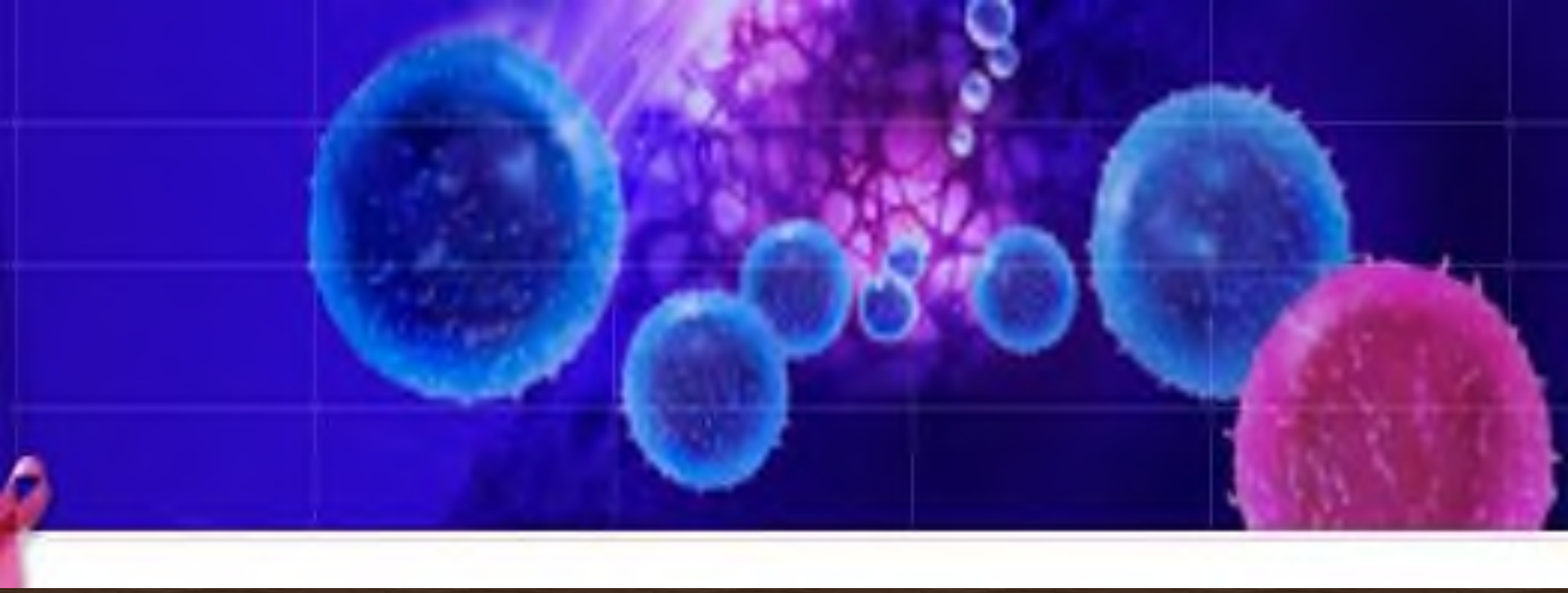


MELANOMA OF THE SKIN

DEPARTMENT OF ONCOLOGY AND MEDICAL RADIOLOGY

Risk factors

- *Physical risk factors:*
- *excessive insolation, especially in childhood;*
- *ionizing radiation;*
- *fluorescent lighting;*
- *chronic traumatism of the skin.*

Risk factors

- *Chemical risk factors:*
- *This group of risk factors is important for people who have professional contacts with chemicals that promote the development of melanoma:*
- *Nitric acid;*
- *vinyl chloride, plastics, benzene;*
- *pesticides;*
- *coal;*
- *pharmaceuticals.*

- *Biological risk factors:*
- *features of nutrition (higher average daily intake of protein and animal fat);*
- *alcohol intake (enhances the formation of Melano-stimulating hormone);*
- *medicinal preparations (estrogen-containing hormonal preparations);*

Risk factors

- *Exogenous risk factors are biological features of an organism, the presence of which increases the risk of developing melanoma and pathological changes in the skin that have the likelihood of malignant degeneration, i.e. precursors of melanoma.*
- *racial and ethnic predisposition;*
- *level of pigmentation of the body;*
- *skin phototype I-II (susceptibility to sunburn, red hair, blue eyes, light skin);*
- *the presence of lentigo and freckles;*
- *three or more episodes of severe skin burns throughout life;*
- *weighed down family history, accumulation of melanoma cases in close relatives;*
- *anthropometric indicators;*
- *immune disorders;*

Risk factors

- *Endogenous factors:*
- *pregnancy;*
- *pigmented xeroderma of the skin;*
- *Doucherayle melanosis;*
- *the total number of benign melanocytic nevi on the skin;*
- *presence of 3 or more atypical melanocytic nevi.*

Risk groups

- *Group of extremely high risk (risk increased more than 50 times)*
- *- change in the appearance of pigmented formation*
- *- dysplastic nevus in a patient with two cases of melanoma in a family history*
- *- mature age (in comparison with children's)*
- *- more than 50 pigmentary nevuses with a diameter ≥ 2 mm*
- *High risk group (risk increased approximately 10 times)*
- *- melanoma in a family history*
- *- sporadic dysplastic nevi*
- *- congenital non-vascular nevi*
- *- belonging to the Europeoid race(in comparison with the Negroid and Mongoloid)*
- *- a melanoma in the anamnesis*
- *Group of moderate risk (risk increased 2-4 times)*
- *- immunodeficiency*
- *- light skin or excessive insolation*

Benign tumor of nevus

- 1. Intradermal nevus.
- 2. Complex nevus.
- 3. The border nevus (junior).
- 4. Epitheloid and (or) spindle cell nevus.
- 5. Nevus from balloon-shaped cells.
- 6. The halo-nevus.
- 7. The giant pigment nevus.
- 8. Fibrous papule of the nose (involutional nevus).
- 9. Cellular blue nevus.
- 10. The blue nevus.

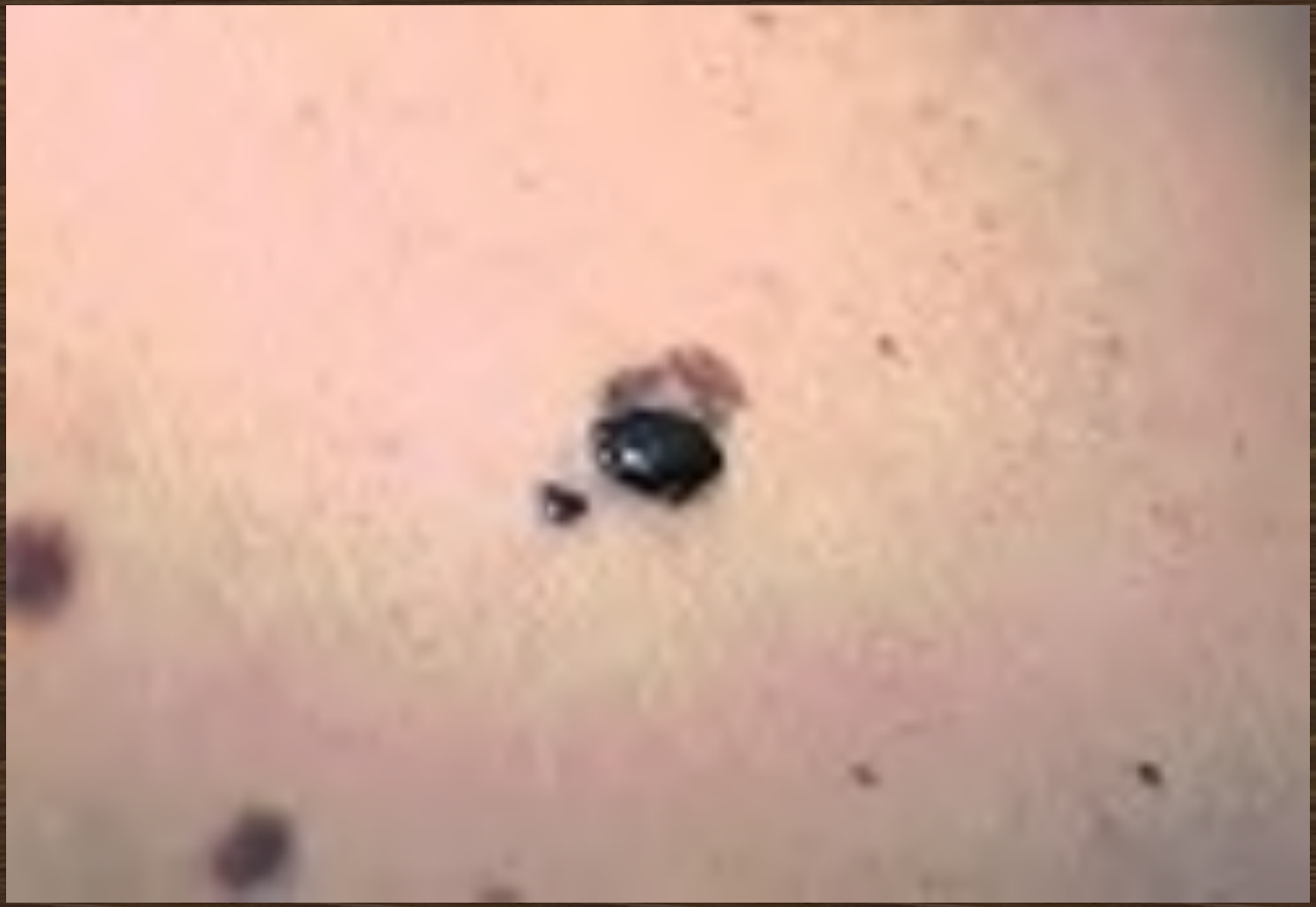
Precancerous changes.

- Precancerous melanosis, Melancholic Hutchinson stain.
- Pigmented xeroderma.

Malignant.

- Malignant melanoma.
- Malignant melanoma originating from precancerous melanosis, which includes Hutchinson's melanotic spot.
- Malignant melanoma, arising from a blue nevus.
- Malignant melanoma, arising from a giant pigmented nevus.

Large, thick melanoma. Has an irregular shape and pigmentation with a small satellite formation and the surrounding nevus.



Non-tumor pigmented lesions.

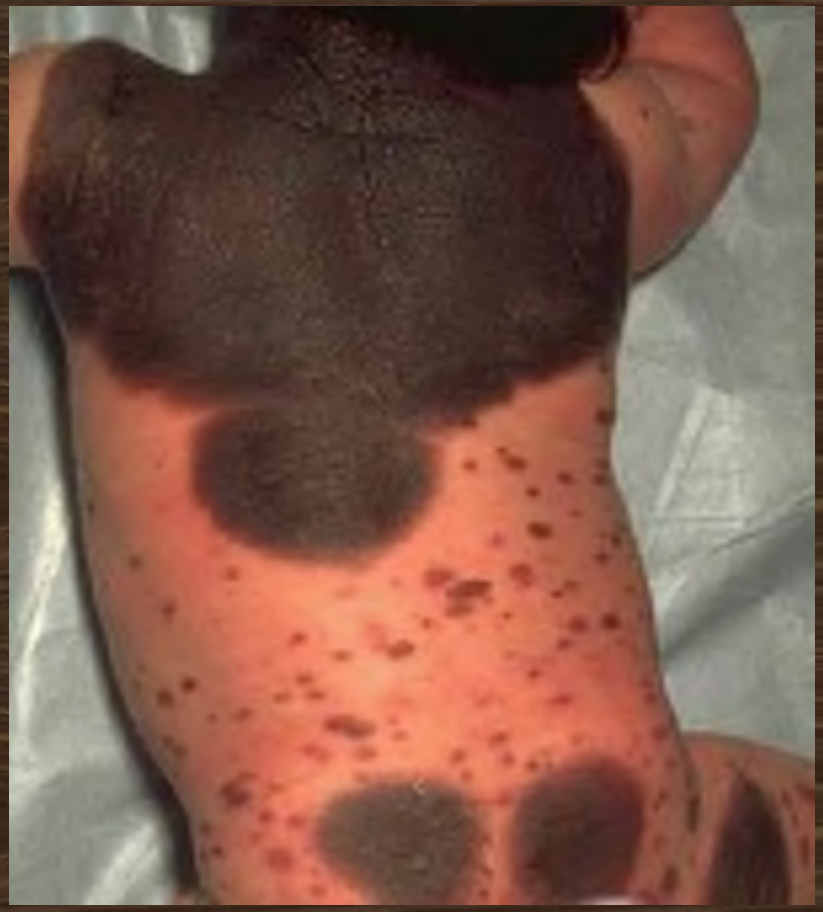
- 1. The Mongolian spot.
- 2. Lentigo.
- 3. Efelid.

melanoma-hazardous nevi

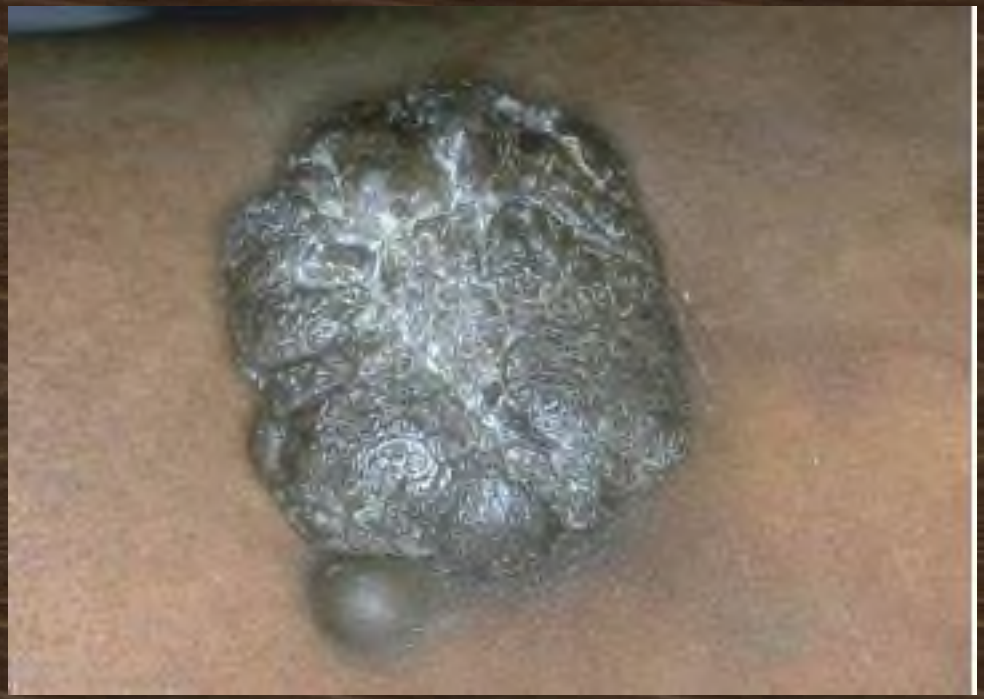
- Melanosis of Dubreuil (in 80% of cases).
- Giant pigmented nevus (up to 13% of cases).
- Blue (blue) nevus.
- Mixed (complex) nevus
- Spindle cell nevus, epithelioid nevus).
- Dysplastic nevus (precursor of melanoma).
- Pigmantary intradermal nevus (in 50-80% of cases).
- Lentigo.

Melanosis of a Dwebrail

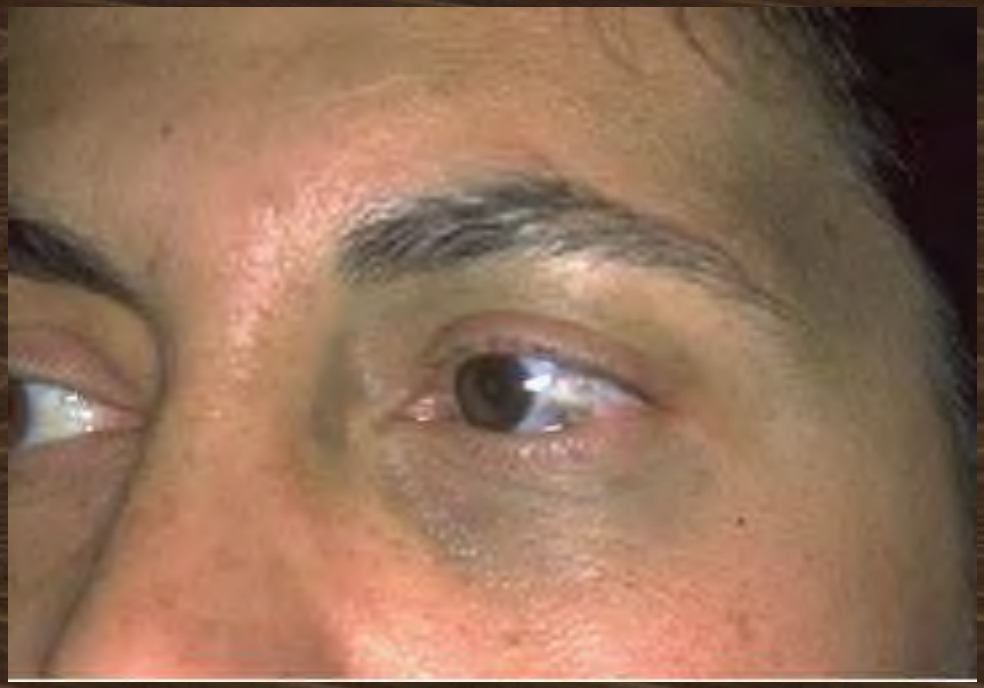
Giant Pigmented nevus



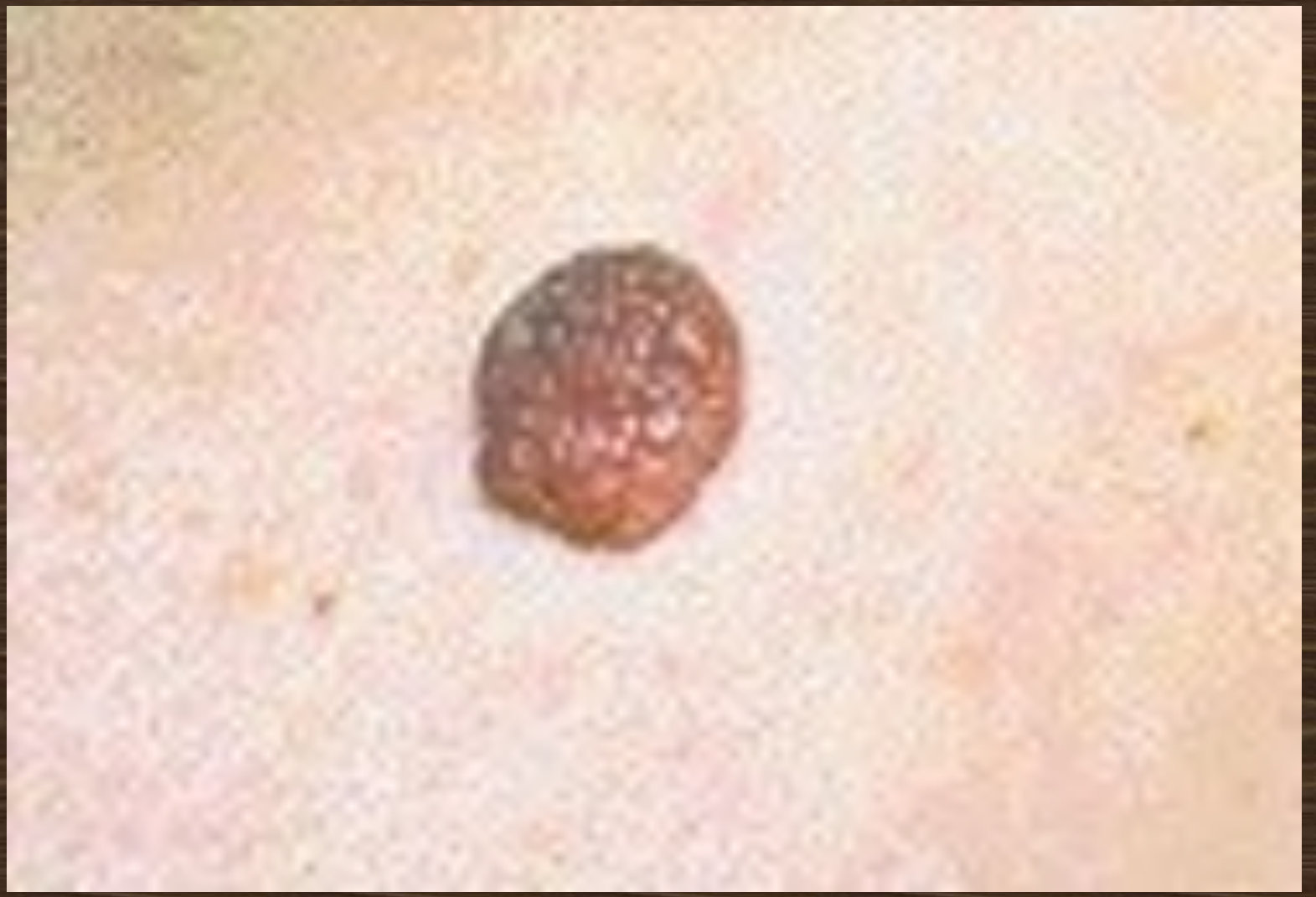
Blue nevus



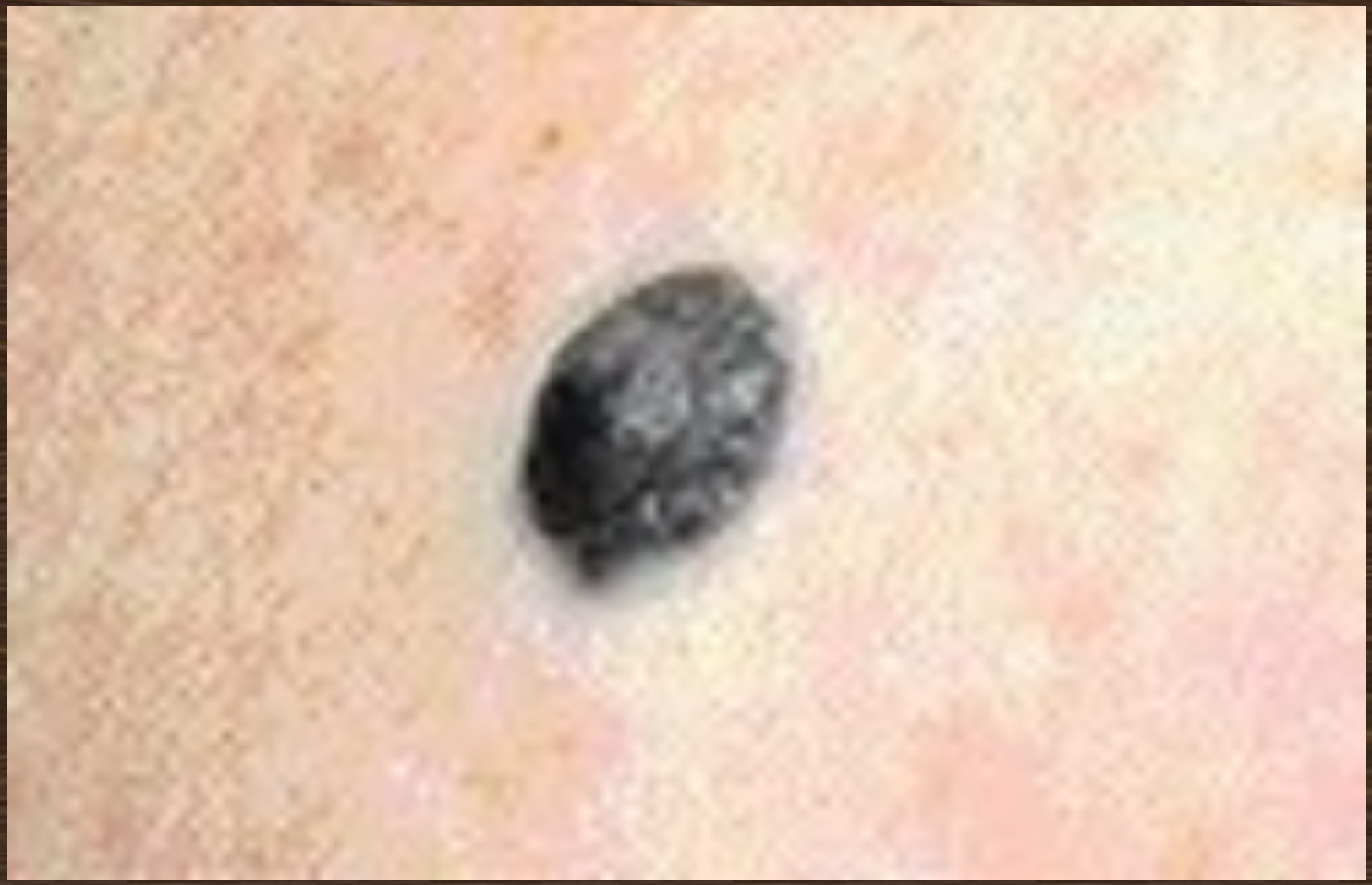
Nevus of Ota



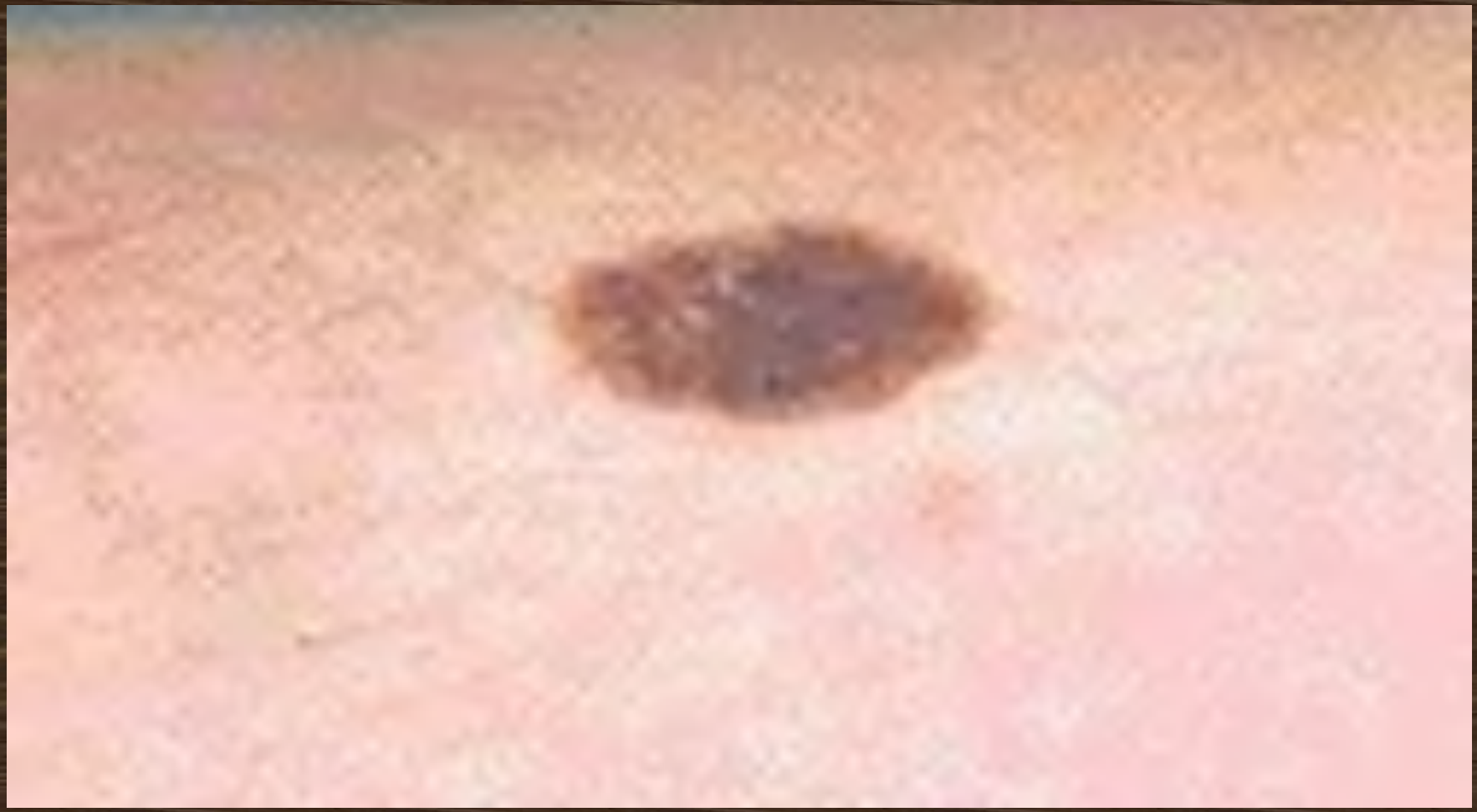
Fleshy melanocytic nevus on legs. This is a benign formation, but it must be removed or subjected to a shaving biopsy.



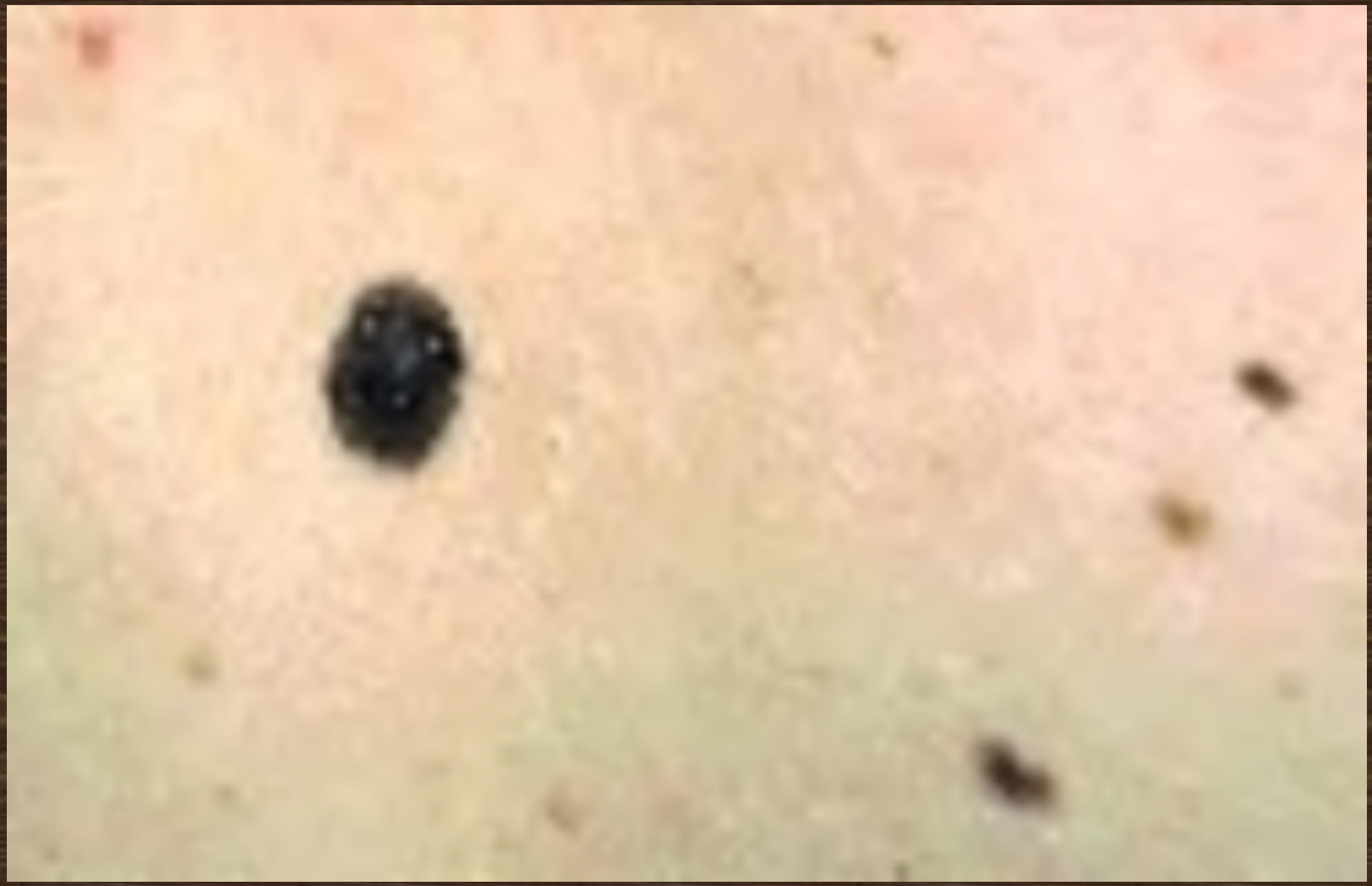
Pigmented seborrheic wart (keratosis). Pay attention to the keratinized rough surface with slightly uneven edges. It is best to make a conventional scraping or slightly burn, and then send to a study.



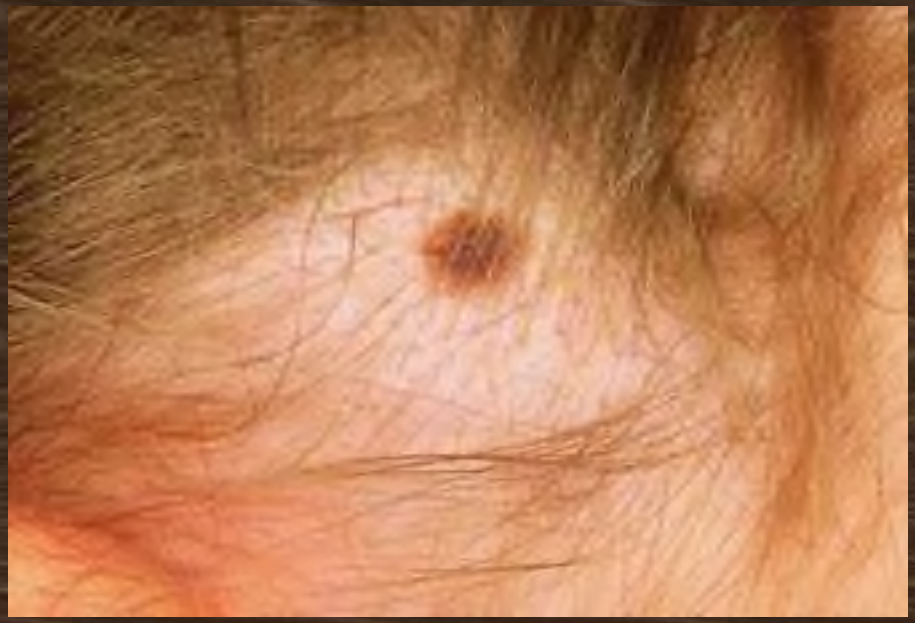
Dysplastic nevus of the skin. Pay attention to the size of more than 7 mm and slightly uneven shape and color.



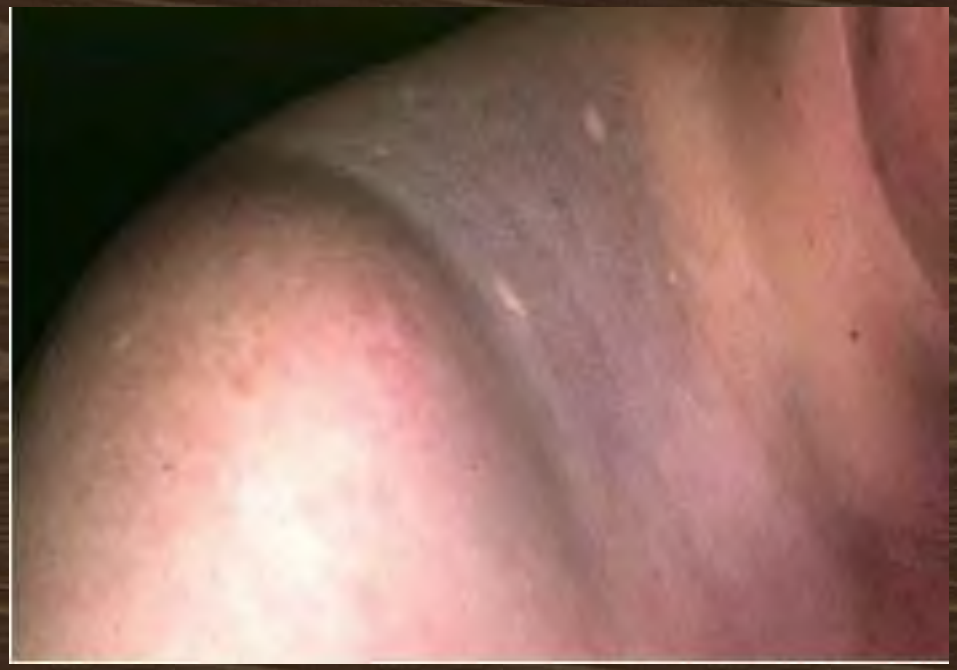
Диспластический невус . Вокруг расположены множественные мелкие доброкачественные невусы. Образование диаметром более 7 мм с неровными контурами.



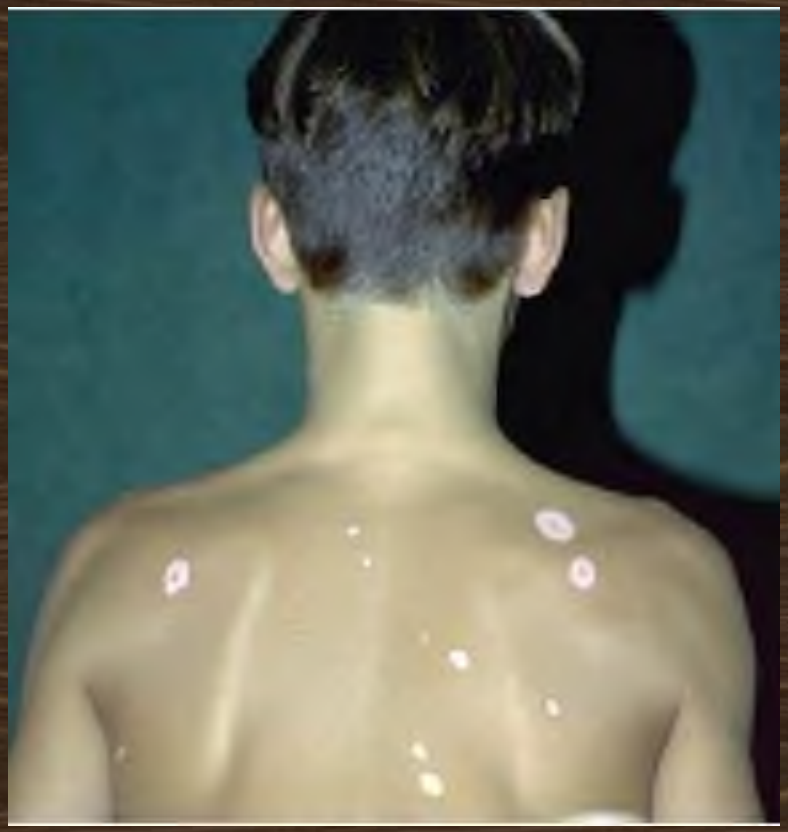
intradermal nevus nedir



Nevus of Ota



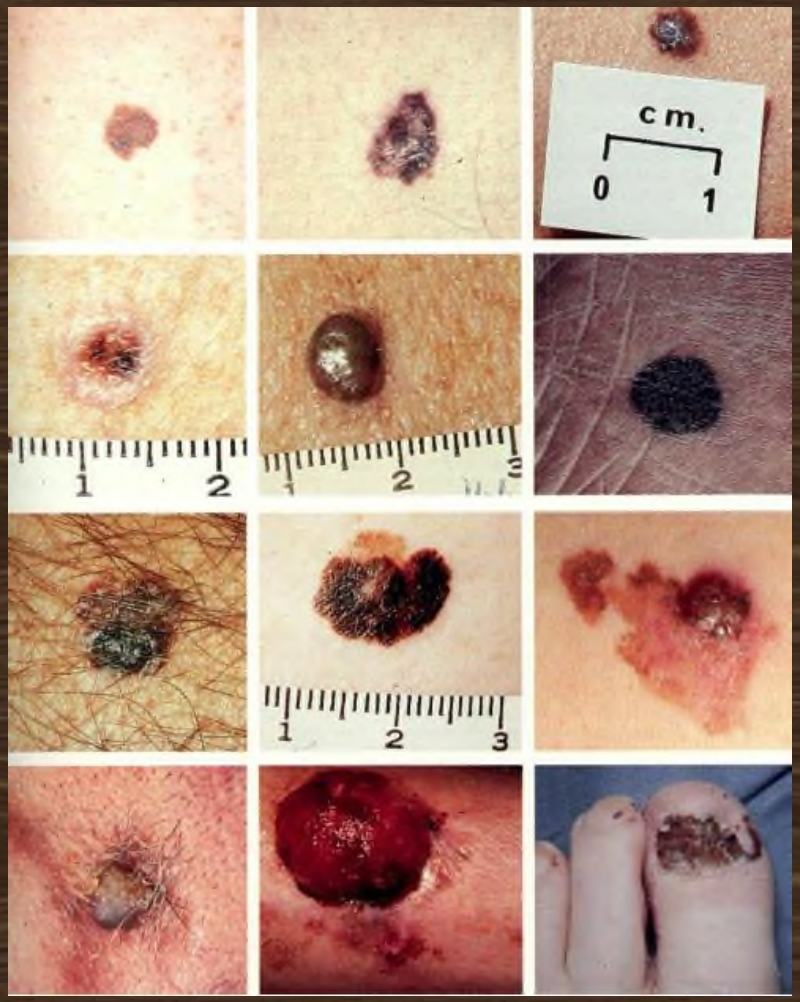
Neville Settona



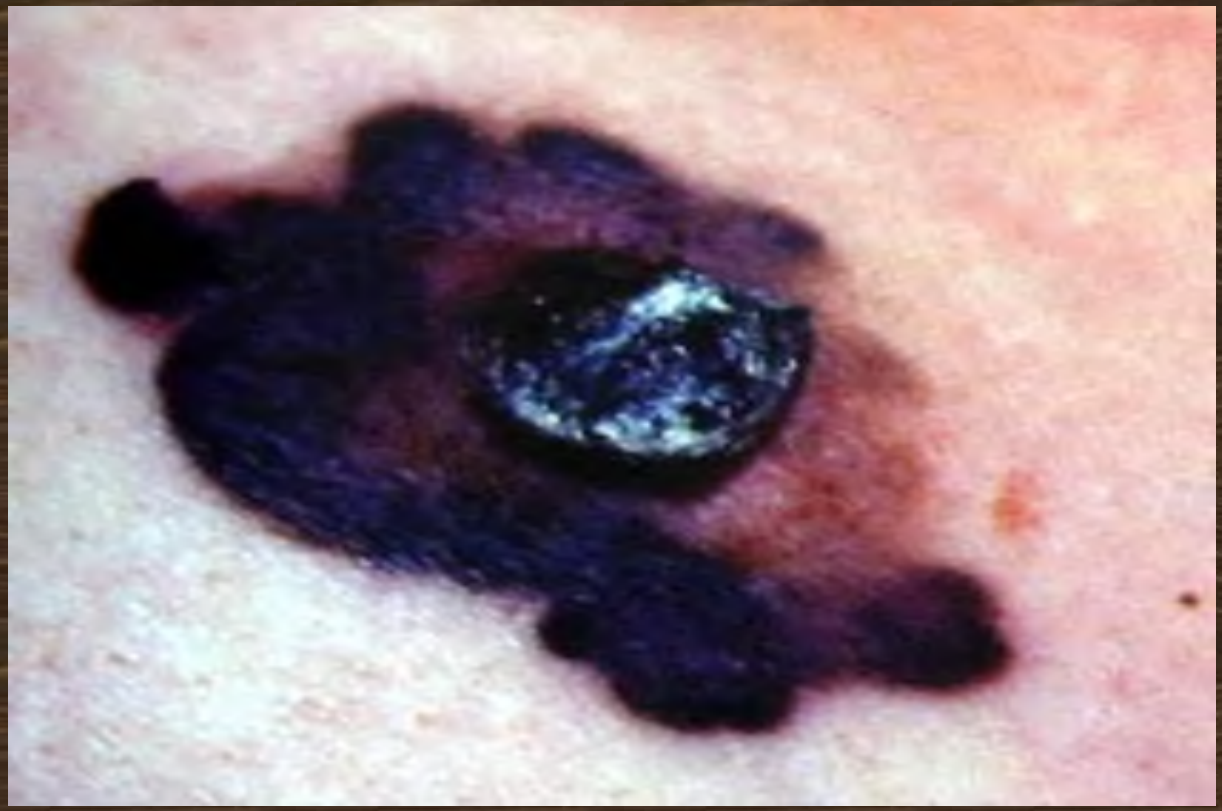
clinical signs of malignancy of nevi (AI Paches, 1997)

- Violation or complete absence of skin pattern, peeling nevus.
- The change in the color of the nevus, its sharp pigmentation (up to black color), and in some cases a decrease in pigmentation.
- Uneven coloration, partial (uneven) or complete change in the color of the nevus melanoma.
- The appearance of the glossy surface of the nevus.
- The appearance of an inflammatory areola around the nevus (the appearance of redness in the form of a corolla).
- Changing the configuration along the periphery, "blurring" the boundaries of the contour of the nevus (falsity of the edges).
- Increase in the size and compaction of the nevus, horizontal growth.
- Vertical growth of a nevus over surrounding tissues.
- Appearance at the base of a nevus and on the surface of a nevus of knobby small papillo-matous elements with foci of necrosis.
- The onset of itching, burning, tingling and tension of the skin in the area of the nevus.
- The appearance of cracks, ulceration, bleeding and mossing of the surface of the nevus-melanoma.
- The appearance of daughter pigmented or pink formations (satellites) in the skin around the nevus-melanoma.
- Absence or inflammation of the hair on the surface of the nevus.

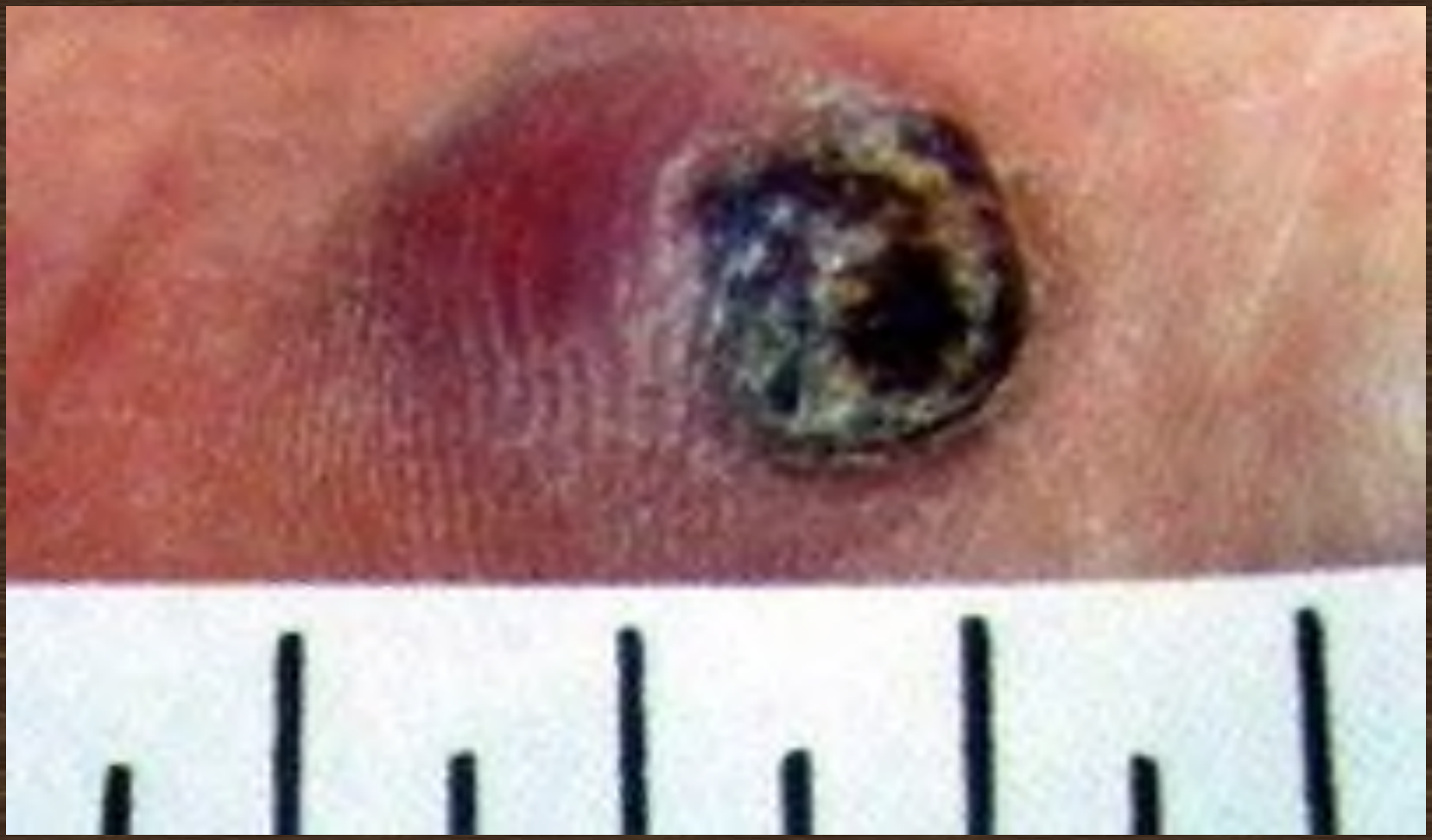
Melanoma



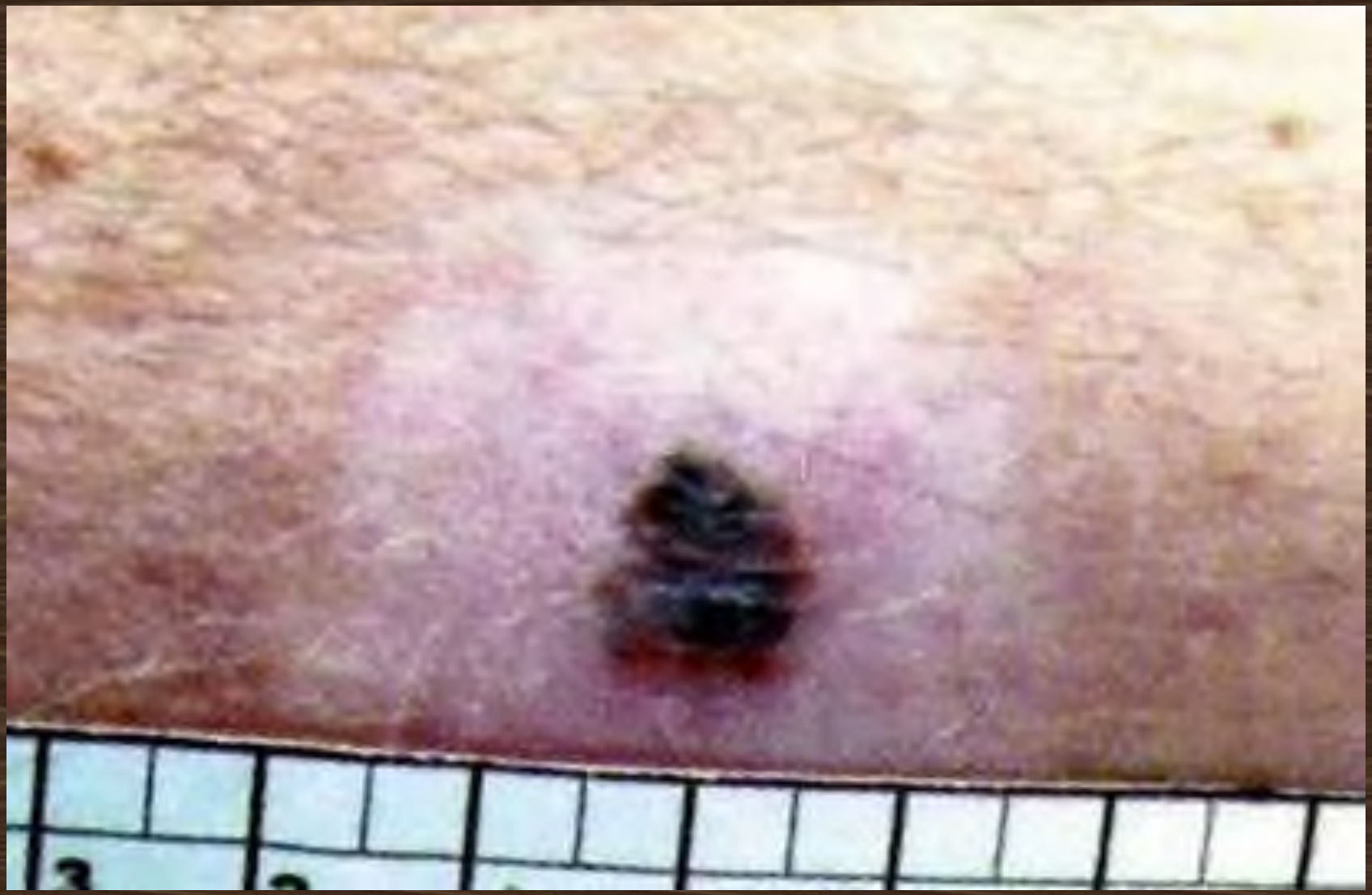
-Violation or total absence
skin pattern
Hyperpigmentation of education
-Uneven coloration, partial (uneven) or complete change in the color of the nevus melanoma
The appearance of a glossy surface



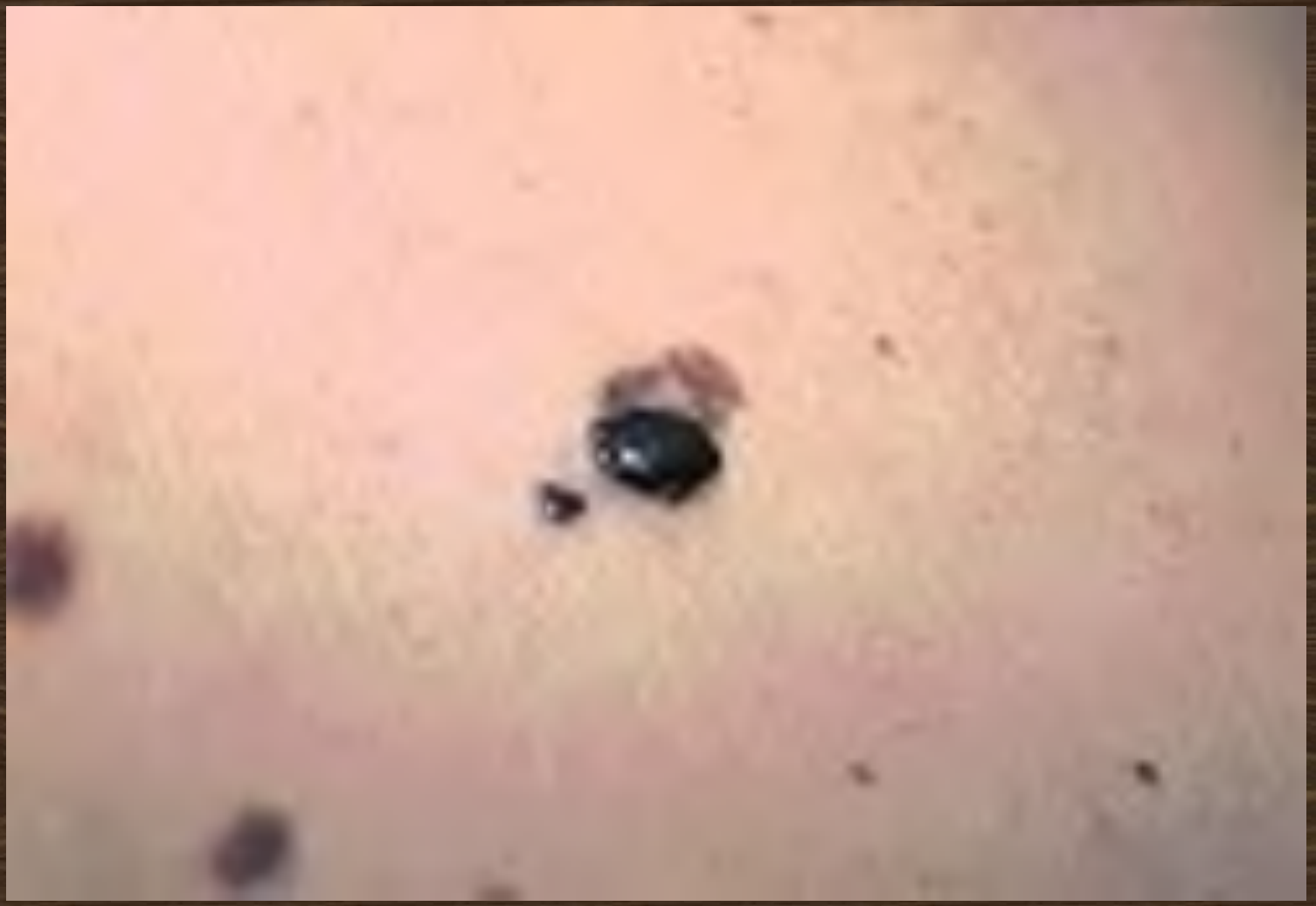
The appearance of an inflammatory areola around



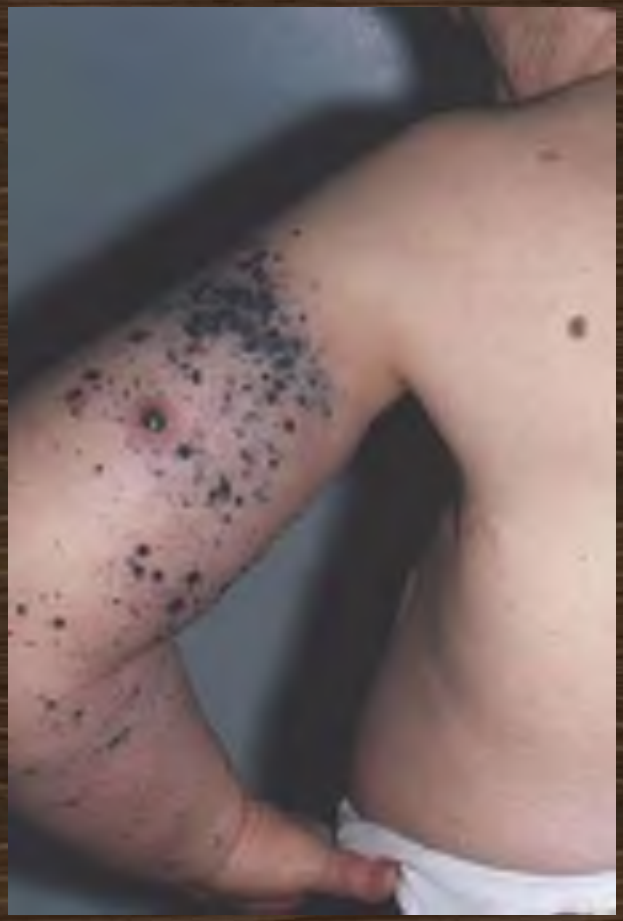
Changing the configuration along the periphery, "blurring" boundary contours



The emergence of pigmented children or pink formations (satellites) in the skin around nevus-melanoma

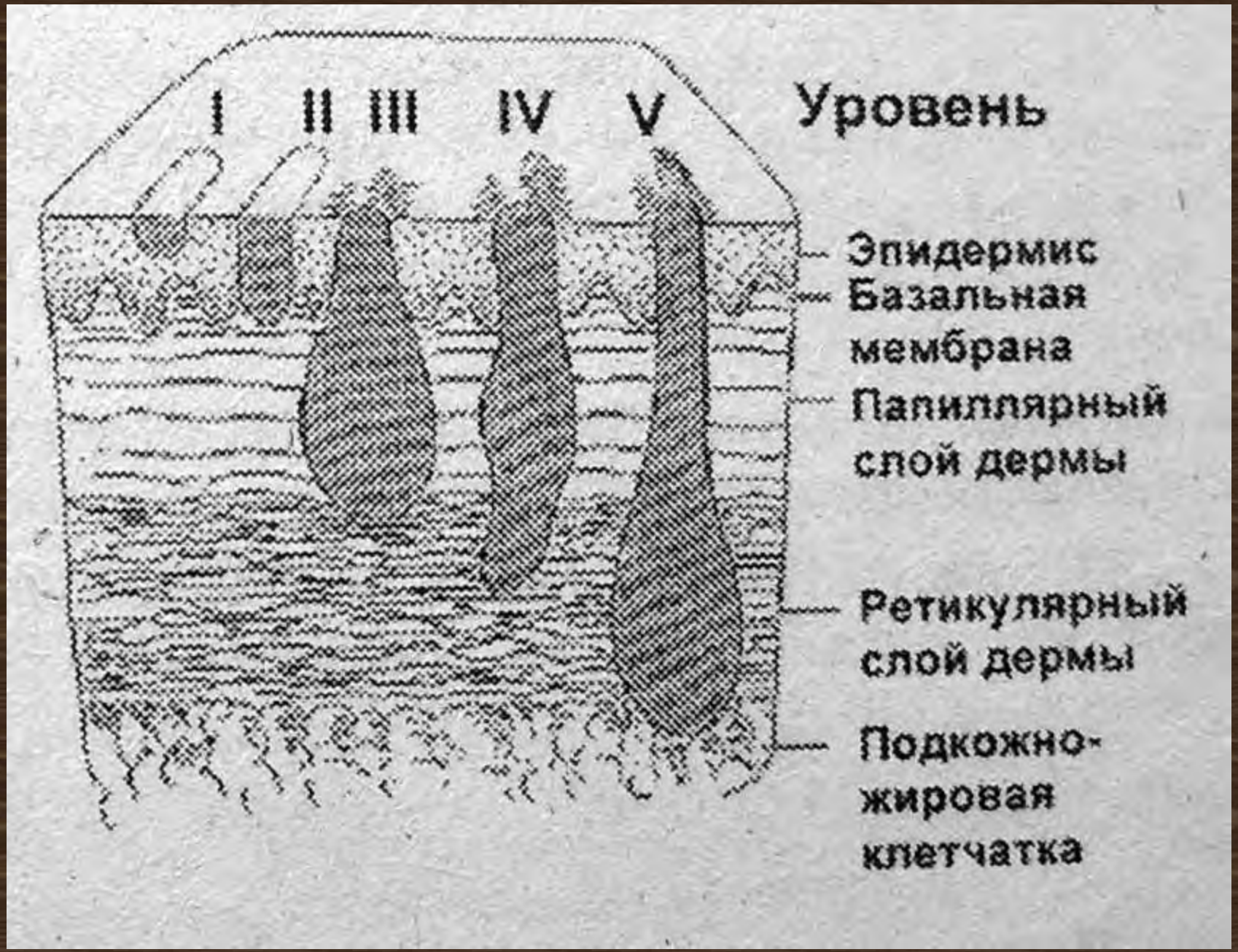


Melanoma with satellites



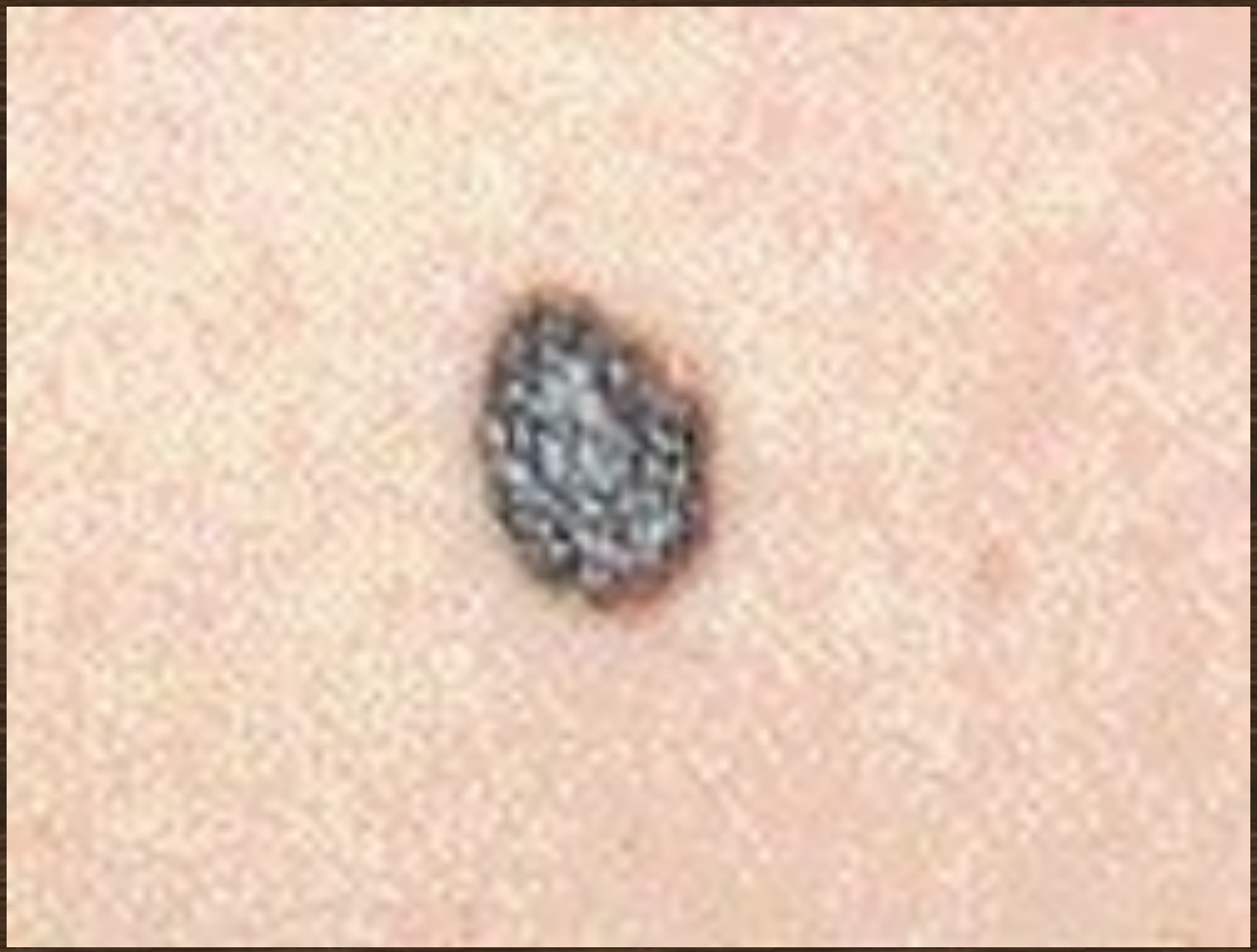
Levels of Invasion by Clark

- I level - melanoma cells within the epidermis (melanoma in situ)
- II - the tumor destroys the basal membrane and invades the upper parts of the papillary layer of the dermis
- III - Melanoma cells fill the papillary layer of the dermis
- IV - invasion of the reticular layer of the dermis
- V - invasion of the underlying fatty tissue

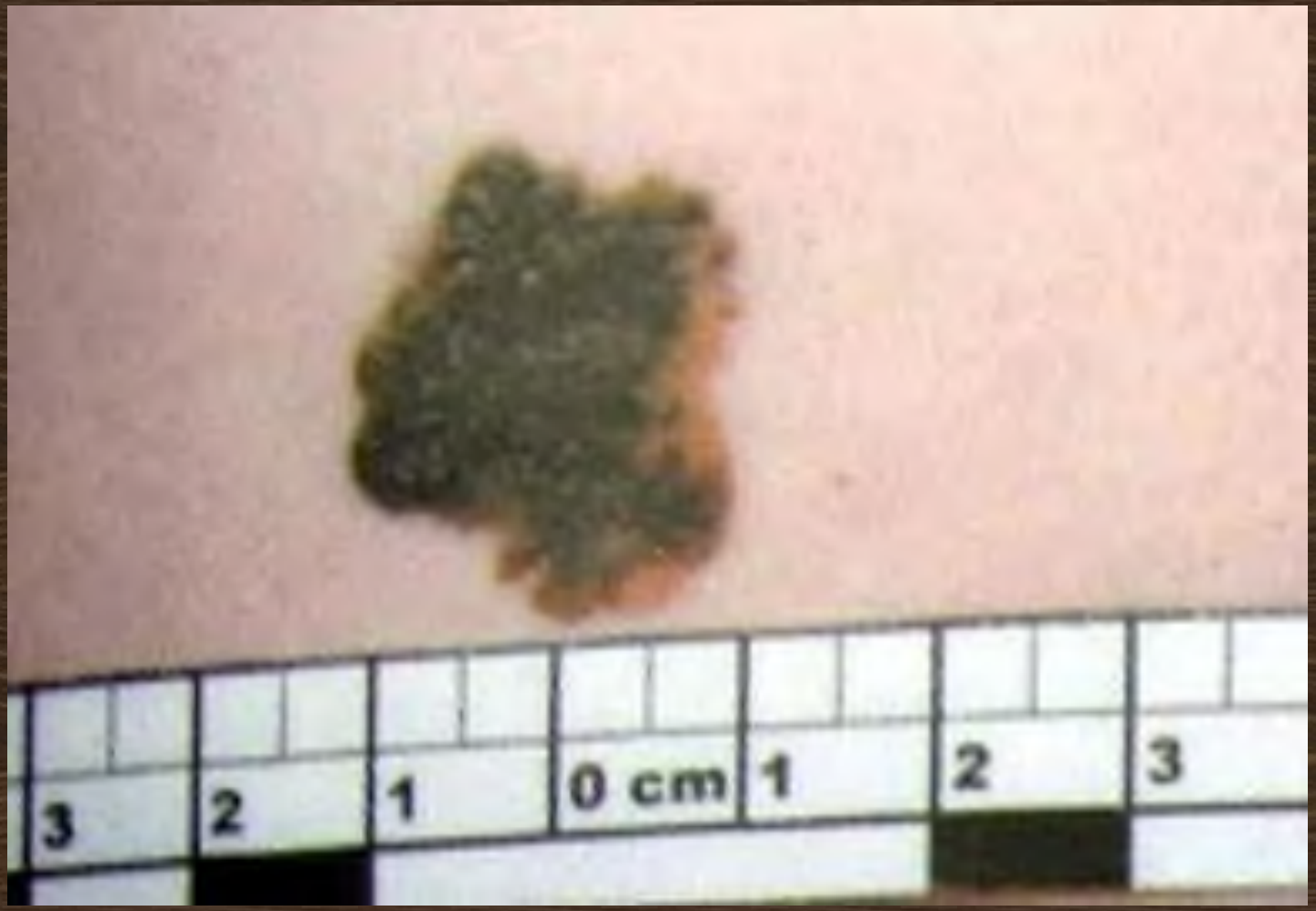

I
II
III
IV
V
Уровень
Эпидермис
Базальная мембрана
Папиллярный слой дермы
Ретикулярный слой дермы
Подкожно-жировая клетчатка

Characteristic	Surface - melanoma spreading	Nodal melanoma	Melanoma of the skin such as malignant lentigo	Acryl-lentiginous melanoma
Average age	45 years	50 years	70 years	60 years
Phases of radial growth	More 5 years	Absent	10 – 20 years and more	About 2 years
Localization	Torso and lower limbs	Any, more often a trunk, a head, a neck	Head, neck, brushes	Palms, soles, area nail bed
color	Characteristic uneven coloring and disorderly mixing of colors-brown of different shades, blue-black, pink; the borders of lesions are at least partially elevated above the skin level (determined visually or by palpation)	Purple or blue - black; color uniform or with impregnations of brown or black areas	Flat areas are characterized by a brown color of different shades, gray and whitish blotches are possible; for the nodes are characterized by reddish-brown, bluish-gray, bluish-black color	On the flat areas, dark brown predominates, on the raised skin above the surface-brownish-black or blue-black color
Frequency(%)	65	25	7	3

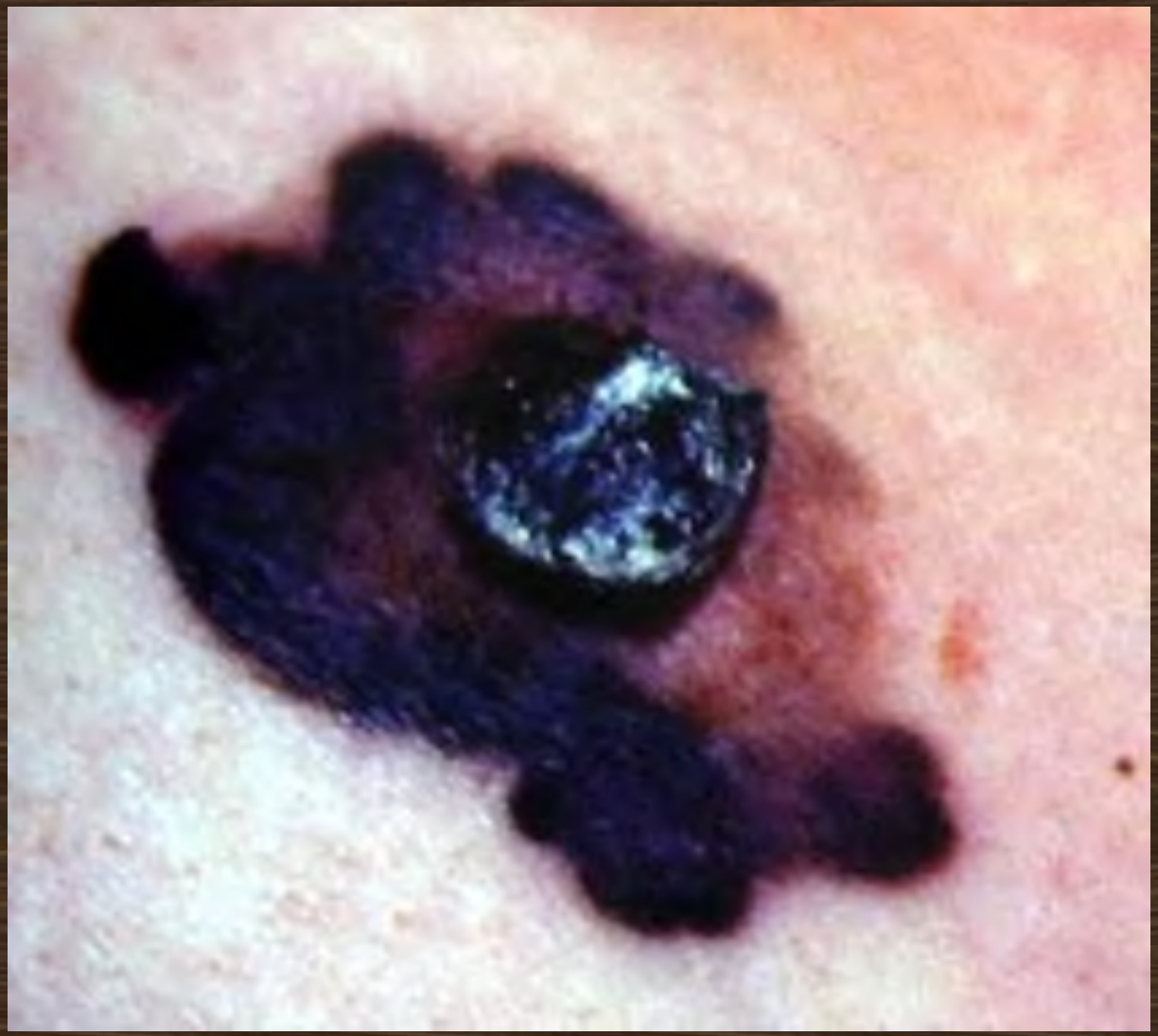
Superficial melanoma. Some roughness of the edges, staining and inflammation of the edges are noted.



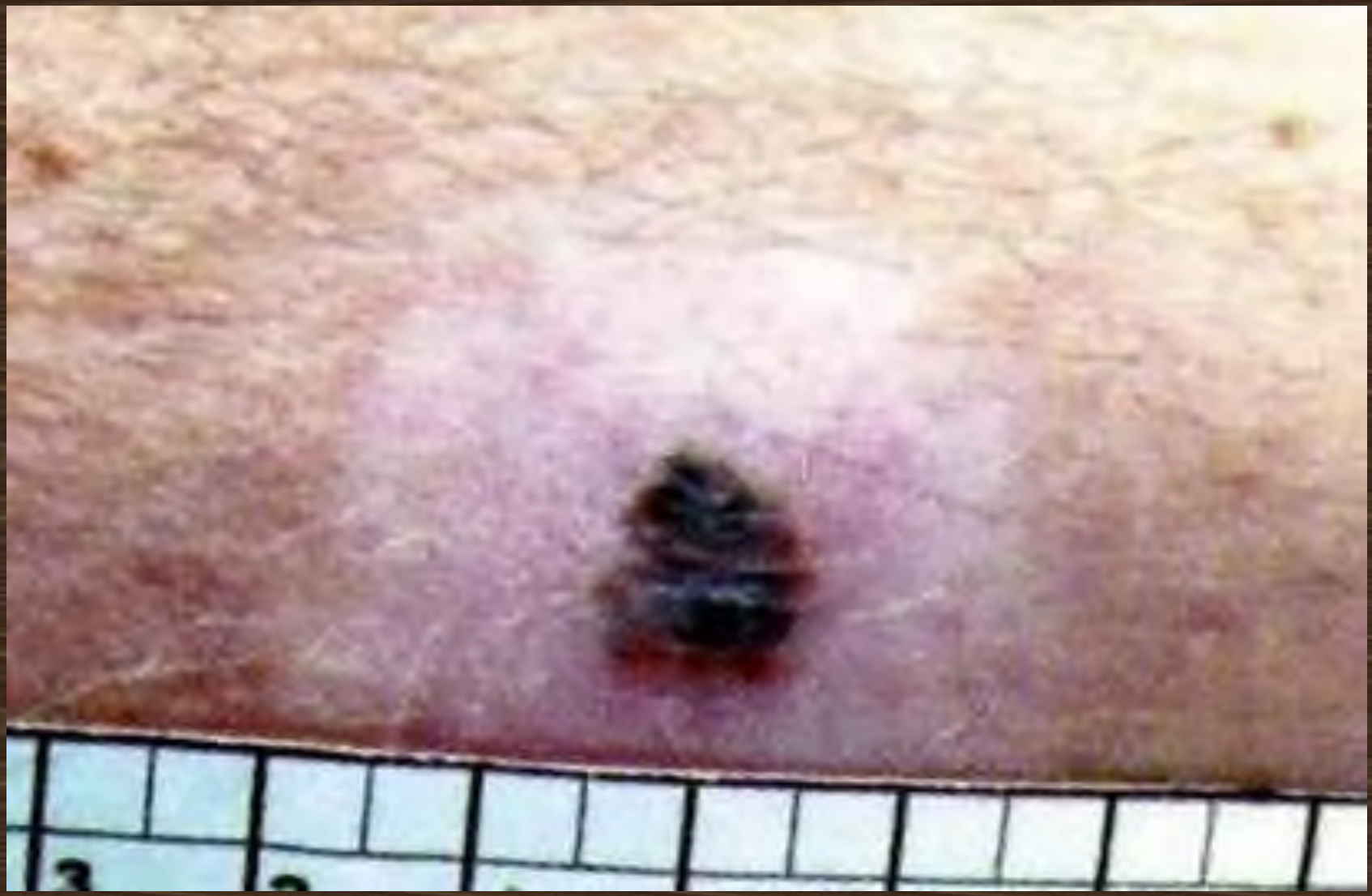
Surface-spread skin melanoma in the radial growth phase



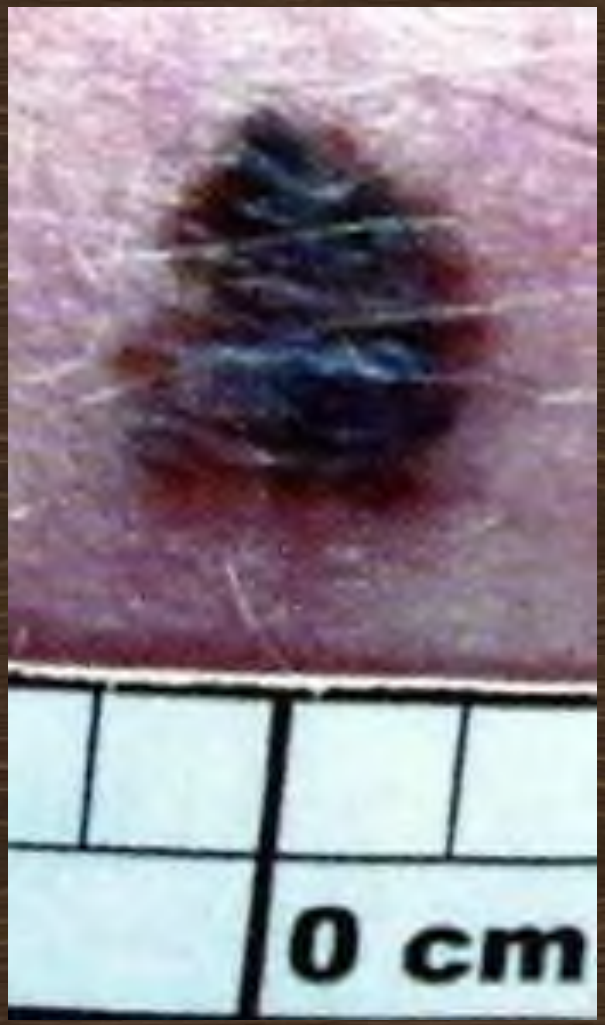
Surface-spreading skin melanoma in the phase of vertical growth.



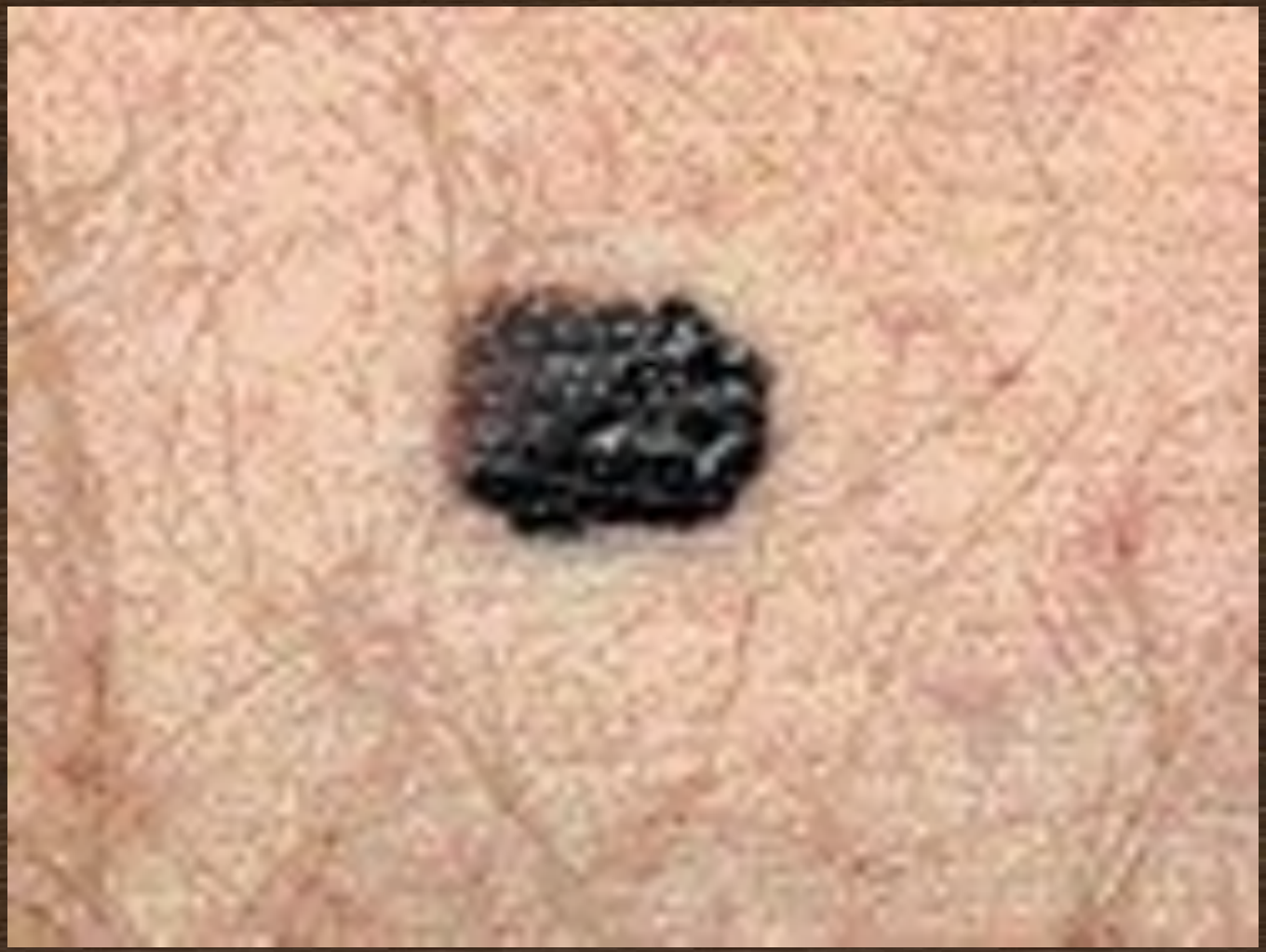
Surface-spreading skin melanoma in the stage of partial spontaneous regression (general plan)



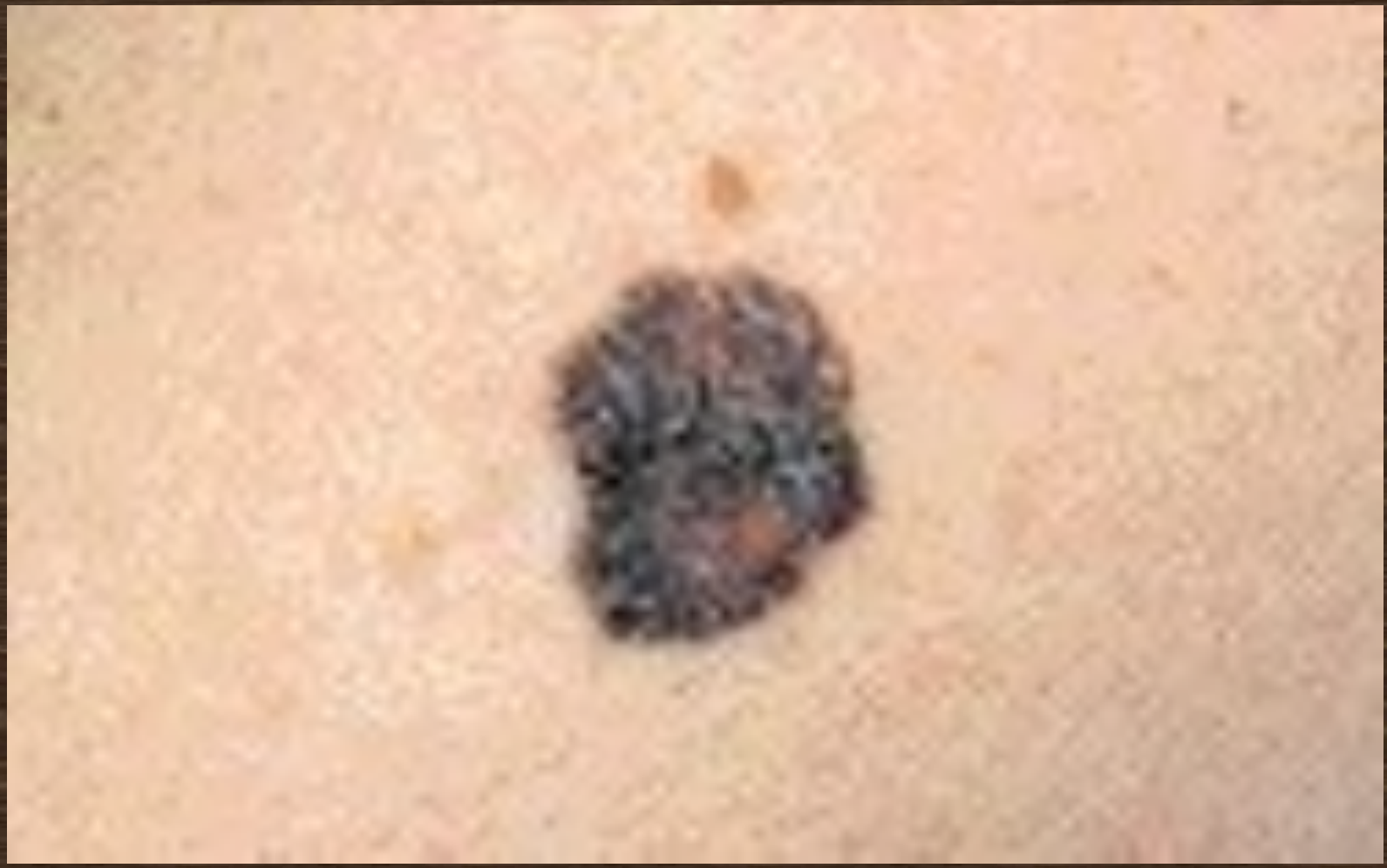
Surface-spreading skin melanoma in the stage of partial spontaneous regression (close-up)



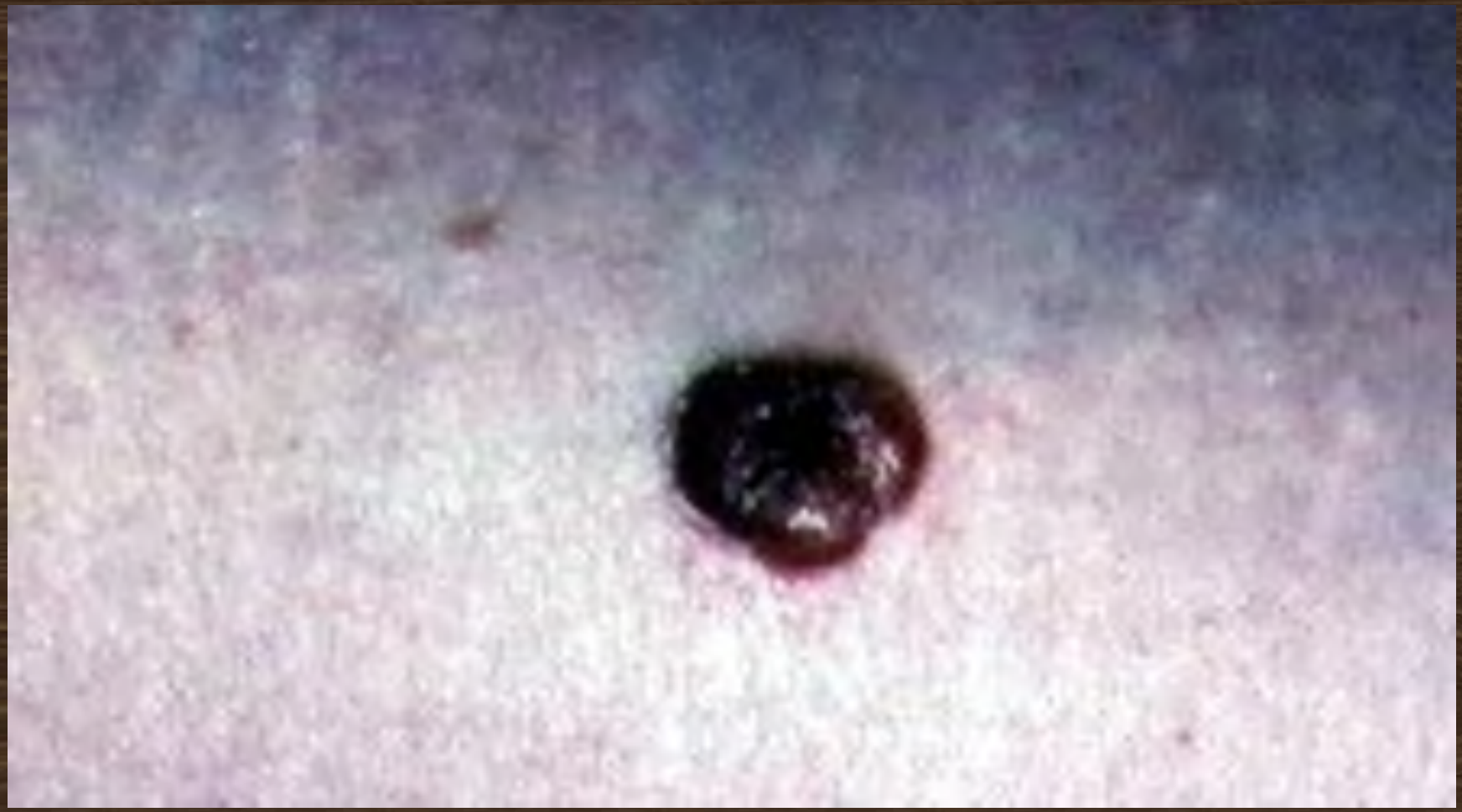
Superficial widespread melanoma. Wrong shapes, uneven contours and staining.



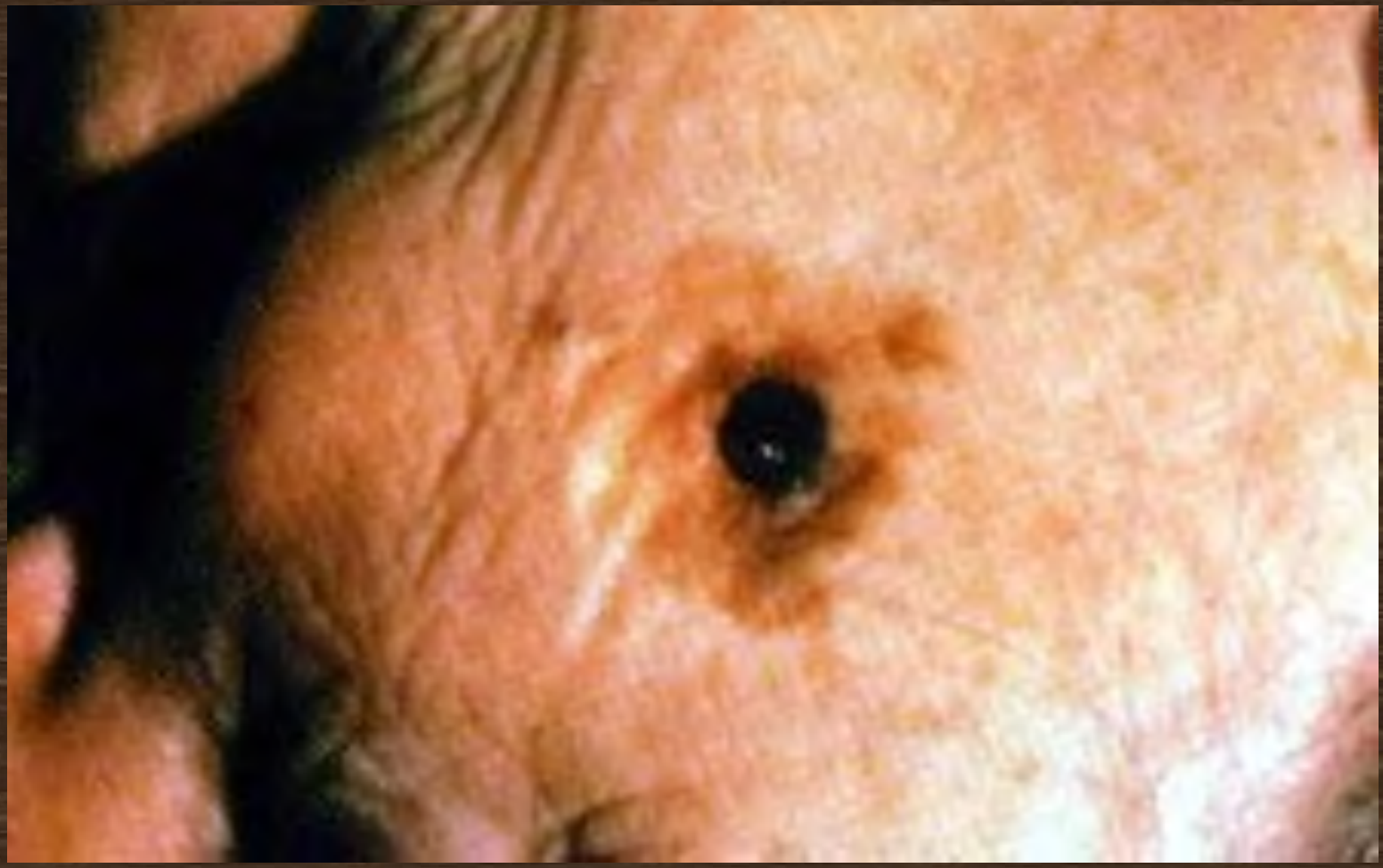
Superficial widespread melanoma. More than 7 mm in diameter, uneven contours and staining.



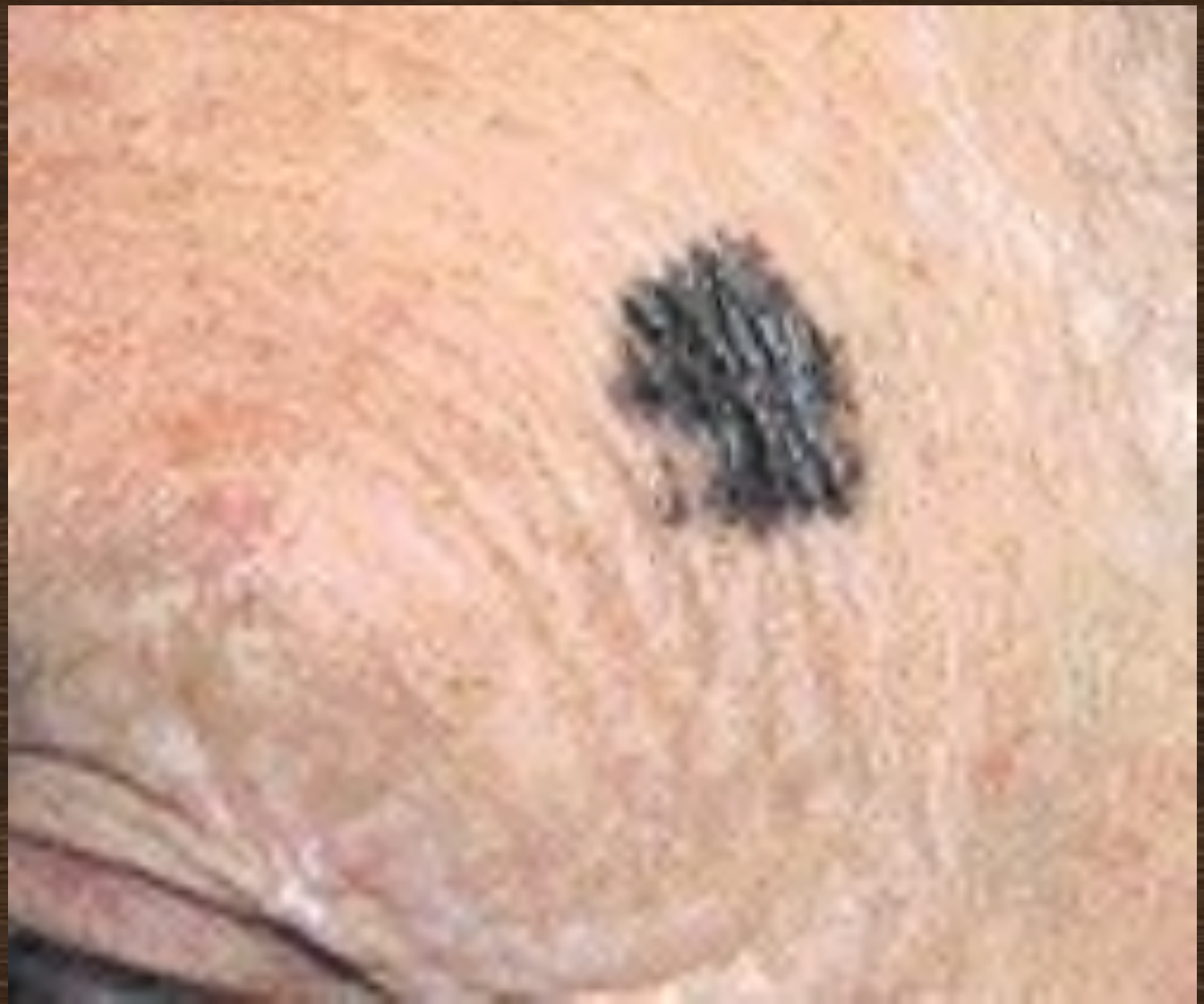
Nodal melanoma



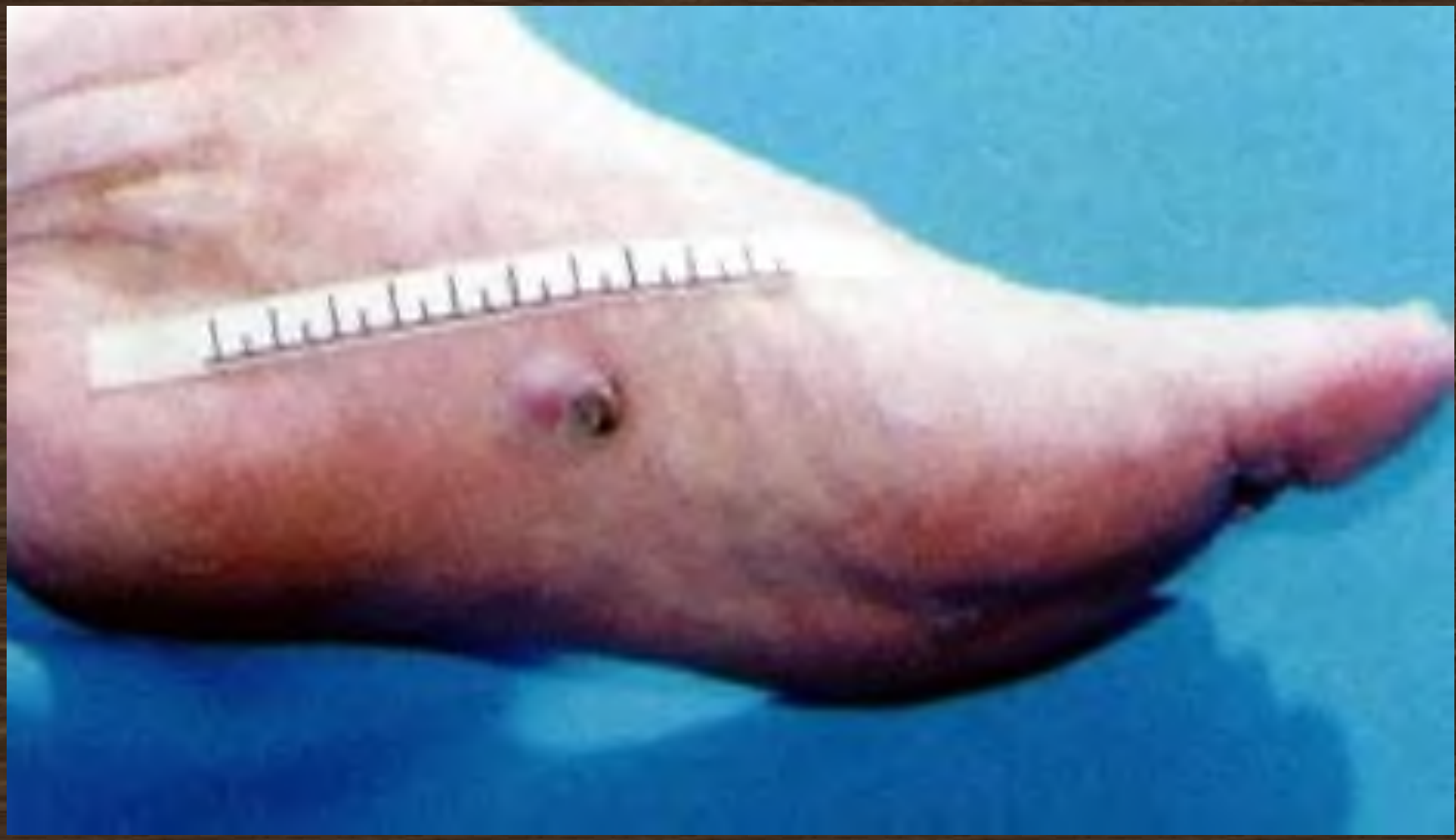
Lentigo melanoma skin



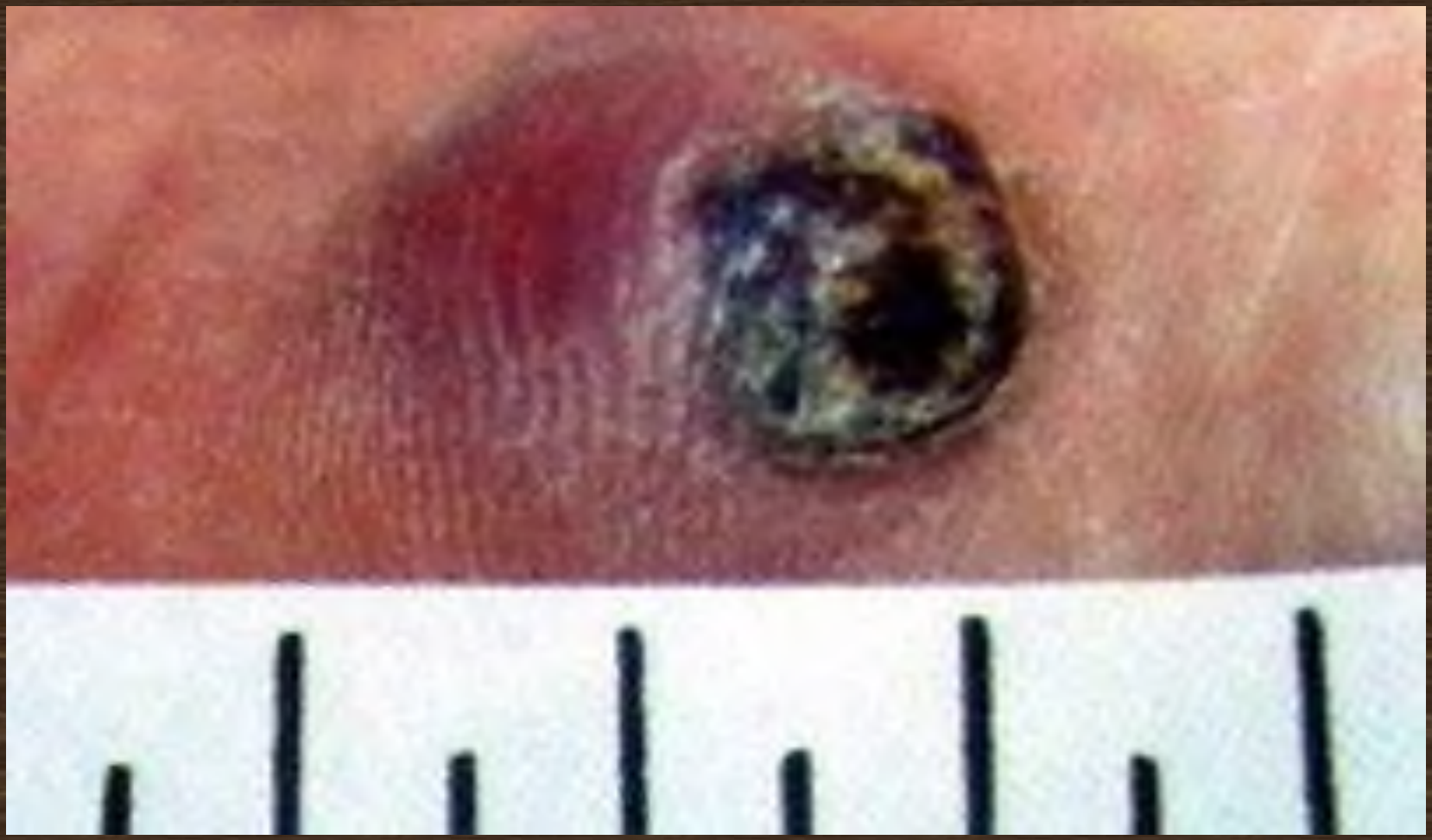
Malignant lentigo.



Acryl-lentiginous skin melanoma (general plan)

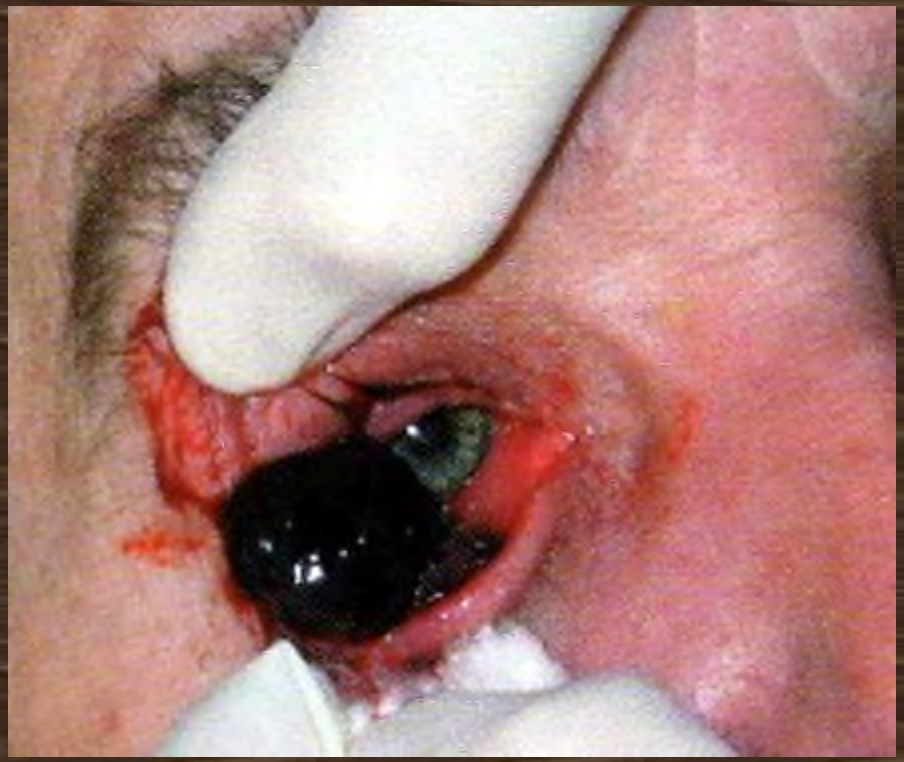


Acryl-lentiginous melanoma of the skin (close-up)

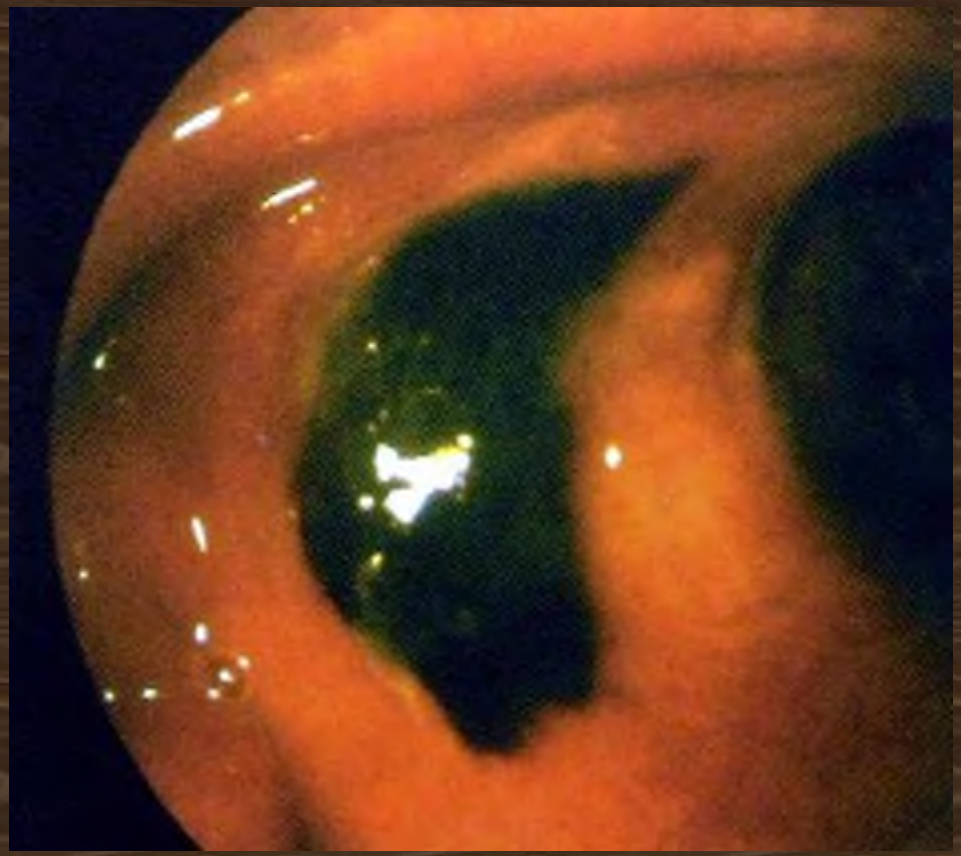


The triggered subungual melanoma

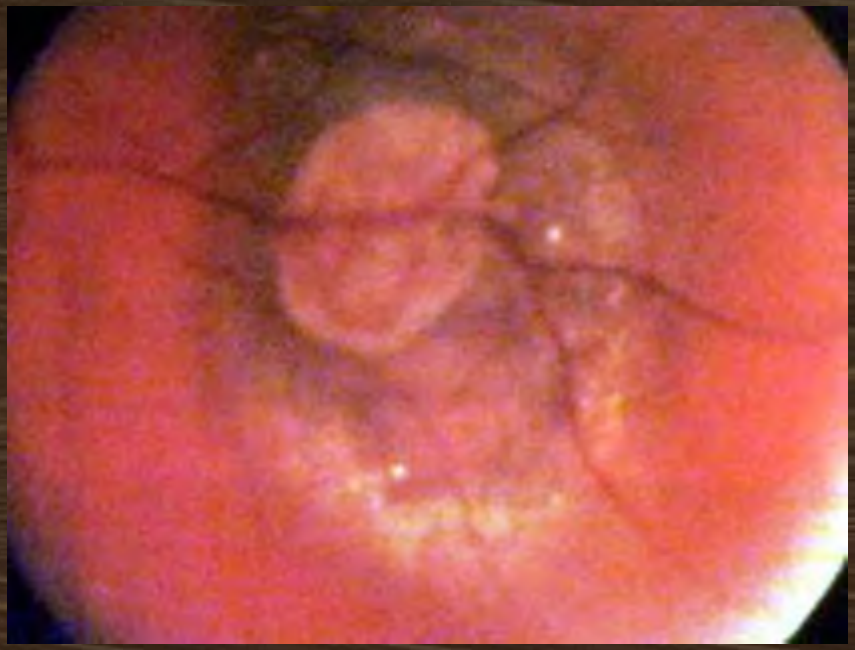
Melanoma of the conjunctiva



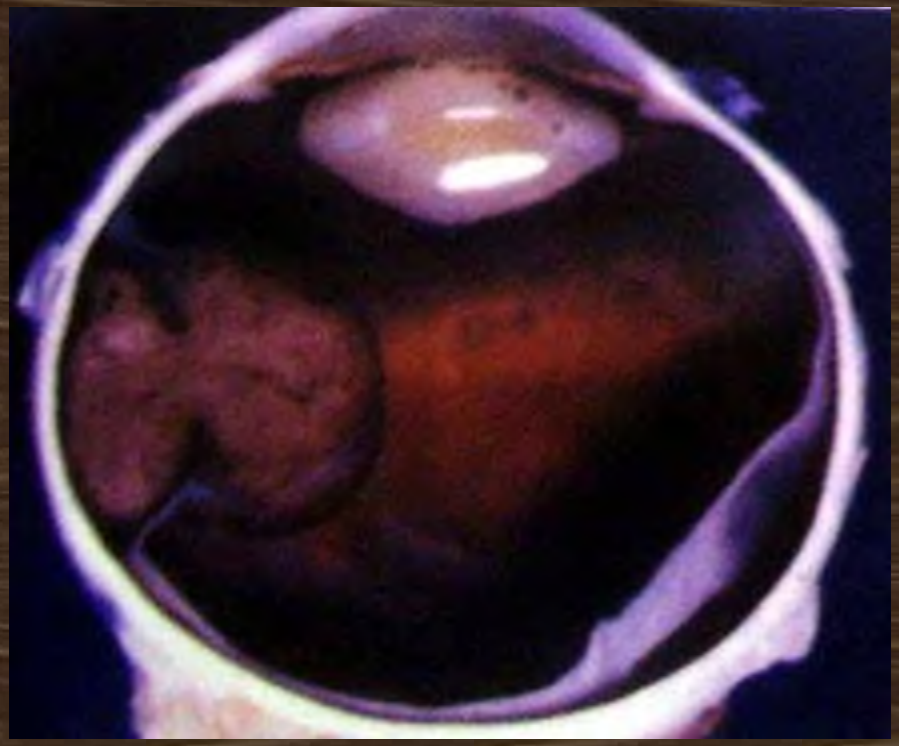
Pigmented melanoma of bulbar conjunctiva



Mushroom form of choroidal melanoma



Enucleated eye. Canine melanoma is visible



Classification of skin melanoma by Sylvain

- I - primary localized melanoma without regional and distant metastases
- call
- Ia - primary melanoma, subjected to excision biopsy of not more than 1
- a month ago
- Ib - local recurrence of the primary tumor
- Ic - primary - multiple melanoma
- II - the presence of metastases in the regional lymph nodes
- IIa - primary tumor with synchronously developed regional metastases
- IIb - regional metastases appeared after excision of the primary tumor
- IIc - local recurrence in combination with regional metastases
- IId - regional metastases without clinically defined primary tumor
- III - disseminated melanoma (with or without primary tumor)
- IIIa - visceral metastases or metastases in more than one regional
- lymphatic reservoir
- IIIb - multiple skin and subcutaneous metastases.

Classification of TNM International Cancer Alliance

- Classification rules:
- There should be a histological confirmation of the diagnosis. When evaluating categories N and M, the following methods are used:
- N categories - physical examination and imaging methods
- M categories - physical examination and imaging methods
- Regional lymph nodes
- Regional lymph nodes are nodes that correspond to the localization of the primary tumor.
- Unilateral tumors:
- Head, neck. Preauric on the lesion side, submandibular, cervical and supraclavicular lymph nodes.
- Rib cage. Axillary lymph nodes on the affected side.
- Arm. Lymph nodes in the ulnar fossa and axillary on the side of the lesion.
- Abdominal wall, loin, buttocks. Inguinal lymph nodes on the affected side.
- Leg. Popliteal and inguinal lymph nodes on the affected side.
- Anal margin and perianal skin. Inguinal lymph nodes on the affected side.
- Переводчик

Stage of the disease	Criteria*	Definition (thickness of the tumor according to Breslow, level of invasion according to Clark)
IA	$pT_1 N_0M_0$	Thickness of the tumor ≤ 0.75 mm, level of infestation-II
IB	$pT_2 N_0M_0$	Thickness of the tumor from 0.76 to 1.5 mm and / or level of infestation - III
IIA	$pT_3 N_0M_0$	Thickness of tumor from 1.51 to and / or level of invasion - IV
IIB	$pT_4 N_0M_0$	Thickness of the tumor> 4.0 mm and, or level of infestation -V
III	$pT_{1-4} N_1M_0$ $pT_{1-4}N_2M_0$	Regional metastases up to 2 cm in diameter Regional metastases more than 2 cm in diameter and / or transient metastases
IV	$pT_{1-4} N_{1-2}M_1$	Remote metastases

Criteria	Definition	
	T - primary tumor	
pT_1	≤ 1 mm	pT1a - invasion level II or III, without ulceration pT1b - level of IV or V invasion, or with ulceration
pT_2	1,01 – 2 mm	pT2a - without ulceration pT2b - with ulceration
pT_3	2,01 – 4 mm	pT3a - without ulceration pT3b - with ulceration
pT_4	> 4 мм	pT4a - without ulceration pT4b - with ulceration
	N - regional lymph nodes	
pN_1	1 lymph node with metastasis	pN1a – micro-metastasis * pN1b – macro-metastasis **
pN_2	2 - 3 lymph nodes with metastases	pN2a – micro-metastasis * pN2b – macro-metastasis ** pN2c - transient metastases / satellites without regional metastases
pN_3	4 or more lymph nodes with metastases or granulose metastases / satellites with regional metastases	
	M - distant metastases	
M_1	M1a: skin, subcutaneous fatty tissue or regional lymph nodes	
	M1b: lungs	
	M1c: other organs or any localization with an increase in LDH level	

Grouping by stages

Stage 0	pT_{is}	N_0	M_0
Stage IA	pT_{1a}	N_0	M_0
Stage IB	pT_{1b} pT_{2a}	N_0 N_0	M_0 M_0
Stage IIA	pT_{2b} pT_{3a}	N_0 N_0	M_0 M_0
Stage IIB	pT_{3b} pT_{4a}	N_0 N_0	M_0 M_0
Stage IIC	pT_{4b}	N_0	M_0
Stage IIIA	$pT_{1a\text{-}4a}$	$N_{1a\ 2a}$	M_0
Stage IIIB	$pT_{1a\text{-}4a}$ $pT_{1b\text{-}4b}$	$N_{1b,\ 2b,\ 2c}$ $N_{1a,\ 2a,\ 2c}$	M_0
Stage IIIC	$pT_{1b\text{-}4b}$ pT any	$N_{1b,\ 2b}$ N_3	M_0 M_0
Stage IV	pT any	N any	M_1

Selection of prognostic groups

- Patients who have a very high risk (more than 80%) die from the progression of the disease within 5 years of diagnosis - in the presence of distant metastases (stage IV).
- Patients who have a very high risk (50-80%) of recurrence of melanoma of the skin for 5 years from the time of surgery, if there are metastases to regional lymph nodes (stage III), and also with a primary tumor thickness exceeding 4 mm (IIb-IIc stage).
- Patients who have an intermediate risk (15-50%) of recurrence of the disease - with a primary tumor thickness of 2.0mm to 4.0mm (IIa - IIb stage).
- Patients with a low risk of recurrence (up to 15%), with primary tumor thickness less than 2.0 mm (I-IIa stage).

Clinical diagnosis

- The change in the appearance of the nevus is the first sign of melanoma in 70% of patients. The nevus lightens or darkens, acquires an uneven color, increases, itching may occur. Ulceration and bleeding occur in neglected cases.
- Unchanged skin is the source of melanoma in 30% of patients.
- Symptoms of distant metastases depend on their localization.

Functional study

- Carefully inspect the skin, including armpits, the scalp, interdigital folds, genitalia, perianal region, the oral mucosa. Palpate all available regional lymph nodes and liver. A palpation study of the primary tumor and surrounding soft tissue is performed.

Instrumental diagnostic methods

- Collection of cytological material from the surface of the tumor in the presence of ulceration of the epidermis above it;
- Ultrasound examination of the primary tumor in order to determine its thickness and depth of invasion;
- Ultrasound examination of the lymph nodes of the regional lymphatic reservoir;
- Ultrasound examination of the abdominal cavity and retroperitoneal space;
- Dermatoscopy or epiluminescent microscopy;
- Radioisotope (radiophosphor) diagnostics;
- Radiography of chest organs;
- Thermometric and thermographic diagnostics.

Indications for biopsy

- A biopsy is indicated in case the whole complex of diagnostic measures has not given the opportunity to verify the diagnosis.
- Biopsy is indicated with small linear incisions (10-15 mm).
- A biopsy is indicated if there is a doubt in the clinical diagnosis, and extensive excision of the tumor can lead to a cosmetic defect in the patient.
- A biopsy is indicated if the patient is scheduled a crippling operation - amputation of the fingers or limbs, mastectomy, one-stage preventive regional lymphadenectomy.

Differential diagnosis of primary skin melanoma

- Nevus: juvenile melanoma (nevus Spitz)
- blue nevus
- halo - nevus
- dysplastic nevi
- Hemangioma: cavernous thrombosed hemangiomas
- Atheroma.
- Benign skin tumors: papilloma, keratoacanthoma, pyogenic granuloma (bortiomycoma), adenomas, cystadenomas, epitheliomas, angio-, dermato-, neurofibromatosis.
- Precancerous tumors of the epidermis: seborrheic keratoma, Bowen's disease.
- Malignant skin tumors: squamous cell carcinoma, basioma, Kaposi's sarcoma, fibro-, leiomyo- and lymphosarcoma, skin lymphoma, adenocarcinoma of the appendages of the skin.
- Dermatovenereological diseases: fungal lesion of the nail bed of the fingers (onychomycosis), extrathin hard chancre.
- Injuries: subungual and subepidermal hemangiomas.
- Metastases of tumors of other localizations: cancer of the lung, esophagus, stomach, pancreas, breast, ovaries, kidneys, melanoma.

Treatment of skin melanoma

Stage of the disease	Methods of treatment
I	Surgical treatment
II	Surgical, adjuvant treatment
III	Surgical, adjuvant treatment
IV	Systemic treatment, cytoreductive surgery

Today, the "gold" standard for the treatment of primary tumor and metastases in regional lymph nodes is surgical intervention, which often allows for a complete cure. However, it is difficult to find another such tumor in clinical oncology, the surgical treatment of which would have so many features:

Typical surgical interventions on the regional lymphatic apparatus are:

- a) fascial - cervical excision of cervical tissue;
- b) fusillary removal of the submaxillary and chin lymph nodes - upper neck excision according to the 1st variant;
- c) fusillary removal of submaxillary, chin and upper deep cervical lymph nodes - upper cervical excision according to variant II;
- d) radical removal of the cervical lymph nodes - Krahl's operation;
- e) axillary lymphadenectomy with removal or abandonment of the pectoralis muscle;
- e) inguinal and femoral lymphadenectomy (Duquesne's operation);
- g) inguinal iliac lymphadenectomy;
- h) monoblock excision of the primary tumor with regional lymph nodes;

Radiation therapy.

- Treatment or adjuvant radiotherapy is used in weakened patients or in refusing surgery. Irradiation significantly reduces the risk of relapse with desmoplastic melanoma.

Systemic Therapy

- Long-term follow-up is necessary to evaluate the effectiveness of any systemic therapy.

Adjuvant (additional) treatment

- Prophylactic or adjuvant therapy is a complementary form of drug therapy complementary to a surgical technique that is performed to eradicate or prolong the suppression of cancer micrometastases after removal or radiotherapy of a primary tumor.

The effectiveness of adjuvant therapy

- Dacarbazine up to 12%
- Interferon alfa 3mln / m2 3p / week up to 10%
- Interferon alfa 10mln / m2 3 r / week 14 - 22%
- Interferon alfa 10 million / m2 daily to 22%
- Intperferon alfa 30 million / m2 3p / week to 27%

The effectiveness of chemotherapy metastatic forms

- Dakarbazin (1 line, mono, N60, research of Ukraine)
- Partial regression 11.7%
- Stabilization of 31.7%
- Progression 56.6%
- Median survival 9 months
- Lomustine (2 lines, mono, N10 from the previous 60)
- Partial regression of 10%
- Stabilization (short-term) 30%
- Progression of 60%

Zelboraf (vemurafenib)

- Vemurafenib is a potent kinase inhibitor of a mutating BRAF molecule that targets its antitumor effects on cells showing the mutation of BRAFV600E, rather than wild-type BRAF.
- The study of BRIM-3 (OB and PFS in 598 patients with inoperable melanoma IIIC or IV stage with mutation BRAFV600E)
- Survival (months) of WWV
- Dacarbazine 9.7 1.6
- Vemurafenib 13.6 6.9

Tafinlar (dubrafenib).

- Dabrafenib is an inhibitor of BRAF
- N = 250 stage IV or inoperable MM stage III, showing the mutation BRAFV600E

- Survival without progression (months)
- Dacarbazine 2.7
- Dabrafenib 5.1

Mechinist (trametinib)

- Activated BRAF phosphorylates and activates the downstream MEK 1/2 proteins, resulting in increased phosphorylation of ERK1 and ERK2 MAPKs and transcription of the genes responsible for cell growth and proliferation.
- Survival without progression months)
- Trametinib 4.8
- Chemotherapy (dacarb or paclit) 1,5
- Survival 6 months
- Trametinib 81%
- Chemotherapy (dacarb or paclit) 67%

Ervoi (ipilimumab)

- A human monoclonal antibody of the IgG1 type, designed to inhibit the activity of CTLA-4 and allowing the activation and proliferation of T lymphocytes
- Phase 3 testing in patients with inoperable stage III or IV melanoma and unsuccessful previous treatment was randomly assigned in a 3: 1: 1 ratio of ipilimumab plus gp100 (a vaccine derived from melanosomal glycoprotein 100), one ipimumab, or one gp100 at a dosage of 3 mg / kg weight every 3 weeks for ≤4 treatment regimens.
- Average survival (month):
- IAS 10
- IPI + gp100 10
- gp100 6.6
- Overall survival (%) 12 months 18 months 24 months
- IPI 43.6 30.0 23.6
- IPI + gp100 45.6 33.2 23.5
- gp100 25.3 16.3 13.7

Keitruda (pembolizumab)

- Pembrolisumab is a highly selective humanized monoclonal antibody of the IgG4 isotype, blocks the PD-1 receptor expressed on effector activated T lymphocytes.
- A randomized phase 3 trial in patients who had not previously received treatment, or who had previously received ipilimumab.
- The annual OS was 67% (63% for those receiving ipilimumab and 71% for those who did not receive ipilimumab); Survival in 2 years was 50% (46% for those receiving ipilimumab and 53% for those who did not receive ipilimumab).

Prevention of melanoma of the skin

- Limitation of the damaging effect on the skin of UV rays, ionizing radiation, electromagnetic radiation, as well as chemical carcinogens. In addition, doctors and the public should be aware of the potential for potential use of certain hormonal drugs (exogenous estrogens).
- Clinical examination of persons with a congenital predisposition to melanoma, including patients with familial melanoma, their relatives, as well as with dysplastic nevus syndrome. For the above categories of individuals and their relatives, it is advisable to observe in the medical genetic consultations.
- Identification and treatment of people with various forms of immunodeficiency, immunosuppression, including drug, in patients with transplanted organs.
- Formation of groups or contingents of an increased risk of developing melanoma by isolating them from the general population based on known risk factors. It:
- people with impaired pigmentation (light phenotype)
- people who take hormonal drugs for a long time
- people with genetically determined or acquired immunodeficiency
- relatives of patients with melanoma
- people with the presence of Melanesia Dibrell
- People with dysplastic nevus syndrome and their relatives
- people who have pigmentation nevus skin size 1.5 cm or more visually black or dark brown in color
- people who have on the skin more than 50 pigmentation nevus's of any size
- People who have a single traumatized pigment nevi or nevi, who are constantly exposed to mechanical trauma.

Secondary prevention of skin melanoma

- Secondary prevention of skin melanoma is the timely detection and surgical removal of pre-blastomatous skin formations in healthy people.
- With Dufreule's melanosis, the need for preventive excision is beyond doubt
- large and giant nevi
- nevi, which because of their localization are subject to traumatization
- dysplastic nevi

Спасибо за внимание!