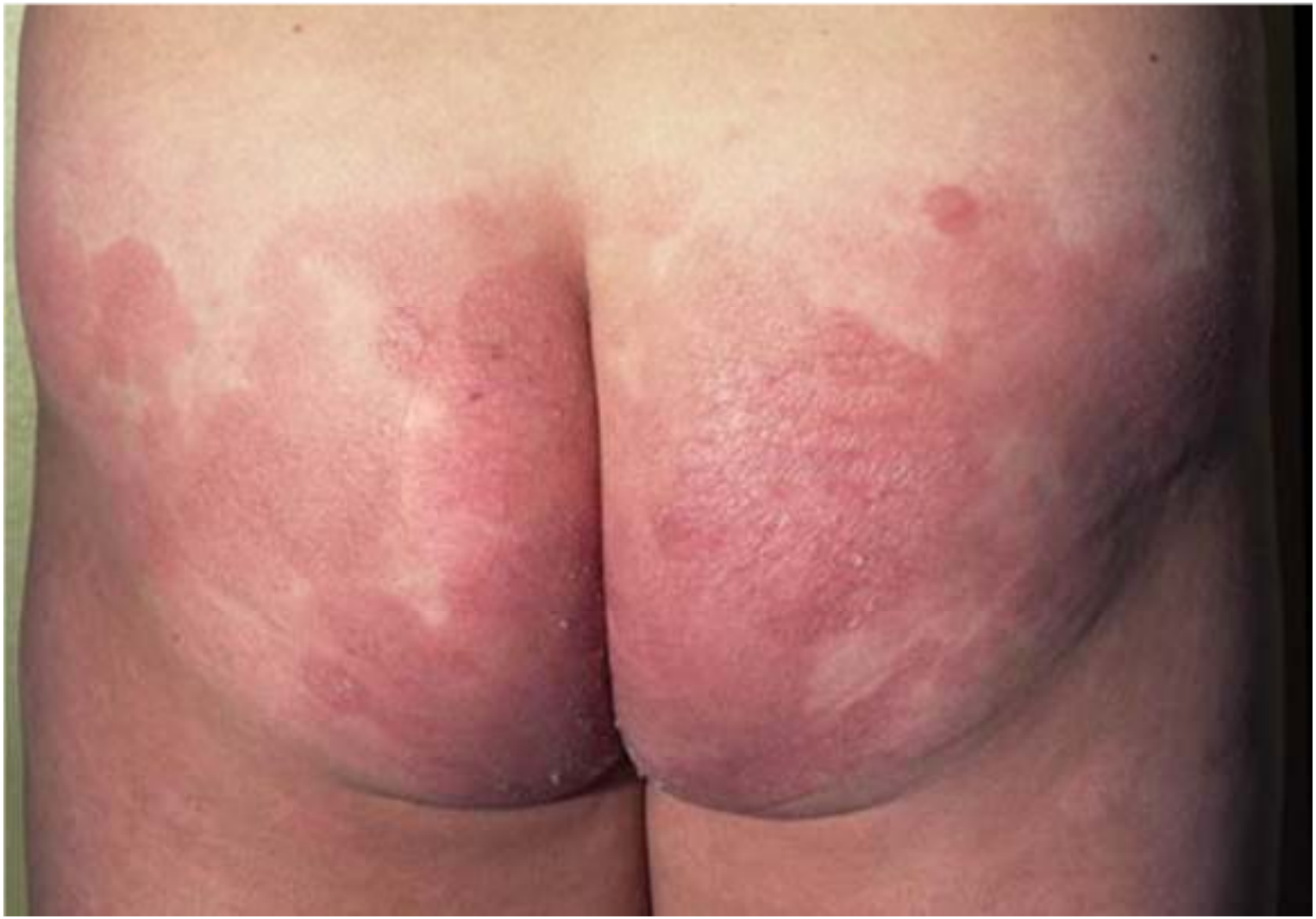
MICOSIS FUNGOIDES

- Mycosis fungoides (MF) is a commonly epidermotropic cutaneous T-cell lymphoma (CTCL) characterized by small-to-medium T lymphocytes with cerebriform nuclei
- The term MF is used only for the classic Alibert-Bazin type characterized by the evolution of patches, plaques, and tumors or for variants showing a similar clinical course
- MF is the most common form of CTCL and accounts for almost 50% of all primary cutaneous lymphomas
- MF has an indolent clinical course with slow progression over years or decades, from patches to more infiltrated plaques and, eventually, tumors.
- Initially, MF has a predilection for the buttocks and other sun-protected areas
- In tumor-stage MF, the usual presentation is a combination of patches, plaques, and tumors; the tumors often show ulceration
- However, if only tumors are present, without preceding or concurrent patches or plaques, a diagnosis of MF is highly unlikely and another type of CTCL should be considered

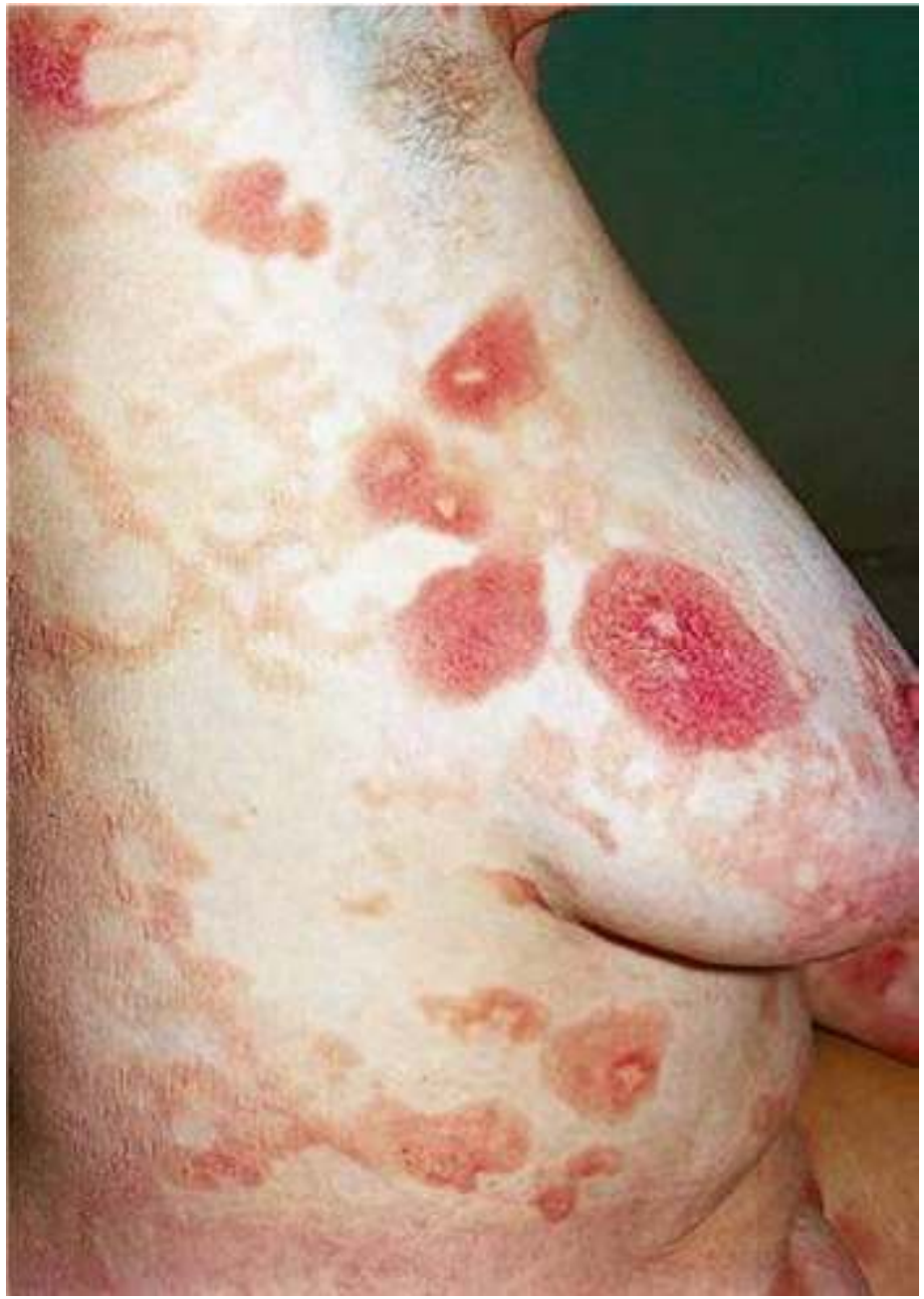
Caz clinic – MF, f. comună, st. eritematos:



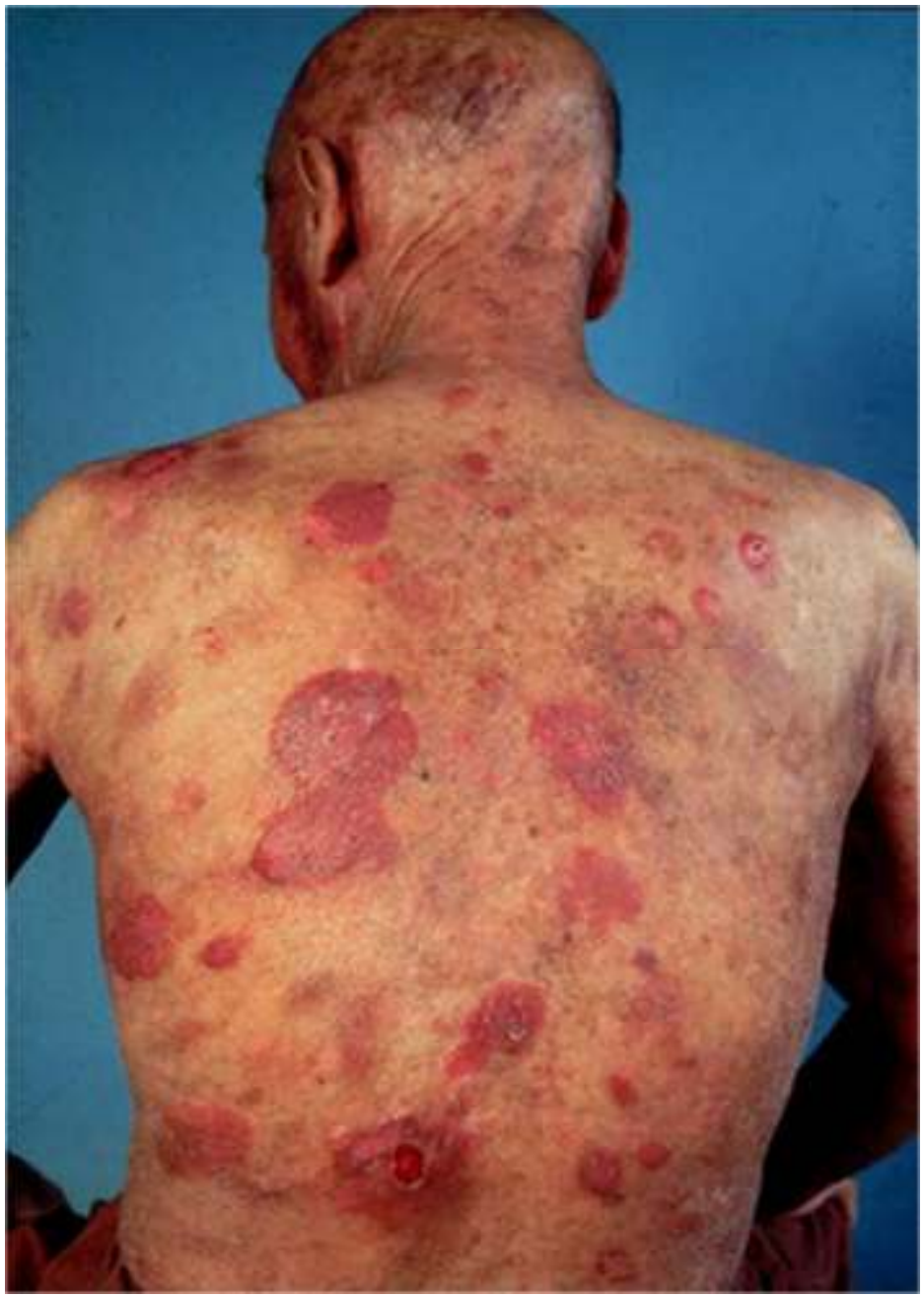
Caz clinic – MF, f. comună, st. eritematos:



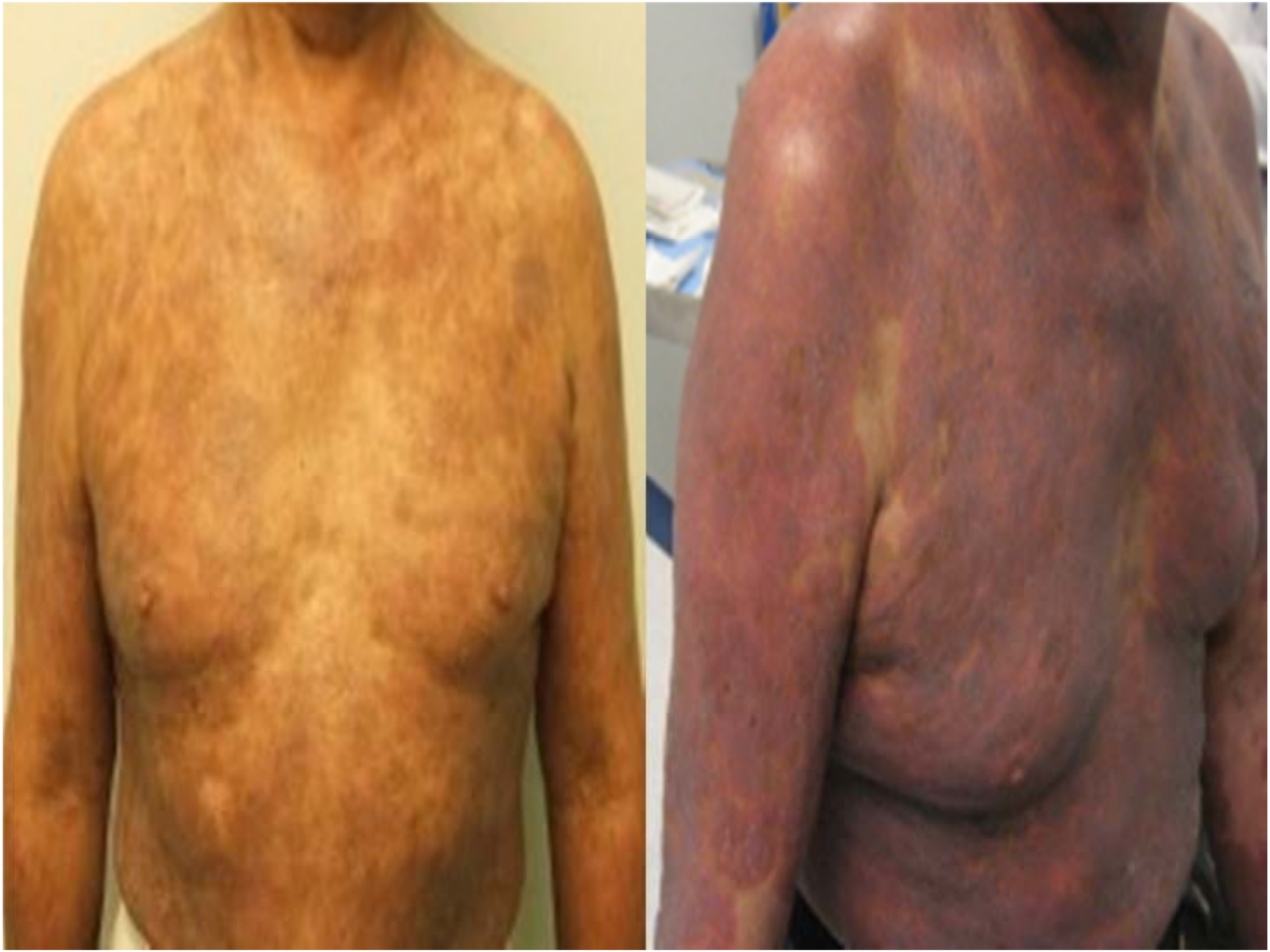
Caz clinic – MF,
f. comună,
st. eritematos &
infiltrativ:



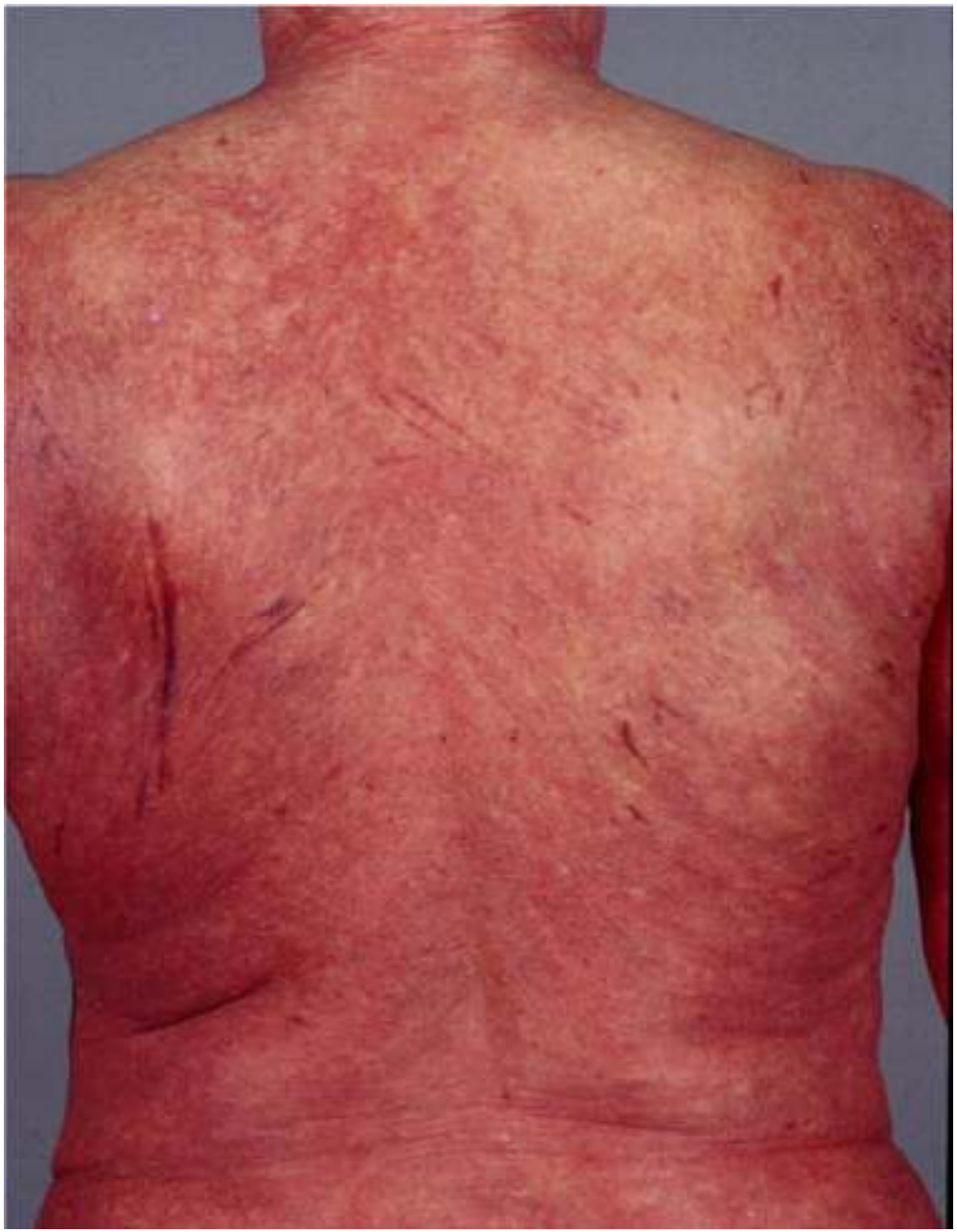
Caz clinic – MF,
f. comună,
st. infiltrativ &
tumoral:



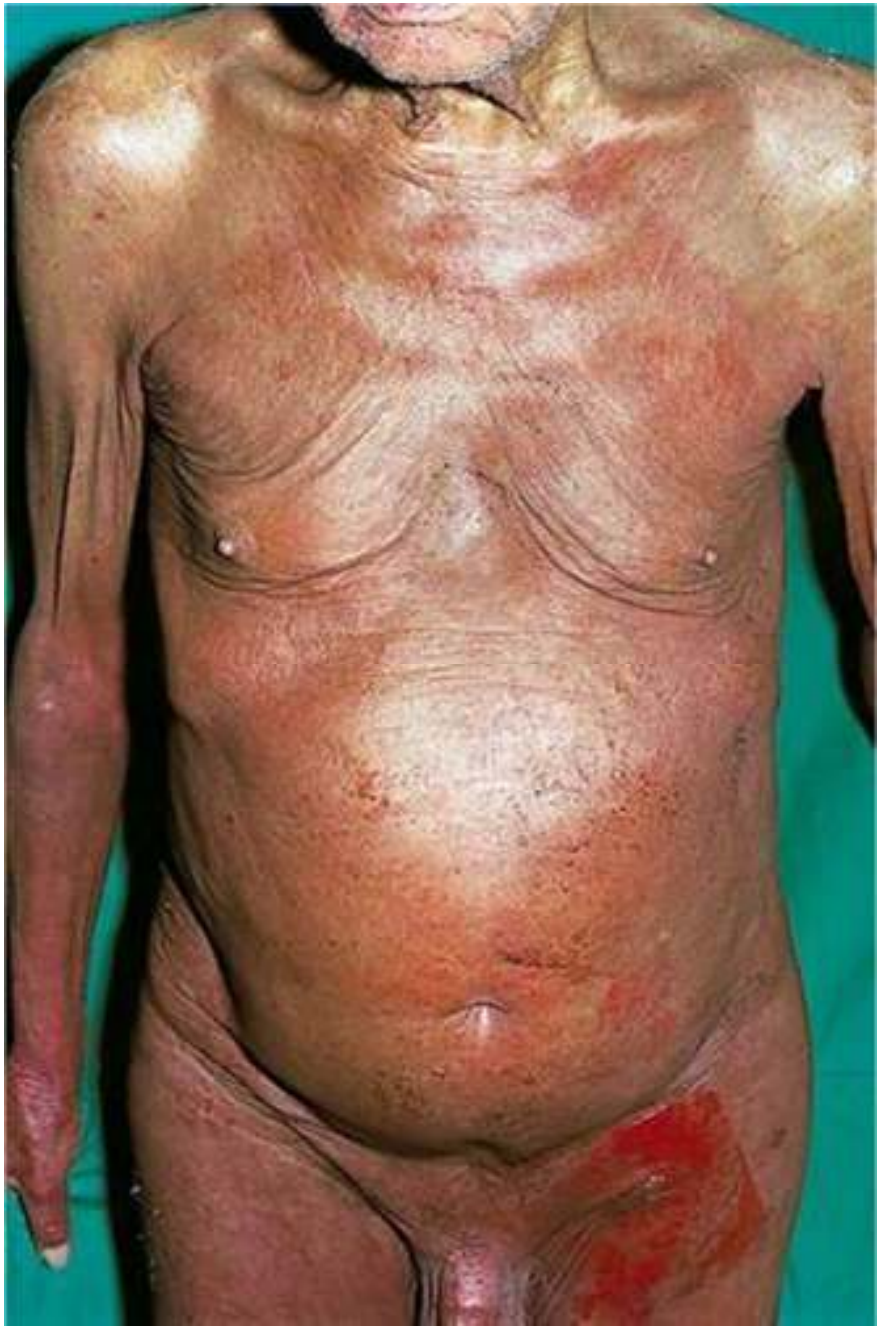
Caz clinic – MF, f. comună,
st. tumoral:



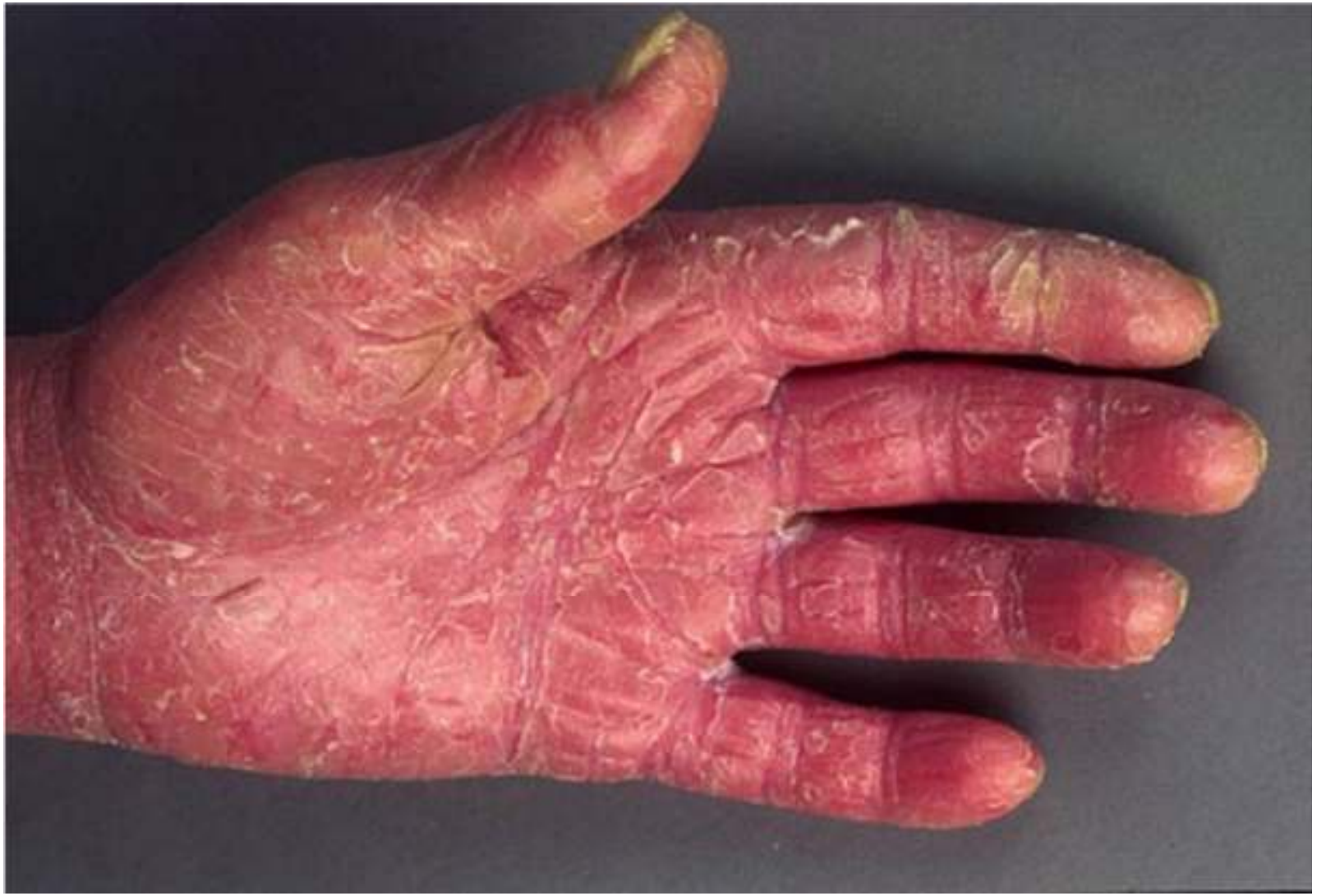
Caz clinic – sindrom Sezary:



Caz clinic – sindrom Sezary cu eritrodermie & pigmentaţie difuză:



Caz clinic – sindrom Sezary cu hiperkeratoză palmară:



Caz clinic – sindrom Sezary cu hiperkeratoză plantară: