There is a diagnostically important group of entities called non-melanocytic melanoma look-alikes, which includes neoplastic processes, lesions that are associated with melanosis, non-neoplastic mimickers of melanoma and melanosis, technical artifacts and immunohistochemical pitfalls.

**BENIGN NEOPLASMS**

**PIGMENTED LICHEN PLANUS-LIKE KERATOSIS**

Pigmented lichen planus-like keratosis with an associated dense inflammatory infiltrate of lymphocytes and melanophages can resemble regressing malignant melanoma. Very often, pigmented basal keratinocytes with vacuolar alteration can look like melanocytes Clues for a diagnosis of LPLK are the presence of necrotic keratinocytes in the upper layers of the epidermis, enlarged keratinocytes in the spinous layer, parakeratosis and adjacent solar lentigo. Immunostains for melanocytic markers are needed to better evaluate these lesions.

**PIGMENTED SEBORRHEIC KERATOSIS**

In patients with dark skin, pigmented seborrheic keratoses are frequently associated with pigmented dendritic melanocytes, which can be confused with a melanoma in situ colliding with a seborrheic keratosis.

**MALIGNANT NEOPLASMS**

Although these lesions are malignant, their prognosis is generally better than melanoma. Therefore, they still qualify for this presentation.

**SQUAMOUS CELL CARCINOMA**

There are variants of squamous cell carcinoma that resemble melanoma in situ. These variants have neoplastic keratinocytes with pale cytoplasm that are arranged in clonal aggregates and as single cells in a pagetoid pattern. Sometimes the intercellular bridges are not evident. Some pigmented squamous cell carcinomas in situ are colonized by pigmented dendritic melanocytes, as seen in pigmented seborrheic keratosis. Positive immunoreaction for keratins AE1/AE3, 34bE12 and p63 will be helpful to define the keratinocytic nature of the squamous cells. There are squamous cell carcinomas in situ with sebaceous differentiation in which the epithelial cells have abundant pale staining cytoplasm which can mimic a subset of melanoma in situ. In these cases, positive immunoreaction for epithelial membrane antigen will confirm the sebaceous differentiation.
PAGET’S DISEASE

The atypical epithelial cells in Paget’s disease usually have pale staining cytoplasm, and are arranged as clusters and as single cells with a pagetoid spread in the upper levels of the epidermis that mimic melanoma in situ. In some cases, Paget’s cells can contain melanin in their cytoplasm. Clues for the diagnosis of Paget’s disease include the location of Paget’s cells, which are usually above the basal keratinocytes that appear compressed beneath them, the presence of some lumens forming glands, and sometimes Paget’s cells have an eccentric nucleus (signet ring cells).

The cytoplasm of Paget’s cells tends to be amphophilic because of the cytoplasmic mucin which is positive for PAS stain with diastase digestion and positive for mucicarmine stain. Positive immunoreaction for high and low molecular weight keratins, CK7 and carcinoembryonic antigen will establish the diagnosis of Paget’s disease.

WORINGER-KOLOPP DISEASE (PAGETOID RETICULOSIS)

This is a rare variant of cutaneous T-cell lymphoma with marked epidermotropism in which very large, haloed, atypical lymphocytes are present as clusters and as single cells at all levels of the epidermis and mimics melanoma in situ. In some cases, atypical lymphocytes are also aligned along the dermoepidermal junction as seen in melanoma. The presence of cells with large hyperchromatic cerebriform nuclei will favor a diagnosis of an epidermotropic T-cell lymphoma. Immunohistochemistry with positive reaction for T cell marker CD3, and often predominance of CD8, but loss of expression of CD 5 and CD7 will be diagnostic.

MELANOSIS

Melanosis in dermatopathology is defined as increased deposits of dermal melanin, usually in macrophages, and frequently associated with fibrosis and epidermal atrophy. Melanosis can be secondary to regressed benign and malignant lesions, but is more commonly associated with melanoma and pigmented basal cell carcinoma. In benign lesions, it is seen in regressing LPLK and pigmented reticulated seborrheic keratosis. Interface dermatitides such as lichen planus pigmentosus, discoid lupus erythematosus, and fixed drug reaction in patients with dark skin can be associated with marked post-inflamatory hyperpigmentation with numerous melanophages in the papillary dermis resembling melanosis.

MALIGNANT MELANOMA

In melanoma, the melanosis is a manifestation of the regression of pigmented melanocytes and is often associated with epidermal atrophy, dermal fibrosis and proliferation of small blood vessels. The melanoses are mostly present in the papillary dermis, and can be focal or involve broad areas. It can be present above, in the center or at the base of nodular areas.

LICHENOID KERATOSIS (LPLK)

In LPLK the melanosis is arranged as evenly distributed small clusters of melanophages in the papillary dermis associated with epidermal atrophy, aggregates of necrotic keratinocytes and variable infiltrate of lymphocytes. The pattern of melanosis in LPLK has been described as “peppery” and is not associated with fibrosis.
BASAL CELL CARCINOMA (BCC)

In pigmented BCC, melanosis is present as large clusters of melanophages usually in the papillary dermis. It has been called tumoral melanosis.

NON-NEOPLASTIC MIMICKERS OF MELANOMA AND MELANOSIS

MONSEL’S SOLUTION GRANULOMA

When Monsel’s solution (20% ferric subsulfate) is applied to biopsy sites it produces ferrugination of collagen and elastic fibers, and a granulomatous reaction. Monsel’s reaction is identified at healing biopsy sites as abundant intra- and extracellular granular iron deposits with a golden brown color. The pigment forms a subepidermal band associated with fibrosing granulation tissue. A diagnostic clue is the presence of degenerated collagen and elastic fibers, which have a purple gray color and some of them are present in the cytoplasm of multinucleated giant cells admixed with iron. The abundant intra- and extracellular iron deposits are readily highlighted with Perls’ stain.

REGRESSION VS. SCAR

Histopathological identification of regression is usually easy. However, there are some instances when it can be difficult to distinguish regression from scarring fibrosis caused by a previous procedure, external trauma or an associated ruptured cyst or hair follicle. When the tissue sections are stained with elastic Van Gieson stain and/or elastin immunostain, both regression and scars have decreased to absent elastic fibers in the areas of fibrosis. However, areas of regression have a well-defined compressed layer of thin elastic fibers pushed down from the papillary dermis to the base of the fibrosis. In contrast, the base of scars lack this compressed elastic layer and have instead an abrupt transition to the thick elastic fibers of the spared reticular dermis.

TECHNICAL ARTIFACTS

SHRINKAGE ARTIFACT

During processing, the tissues may partially dehydrate and the cells may show partial shrinkage of the cytoplasm and nucleoplasm, which can produce artifactual intracellular and extracellular spaces. Melanocytes exhibit a pericellular halo or space. On the other hand, in keratinocytes the artifact appears as a perinuclear halo. In addition, closer examination reveals the presence of intercellular bridges between keratinocytes in routine sections. Melanocytes should be distinguished from Langerhans cells, which are also dendritic and exhibit a pericellular halo, however, they are usually smaller than atypical melanocytes, have scanty cytoplasm, and have a small nucleus with condensed chromatin. In addition, Langerhans cells are usually located in the mid-spinous layer and are evenly distributed.

TANGENTIAL SECTIONING

Tangential sectioning of the skin will make melanocytes appear positioned above the basal layer, artifactually increased in number and larger than normal. Tangential sectioning is one of the causes for over-diagnosing junctional nevi as malignant melanoma in situ. Serial
sections in mildly tangentially oriented specimens or re-orientation of the specimen in more severely tangentially cut cases will demonstrate that the melanocytes are actually positioned in the basal layer.

AIR BUBBLES UNDER THE COVERSGLIP PRODUCE PSEUDOMELANONYCHIA

When hematoxylin and eosin (H&E) stained tissue sections of nail plates are placed on glass slides and mounted with a plastic coverslip, the sections can show a localized linear area of brown “pigment” in the nail epithelial cells and nail plate. This artifact is produced by tiny air bubbles between the tissue and the coverslip, which can mimic the appearance of melanin deposits, and thus lead to an incorrect diagnosis of melanonychia. Since melanonychia can be a sign of underlying benign or malignant proliferation of melanocytes, recognizing this artifact is essential when evaluating tissue sections. The clues for identifying this artifact are the presence of tiny and more apparent air bubbles. In addition, a Fontana-Masson stain will be negative for melanin.

IMMUNOHISTOCHEMICAL PITFALLS

Immunohistochemical staining for melanocytic markers is nowadays widely used – and sometimes overused – for the evaluation of melanocytic proliferations. However, sometimes the interpretation is incorrect due to the lack of 100% sensitivity, false negative reactions, non-specific reactions reported as positive, and the positive staining of other cell types that are interpreted as melanocytes.

- Melan A is the most widely used melanocytic marker. However, there are non-melanocytic cells, which sometimes can react positively. It has been reported that in lichen planus-like keratosis and in lichenoid dermatitis on sun damaged skin there are single cells and small "pseudo-melanocytic nests" that react strongly positive for Melan-A. Because these cells are located at the dermoepidermal junction, they can be confused with melanoma in situ.

- S-100 protein is highly sensitive, but less specific.
  - Regenerating nerve fibers within scars can be confused with residual spindle cell melanoma.
  - Langerhans cells and dermal dendritic cells can be interpreted as melanocytes.
  - Histiocytes sometimes are positive for S-100 protein.
  - Paradoxically, often junctional melanocytes are not reactive for S-100 protein.

- HMB-45 is negative in spindle cell and desmoplastic melanomas and sometimes negative in the dermal component of thin melanomas.

- Neutrophils, angiomyolipomas, chronic myeloid leukemias and a case of a malignant peripheral nerve sheath tumor with heterologous differentiation have been reported to be positive for PNL2.

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