Lighter shades of pale- the histopathology of disorders of pigmentation

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Disorders of pigmentation are a common problem for dermatologists who see dark-skinned patients. Most of the time, a diagnosis can be made clinically. Many American dermatologists are less familiar with these conditions than are, for instance, Indian dermatologists and may resort to a biopsy to establish a diagnosis. At the same time, there are some conditions (e.g. hypopigmentation due to sarcoidosis or mycosis fungoides) in which a diagnosis cannot be properly established without a biopsy.

We will begin by examining disorders that lead to hypopigmentation, and then consider hyperpigmentation.

**Hypopigmentation**  
(Leukoderma)

**Vitiligo**

Essential features-
- Loss of pigment in skin and hair
- Localized, generalized and universal forms
- Symmetrical distribution
- Early inflammatory form (trichrome vitiligo)
- Lack of melanocytes in basal layer

Vitiligo is one of the most common causes of hypopigmented skin, with significant social consequences to those who suffer from it. The condition usually has its onset in the first half of life, with fewer cases in the middle aged and only rare cases in the elderly. Lesions begin as hypopigmented to completely white macules or patches, usually less than 3 cm in diameter, and having distinct margins. A sharp border is typical. A variegated color is notable
in so called trichome vitiligo, in which the edge of the lesion may be light brown or tan.

In many cases, lesions are single but multiple lesions are often present. Lesions can be single at first, with multiple ones appearing later. There are several clinical forms of vitiligo, focal, segmental and mucosal localized types, and generalized types such as acrofacial, vitiligo vulgaris (randomly scattered) and mixed (acrofacial and vulgaris). In universal vitiligo, there is nearly complete or complete depigmentation.

Vitiligo is caused by a loss of melanin from the epidermis coupled with a decrease in melanocytes. Early lesions can show lymphocytes around the superficial plexus or in the basal layer, some in contact with melanocytes if ultrastructural studies are performed. Some “collateral damage” to keratinocytes can also occur.

Melanocytes are visible as single cells in the basal layer of the epidermis surrounded by a clear halo. One can appreciate their disappearance by light microscopy, but it is best to confirm that impression by an immunoperoxidase stain. S100 staining is widely available, but has the disadvantage of marking Langerhans cells much more strongly than melanocytes. Vastly preferable is staining for Melan-A or MART-1, which marks melanocytes without staining Langerhans cells. There is an imperfect association between the presence of melanocytes ultrastructurally, and their appearance in immunoperoxidase-stained sections. It is also useful to obtain a Fontana-Masson stain. Vitiligo usually has no or few melanophages in the capillary dermis, unlike the case in post-inflammatory hypopigmentation.

A useful internal control is the presence of residual melanocytes in the basal layer of the follicular bulb. These are destroyed in some lesions of vitiligo (in which there are white hairs), but in most cases melanocytes survive within follicular bulbs. Follicular melanocytes are believed to be the source of the melanocytes that repigment the skin in recovering lesions.


Bhawan J, Bhutani LK. Keratinocyte damage in vitiligo.
**Incontinentia pigmenti achromians**

- Incontinentia pigmenti achromians, linear and whorled hypomelanosis and nevus depigmentosus may lie on a spectrum
- Musculoskeletal and neurologic problems
- Reduced melanocytes, short dendrites, vacuolization of keratinocytes in basal layer

Incontinentia pigmenti achromians is a rare condition that results in whorled areas of hypopigmentation. It appears to be on a spectrum with linear and whorled hypomelanosis and nevus depigmentosis. There can be associated musculoskeletal and neurological problems.

The lesions tend to be distributed along the lines of Blaschko. Mosaicism for trisomy 18, tetrasomy 12p and other genetic defects have been found in lesional skin.

Usually the diagnosis of this condition can be made clinically. In cases in which a biopsy is performed, the hypopigmented skin will generally show a pallid appearing basal layer with reduced numbers of melanocytes. Electron microscopic examination shows that they have short dendrites. There is a loss of melanin from the basal layer of the epidermis.

**Idiopathic guttate hypomelanosis**

- Hypopigmented macules, sun exposed skin of older patients
- Extremities > trunk
- S/P bone marrow transplant
- Diminished (but not absent) melanocytes
- Basketweave hyperkeratosis
- Reduced dendrites and melanosomes

Idiopathic guttate hypomelanosis is a fairly common condition in which hypopigmented macules are found, generally on the sun exposed skin of older patients. They are sometimes noted after vacations (or medical meetings such as
this one in which generous actinic exposure is involved). This occurs because the adjacent, unaffected skin becomes darker and the macules become better noticed. The macules are found to a greater degree on the extremities than on the trunk. They have also been noticed after bone marrow transplantation.

The lesional skin of idiopathic guttate melanosis has diminished, but not absent melanocytes.


Hypopigmented mycosis fungoides
- Often in children, young persons
- Hypopigmented macules
- CD8+ phenotype common
- Reduced melanocytes in some studies
- Difficult ddx with inflammatory stage of vitiligo, pityriasis alba and pityriasis lichenoides chronica

The subject of hypopigmented mycosis fungoides is controversial. Many cases have been diagnosed in children, or in young adults. Conventional mycosis fungoides usually has its onset in middle or later years. Because there are several conditions that can cause a similar clinical picture and can feature lymphocytes in and around the basal layer of the epidermis, such as vitiligo, pityriasis alba and pityriasis lichenoides chronica in this age group, many of the reports of hypopigmented mycosis fungoides in the literature must be viewed with skepticism. The usual presentation is as hypopigmented macules or patches. Many of the cases have been noticed in dark skinned patients. Whether this is because the condition is really more frequent in this population, or because it is noticed more readily in it is undetermined.
The histopathologic features are those of patches of mycosis fungoides. It is rare for there to be striking cytologic atypia of the intraepidermal lymphocytes. Some studies show reduced melanocytes in the basal layer of the epidermis, while others imply that the hypopigmentation is due to pigment incontinence, with melanophages being evident in the papillary dermis.


Hyperpigmentation

Melanotic macules

- Hyperpigmentation in basal layer
- Normal numbers of melanocytes
- Some melanophages in papillary dermis or submucosa
• Oral mucosa (lips esp.), genital, volar, ungual, back are most common sights
• Benign genital melanosis, ink spot lentigo are synonyms

The term “melanotic macule” has been proposed as a unifying concept for several conditions in which hyperpigmentation is the result of increased deposition of melanin in the basal layer of the epidermis with normal numbers of melanocytes. The best known forms are labial melanotic macule (of the lips), and genital melanotic macules (known otherwise as vulvar and as penile melanosis). Lesser-known forms are vulvar melanotic macules (found on the palms and soles) and so-called ink spot solar lentigo (usually seen on the upper back). Most cases of melanonychia striata are due to melanotic macules.

The most biopsies of melanotic macules are from those on the lips and genitalia. These feature hyperpigmentation of the basal layer, usually accentuated at and toward the bases of rete ridges, with normal numbers of cytologically inconspicuous melanocytes. Especially in labial melanotic macules a sprinkling of lymphocytes may be present around the basal layer of the epidermis, resulting in the deposition of melanophages as well. Ink spot solar lentigo generally shows more intense hyperpigmentation of the basal layer, usually limited to the bases of elongated rete ridges.

A vexing problem with regard to melanotic macules on or near mucosal surfaces is that mucosal melanomas in situ can be extraordinarily subtle in their initial presentations. We have seen cases of genital melanoma in situ in which nondiagnostic areas gave the impression of a melanotic macule. It is important for clinicians to verify that the pigmentation that they observe is relatively homogeneous, and if there is any doubt with respect to a large pigmented patch on the genitalia or mucous membrane of the mouth, several biopsy samples may be appropriate rather than one.

Gupta G, Williams RE, Mackie RM.
The labial melanotic macule: a review of 79 cases.

Ho KK, Dervan P, O'Loughlin S, Powell FC.
Labial melanotic macule: a clinical, histopathologic, and ultrastructural study.

Bolognia JL.
Reticulated black solar lentigo ('ink spot' lentigo).
Melasma

- Hyperpigmentation of forehead and cheeks
- Usually in pregnancy or with oral contraceptives
- Pigmentation usually in basal layer, but there can be dermal melanophages

Melasma is a condition that can be diagnosed without a biopsy in nearly one hundred percent of cases. Its’ presentation as hyperpigmented patches in the forehead and cheeks in pregnant women is readily recognizable. Biopsy is sometimes done to see what the depth of pigmentation is (as a guide to treatment). Usually, pigmentation is present in the basal layer but melanin can be found in subepidermal melanophages as well. A recent study showed that melanocytes in the hyperpigmented areas of melasma are more intensely stained than normal ones, with more permanent dendrites. Ultra structurally, more melanosomes are present, both in keratinocytes and melanocytes.

Grimes PE, Yamada N, Bhawan J.
Light microscopic, immunohistochemical, and ultrastructural alterations in patients with melasma.

Becker’s nevus

- Most commonly on shoulder
- Onset birth-teenage years
- Hypertrichosis and nodules, sometimes
- Associated skeletal and other malformations
- Increased androgen sensitivity
Becker’s nevus occurs on the shoulder of teenagers typically, but has many other presentations. It can be found in children and in young adults, and can occur at other sites. It is often associated with hypertrichosis. When nodules are present, they are often due to a concurrent smooth muscle hamartoma. Becker’s nevus is thought to be due to a local increase in androgen sensitivity.

Biopsy of a Becker’s nevus shows hyperpigmentation of the basal layer of the epidermis. A noteworthy clue is the presence of “squared off” rete ridges (with straight sides and a flat base). In cases in which there is an associated smooth muscle hamartoma, one finds increased fascicles of smooth muscle in the dermis.


Dowling-Degos disease
• Reticulate pigmented anomaly of the flexures
• Variants: Haber syndrome, reticulate acropigmentation of Kitamura
• Pigmented macules in reticulated pattern in flexures, comedo-like lesions
• Rarely, hidradenitis suppurativa or vitiligo are associated

Dowling-Degos disease is increasingly recognized as a spectrum, in which pigmented macules are found in association with follicular pits. If the face is involved, with prominent pits and cysts the designation Haber’s syndrome is used. If the lesions are on the hands or feet, reticulate acropigmentation of Kitamura is applied. Follicular occlusion by laminated keratin is present in the pits, and in rare cases there can be hidradenitis suppurativa (a condition that is one of the follicular acclusion tetrad). Rare cases have been associated with vitiligo.

Biopsy specimens from patients with Dowling-Degos disease show club shaped rete ridges that branch to form an antler-like pattern, often at the sides of cystically dilated follicular indfundibula.

An interesting condition that some have linked to this spectrum is Galli-Galli disease, which may be an autosomal dominant condition in which disseminated pigmented macules occur. These have the branching rete ridges of Dowling-Degos disease, but also
show acantholysis, so that they have overlapping histopathologic findings with Grover’s disease as well.


**Hemochromatosis**

- 90% of patients have darkened skin (bronze diabetes)
- Most darkening is from increased melanin
- Mechanism by which metals increase melanin production is unknown
- Increased melanin in basal layer of epidermis, hemosiderin in dermis

The diagnosis of hemochromatosis is seldom made by skin biopsy, but darkened skin is a common symptom of this condition which has been called “bronze diabetes”. The salient histopathologic features are an increase in the amount of melanin in the basal layer of the epidermis, and the presence of pigment-laden macrophages around adnexal structures. A Perls’ or Prussian blue stain will show that the latter contain iron metabolites.
Drug induced hyperpigmentation

- Often photo distributed
- Minocycline, imipramine, amiodarone most common causes
- Makeup of pigment differs per each drug, and with some, there are different mechanisms in different distributions

There are a variety of drugs that can cause hyperpigmentation, often in a photo distribution. The most common of these is minocycline. The anti-depressant, imipramine and the cardiac medication, amiodarone are also common culprits. Minocycline can produce hyperpigmentation within acne scars, in non-scarred photo distributed skin and as “muddy” patches on the legs.

Imipramine hyperpigmentation features golden-brown granules in the superficial dermis. These are strongly positive for the Fontana-Masson stain and on ultrastructural examination appear as electron dense inclusion bodies in the cytoplasm of macrophages. The refractility and discrete nature of the globules is distinctive.

The histiopathologic findings in minocycline hyperpigmentation, despite claims in the literature, appear to be consistent. There are histiocytes within the superficial and mid-reticular dermis that contain some granules that appear to contain a melanin containing compound (Fontana positive) and some granules that contain an iron containing compound (Perls’ positive). Rarely, granules are present containing adipocytes in the subcutis without involving the dermis.


Zachary CB, Slater DN, Holt DW, Storey GC, MacDonald DM.

**Tinea nigra**
- Macule, rarely patch
- Palms, palmar surface of fingers, rarely soles
- Usually one lesion, rarely bilateral
- *Phaeoannellomyces (Exophiala) wernickii*

The macules or patches of brown pigmentation due to tinea nigra are usually biopsied because a dermatologist is considering the possibility of the melanocytic nevus or melanoma. At first, histopathologists may believe that they are not in the middle of the lesion and request level sections. The pathologic changes are quite subtle, and consist of pigmented hyphae in the cornified layer, sometimes accompanied by oval or diamond shaped spaces in the cornified layer.

**Talon noir (black heel)**
- Post-traumatic
- Subungual hemorrhage is more difficult diagnostically
- Diaminobenzidine stain if problematic

*As with tinea nigra, talon noir is usually biopsied to rule out melanoma. The condition is post-traumatic, and is due to the presence of degenerating erythrocytes trapped in the cornified layer. While many conceive of Prussian blue or Perls’ as “iron” stains, in fact they are stains for the reduced iron found in hemosiderin and will not react with the packed erythrocytes of this condition. The diaminobenzidine stain can be useful. This is simply the last portion of the immunoperoxidase reaction, without a specific antibody and without the crunching of endogenous peroxidase by hydrogen peroxide. The stain reacts with the peroxide moiety found within erythrocytes. Other stains for erythrocytes such as Ulex europeaus agglutinin and Glut-1 can also be used in...*
Tattoos are increasingly common causes of dermatologic problems, from infection to forming a nidus for the localization of an inflammatory disease. Reactions to tattoo pigment are listed below, and are manifold. Sarcoidal granulomas can accumulate within tattoos, resulting in elevation of the lesion clinically. This can be a presenting sign of sarcoidosis.

Reactions to tattoo pigment

- Lymphocytes and histiocytes
- Lymphocytes, histiocytes, plasma cells and eosinophils
- Lichenoid
- Granulomatous
  - Sarcoidal
  - Foreign body
  - Palisaded
- Pseudolymphomatous
- Pseudocarcinomatous

Monsel’s solution tattoo

- Aqueous ferric subsulfate, 20%
- Used to stop bleeding
- Ingested by macrophages
- Sometimes stimulates proliferation of melanophages
A discussion of Monsel’s solution tattoo in full is left for the lecture on secondary changes.

**Amalgam tattoo**
- Usually buccal mucosa in contact with dental filling
- Rarely, similar tattoo in piercing sites
- Impregnation of silver on elastic and reticulin fibers

Amalgam tattoos are common, and due to the silver on reticulin fibers in the submucosa. The picture can simulate a blue nevus both clinically and pathologically. The very thin fibers of an amalgam tattoo are not accompanied by melanophages, as would be the case in a blue nevus.

**Tinea versicolor**
- Superficial infection by *Malassezia globosa (was called M. furfur also Pityrosporum orbiculare or ovale)*
- Dicarboxylic acids inhibit tyrosinase
- Upper trunk, abdomen, back and face
- Diagnosis by clinical appearance and KOH prep
- Rare solitary or atypical lesions

Tinea versicolor is another condition that can usually be diagnosed clinically. Occasional cases are biopsied to rule out other pigmentary disorders. Inflammatory infiltrates are scant, and are usually limited to a few local sites around the superficial plexus. Stubby, hyphae and large round pieces are seen in the cornified layer. The hypopigmentation of tinea versicolor is usually not evident on biopsy unless one has a large specimen containing unaffected skin as well.

**Post-inflammatory pigmentary alteration (PIPA)**
- Hypo- or hyperpigmentation
- Depends on melanin content of basal layer

Post-inflammatory pigmentary alteration results in hypo- or hyperpigmentation, but as hypopigmentation is more of a problem clinically we have listed it herein.
Inflammatory cells in a variety of conditions attack keratinocytes in the basal layer, and the liberation of their pigment into the dermis ensues. The pigment is ingested by histiocytes (melanophages). In post-inflammatory hypopigmentation, the basal layer of the epidermis has little pigment, whereas in post-inflammatory hyperpigmentation, pigment is abundant.

The diagnosis of post-inflammatory pigmentary alteration is applied to cases in which the cause of pigmentation cannot be found. Some inflammatory conditions that often end in this picture are discussed below.

**Fixed drug eruption**

- Uni- or oligolesional, sometimes generalized
- Same area flares with each exposure to drug
- Rare variants (eczematous, urticarial, wandering)
- Fixed food eruptions

Fixed drug eruption is the most distinctive drug-induced dermatitis. Its’ clinical lesions are usually round and are typically mercurochrome-colored. Early lesions may be red, whereas later ones are more reddish brown. Over time the redness fades, leaving an oval or round macule that becomes erythematous on the next exposure to the offending drug. There are rare variants in which spongiosis results in clinically evident vesiculation or scale, in which urticarial lesions occur, or in which lesions appear at different sites.

The histopathologic findings in fixed drug eruptions vary depending on the time of the biopsy. Early lesions can feature a predominant infiltrative neutrophil, although this is quite rare. Usually, lymphocytes, neutrophils and eosinophils comprise the dermal filtrate, with lymphocytes obscuring the junctional zone accompanied by diffuse spongiosis in the lower half of the epidermis and scattered necrotic keratinocytes. Although conventionally viewed as an “interface dermatitis”, examination of the epidermis in fixed drug eruption shows that many of the necrotic keratinocytes are above the dermal-epidermal junction.

With progressive exposures it is common to define more and more melanophages in the dermis. These can drop lower and lower with each exposure, so that melanophages can be found at the level of the mid-ripterular dermis in some cases.
Prurigo pigmentosa
- Condition most often in Asians
- Reticulated papules on back, ending in PIPA
- Cause unknown
- Rapid evolution of lesions

Prurigo pigmentosa is a little known inflammatory disease that is probably more common than the literature up to now would suggest. It was described initially in Japan, but clearly affects non-Japanese patients as well. It features rapidly evolving lesions that result in reticulated papules on the back due to post-inflammatory hyperpigmentation. The initial infiltrates include neutrophils which may lie within the dermis at first, but infiltrate the epidermis (neutrophilic spongiosis) where they are seen in apposition to necrotic keratinocytes, and are accompanied by ballooning alteration. The papillary dermis can be strikingly edematous. Later lesions feature melanophages in the papillary dermis.

Boer A, Ackerman AB.
Prurigo pigmentosa is distinctive histopathologically.

Prurigo pigmentosa: a distinctive inflammatory disease of the skin.

Incontinentia pigmenti
- Inflammatory disease with three stages
- Ocular, skeletal, dental, neurologic abnormalities
- X-linked dominant disorder of chromosomal instability (Xp11.21, Xq28)
• Defects in leukocyte chemotaxis/neutrophil function

Incontinentia pigmenti is usually suspected clinically, with biopsy done more to document the condition than to make the diagnosis. It presents with vesicular lesions within the lines of Blaschko, and ends with hyperpigmentation in the same distribution. The earliest lesions feature “eosinophilic spongiosis”, in other words spongiosis of the epidermis in which unusual numbers of eosinophils are present. Later on, the epidermis becomes papillated and hyperplastic, with scattered necrotic keratinocytes with little spongioses. Finally, the epidermis reverts to its normal thickness, with melanophages in the subjacent dermis.

**Erythema ab igne**

- Chronic heat exposure (hot water bottle, fire)
- Lower legs most common
- Can have thermal keratosis, squamous cell carcinoma
- Pigment from melanin, hemosiderin

Erythema ab igne is a form of post-inflammatory hyperpigmentation due to chronic heat exposure. It was typically found in parts of the world in which heating was inadequate, and people sat close to fires or furnaces. It is now seen less and less in the developing world, where the heat from laptop computers is a new cause. It can result in the exposure of older people to heating pads or hot water bottles. The lower legs are the most common site of involvement, but those who sit with their back to the fire can have involvement of that surface as well. Squamous cell carcinomas can complicate erythema ab igne.

The histopathologic features include solar elastosis, atypia of keratinocytes and of fibroblasts, teleangectases and melanophages.


Mitsuhashi T, Hirose T, Kuramochi A, Tsuchida T, Shimizu M.

Bilic M, Adams BB.
Erythema ab igne induced by a laptop computer.

Jagtman BA.
Erythema ab igne due to a laptop computer.
Contact Dermatitis. 2004 Feb;50(2):105.