Acquired, Circumscribed Hypermelanotic Disorders

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INTRODUCTION

Hypermelanotic disorders, whether congenital or acquired, circumscribed or generalized, are pigmented by the depositing of melanin in the epidermis and/or dermis, an increase of epidermal and/or dermal melanocyte numbers, and tumors of melanocytes or melanin producing cells.

When approaching the diagnosis of hypermelanotic disorders, the age of onset, whether hypermelanosis was congenital or acquired, the extent and pattern of involvement, the degree of pigmentation, and the hues of pigmentation are generally considered.

Acquired melanocyte proliferation and/or increase of melanosome production in melanocytes are induced by either hormones, UV radiation, or peptide growth factors such as basic fibroblast growth factor (bFGF), chemical mediators or cytokines, and the result is increased melanin deposition in epidermal keratinocytes. An increase of melanin in the basal layer of the epidermis induces brown to black pigmentation. An increase of melanin in the papillary dermis induces purplish slate-grey pigmentation. Deposition of melanin in the middle to deep dermis results in blue or purplish-blue coloration of the skin.

When any increase of keratinocyte turnover rapidly gets ahead of melanosome formation in epidermal melanocytes, hypermelanosis may
occur as a result of deposition or the
sustaining of many melanosomes in
dendritic processes of melanocytes, a
condition which is designated "pig-
ment blockade."

Although increase of melanin in
the epidermal basal and suprabasal
cells is more or less associated with
increase of melanophages in the
upper dermis, acquired pigmentary
disorders are classified into two sub-
groups in this chapter, epidermal
and dermal. Acquired circumscribed
hypermelanotic disorders are classi-
fied as in Table 1 from the points of
the main site of melanin deposition
and of the main changes of the skin.

Dermal pigmentary disorders are
rather rare in fair-skinned Caucasoid
skin but more common in Asatics and
other pigmented people, including
dark-skinned Caucasoids, Mediterra-
eans, Middle Easterns and East
Indians.

In this chapter, acquired circum-
scribed hypermelanotic nonneoplas-
tic disorders are described.

1. EPIDERMAL MELANOSIS

A. Increase of melanin in epidermal
keratinocytes (melaninotic)

1. Melasma

Melasma (or chloasma) is a
sharply demarcated light-brown to
dark-brown colored macule which
occurs symmetrically on the face,
especially on the forehead, palpe-
brae, cheeks, temples, upper lip and
chin, and sometimes involves the
neck, and which is exacerbated by
sun exposure. Melasma is mostly
seen in women, especially after
puberty and in middle-age. Some
women develop melasma with preg-
nancy (melasma gestationis, preg-
nant melasma). Although melasma
is far more common in women than
in men, it is also seen in men and in
the terminal stage of malignancies in
both men and women (cachectic
melasma).

The etiology of melasma in-
cludes hormonal factors (estrogen and
progesterone change) and familial
factors. The two most important
determinants, genetic predisposition
and solar UV radiation, were pos-
tulated by Pathak. Excessive sun
exposure at a young age may cause
melasma in adulthood in genetically
predisposed persons.

Histologically, an increase of
melanin is observed in epidermal
basal and suprabasal cells, and
melanophages are recognized in the
upper dermis.

Melasma is classified into 1) epidermal melasma, 2) dermal melas-
ma and 3) mixed melasma, according
to the major site of melanin deposi-
tion.

Pigmentation of melasma is
darkened by sun exposure, menstrua-
tion and general fatigue. Certain
ethnic groups have a tendency to
develop melasma; namely, Asatics,
Hispanics and Mediterraneans.

Habitual and excessive sun-
exposure may cause early onset of
melasma and accentuate melanin
pigmentation, although genetic pre-
disposition may play a certain role
Table. 1 Classification of Acquired, Circumscribed Hypermelanotic Disorders

I. Epidermal Melanosis (Brown)
   A. Increase of melanin in epidermal keratiocytes (Melaninotic)
      1. Melasma
      2. Mastocytosis (Urticaria pigmentosa)
   B. Increased number of epidermal active melanocytes (Melanocytic)
      Solar lentigo (Senile lentigo, Senile freckle)
   C. Increased keratinocytes (Acanthosis and elongation of epidermal rete ridges)
      1. Becker's melanosis
      2. Confluent and reticulate papillomatosis (Gougerot-Carteaud)
      3. Punctate and reticulate hyperpigmentation syndrome
      4. Acanthosis nigricans
      5. Dermatofibroma

II. Dermal melanosis (Blue, purplish, slate-grey, purplish-grey, blue-grey, ashen-grey)
   A. Melanin deposition in the dermis (Histological incontinence of melanin: melaninotic)
      1. Postinflammatory hyperpigmentation
      2. Ashy dermatosis (erythema dyschromicum perstans)
      3. Macular amyloidosis
      4. Friction melanosis
   B. Increased number of active dermal melanocytes (Melanocytic)
      Acquired dermal melanocytosis.

Fig. 1 Clinical features of urticaria pigmentosa, 6-month-old boy.
in its etiology.

Melasma (epidermal, dermal or mixed) should be differentiated from postinflammatory pigmentation, female facial melanosis, Riehl’s melanosis, friction melanosis, drug-induced melanosis, (acquired) dermal melanosis, systemic pigmentary disorders such as Addison’s disease, Kronkhite-Canada syndrome, hemochromatosis, and so on.

2. Mastocytosis (Urticaria pigmentosa)

The lesions of mastocytosis (Fig. 1) may be isolated single or multiple brown macules, or slightly elevated plaques which often become pruritic, raised and reddish or whitish with rubbing or stroking (Darier’s sign). Stroked or rubbed lesions of infant patients may be associated with blisters.

Histologically, many mast cells are recognized in the dermis of brown macules. Mast cells release histamine, prostaglandins, serotonin and many other inflammatory mediators, especially upon rubbing or stroking of the lesions and then wheals of dermographism are formed.

Melanin deposition in epidermal basal cells of the lesions is increased. Increase of melanin in epidermal basal cells may be induced by increased production of melanin in epidermal melanocytes, which is stimulated by histamine, prostaglandin E2 and other chemical mediators.²

B. Increased number of epidermal active melanocytes (melanocytic)

1. Solar lentigo (Senile lentigo, lentigo senilis, senile freckles)

Solar lentigines are varied in size, from a few millimeters to several centimeters, and exhibit circumscribed brownish macules on the exposed areas of the skin such as face, neck, hand, forearm, and so forth; they are induced by long-term UV radiation.

The histology of solar lentigo is characterized by localized proliferation of epidermal melanocytes with elongated epidermal rete ridges. In the early stages of solar lentigo, however, the elongation of rete ridges is not remarkable.

Synonyms for solar lentigo are senile lentigo (lentigo senilis) and senile freckles. Inasmuch as solar lentigo can appear in the first several decades of life, the term “senile” is not appropriate.

C. Increased keratinocytes (Acanthosis and elongation of rete ridges)

1. Becker’s melanosis

Becker’s melanosis(Fig.2) is a uniformly light brown to dark brown colored macule of several centimeters in diameter which shows a sharply demarcated border with an irregular outline and which usually appears in the second or third decade of life, mostly in adolescence; it is more common in males than in females, and it unilaterally
or asymmetrically involves shoulder, upper arm, upper back or upper chest.

Besides hyperpigmentation, Becker’s melanosis is characterized by hypertrichosis in 56% of cases; hair may appear several years after the onset of hyperpigmentation, and it is associated with underlying tissue hyperplasia.4

Histologically, a normal or slightly increased number of epidermal melanocytes, increased melanin deposition of basal and suprabasal cells, acanthosis, papillomatosis and thickening of the dermis with hyperplasia of hair follicles and smooth muscles are observed.

Therefore, Becker’s melanosis is regarded as a late-onset organoid nevus.5

2. Confluent and reticulate papillomatosis (Gougerot-Carteaud)

Confluent and reticulate papillomatosis (Fig.3) is regarded as a non-hereditary disorder, is seen mainly in girls, and appears at or soon after puberty. The lesions of this disease are commonly seen between the breasts and in the upper or middle portion of the back; however, in some cases lesions gradually spread over the chest, abdominal region, neck, axillae, inguinal region, elbows, knee or the back to hip.

The clinical features of this disease include reticulated, brownish pigmented, and slightly elevated keratotic papules which become confluent in the center of the affected area (Fig.4).

Differential diagnosis includes acanthosis nigricans and tinea versicolor, although pityrosporum orbiculare may play an etiological role in confluent and reticulate papillomatosis inasmuch as the lesions disappear rapidly after the treatment with antifungal agent.6

Histologically, hyperkeratosis, papillomatosis without acanthosis, and hyperpigmentation of epidermal basal and suprabasal layers are present7 (Fig.5).

3. Punctate and reticulate hyperpigmentation syndrome

a. Reticulated pigmented anomaly of the flexures (Dowling-Degos disease)

Reticulated pigmented anomaly of the flexures (Dowling-Degos disease)8 or dark-dot disease9 was first described by Dowling and Freudenthal in 1938,10 and then by Degos and Ossipowski in 1954.11 Dowling-Degos disease is believed to be a familial nevoid anomaly with delayed onset in adolescence or early adulthood.

The typical clinical features are progressive symmetric brown to grey pigmentation in reticular fashion of the flexures: axillae, neck, groin, inner thighs, scrotum, intergluteal area, and so forth.

Epidermal and trichilemmal cysts and comedo-like lesions are associated with this condition. Mucous membranes are spared.

Histological observations reveal budding of the epidermis and fol-
Fig. 2 Clinical features of Becker’s melanosis on the chest, 20-year-old man.

Fig. 3 Clinical features of confluent and reticulate papillomatosis (Gourgerot-Carteaud) on the chest and abdomen, 13-year-old girl.

Fig. 4 Close up view of confluent and reticulate papillomatosis (Gourgerot-Carteaud) on the chest, 15-year-old girl.

Fig. 5 Light microscopic features of the lesion in confluent and reticulate papillomatosis (Gourgerot-Carteaud). Hyperkeratosis, papillomatosis, and hyperpigmentation of epidermal basal and suprabasal layers are recognized. HE stain.
licular wall, and hyperpigmentation of the tips of the buds.

Dowling-Degos disease is not associated with any systemic disease and is usually asymptomatic.\textsuperscript{12}

Dowling-Degos disease may be considered to be a part of a “spectrum” of similar disorders including Kitamura’s acropigmentatio reticularis, pigmentatio reticularis faciei et colli with epithelial cystomatosis, Harber’s syndrome and familial multiple follicular hamartoma.\textsuperscript{13}

b. Pigmentatio reticularis faciei et colli with epithelial cystomatosis

The clinical features of pigmentatio reticularis faciei et colli with epithelial cystomatosis\textsuperscript{14} are relatively well circumscribed brown-black macules(Fig.6) on the cheek, chin, nose, forehead, temple and neck, and seborrhea on the face and trunk, folliculitis and multiple epithelial cysts on the chest and back.

Each brown macule gradually increases in size, and they expand and fuse to form a reticular pattern. Non-coalesced macules are about 5 mm in diameter. Many of the macules are not associated with hair follicles.

Light microscopic examinations of pigmented macules show elongation of rete ridges or budding of epidermis with hyperpigmentation of tips of the buds(Fig.7). Histology of a cyst reveals budding rete ridges of the cyst wall and melanin deposits in the buds.

4. Acanthosis nigricans

Acanthosis nigricans is characterized by unsharpily demarcated, localized and dark brown pigmentation, and hyperkeratosis and papillomatous portions of the body, especially the neck, axillae, groin, buttocks and umbilical region. Palpebrae, face (Fig.8) and palms are also involved in severe cases.

Histologically, hyperpigmentation of epidermal basal and suprabasal layers, hyperkeratosis, and papillomatosis are characteristic features of acanthosis nigricans (Fig.9), and histological acanthosis is not always observed in spite of the clinical term “acanthosis”.

Acanthosis nigricans is associated with endocrine abnormalities, obesity, genetic factors, and internal malignancies (Table 2).

Acanthosis nigricans may be induced by epidermal growth factor, proinsulin, or other factors.\textsuperscript{15}

5. Dermatofibroma

Most lesions of dermatofibroma range from 0.5 to 1.0cm in diameter and dark brown colored. Proliferation of fibroblasts admixed with increased collagen bundles and vascular endothelial cells is induced by basic FGF\textsuperscript{1} released from tissue fixed macrophages.

The pigmentation is due to elongation of overlying epidermal rete ridges and to hypermelanosis in epidermal basal cells which may also be induced by basic FGF and there is no increase in epidermal as well as dermal melanocytes.
Fig. 6 Clinical features of pigmentatio reticularis faciei et colli with epithelial cystomatosis, 50-year-old man.

Fig. 7 Light microscopic features of a pigmented macule in pigmentatio reticularis faciei et colli with epithelial cystomatosis. Elongation of rete ridges with increased melanin deposition in tips of rete ridges are recognized. HE stain.

Fig. 8 Clinical features of acanthosis nigricans on the face, 70-year-old woman with gastric cancer.

Fig. 9 Light microscopic features of acanthosis nigricans. Hyperkeratosis, papillomatosis, irregular configuration of epidermis, and hyperpigmentation of epidermal basal and suprabasal layers are recognized. HE stain.
Table 2. Acanthosis Nigricans Associated Disorders

A. Internal malignancies (carcinomas, malignant lymphomas)
B. Endocrine disorders
   1. Acromegaly, Gigantism
   2. Cushing's syndrome
   3. Addison's disease
   4. Thyroid dysfunction
   5. Diabetes mellitus (insulin-resistant)
   6. Insulinoma
   7. Diabetes insipidus
   8. Hypogonadal syndromes
C. Obesity
D. Hereditary Abnormality
E. Drug

Fig. 10 Schema of melanosome transfer from an epidermal melanocyte to keratinocytes and to a melanophages.
II. DERMAL MELANOSIS (blue, purplish, blue-grey, ashen-grey)

A. Melanin deposition in the dermis (histological incontinence of melanin; melaninotic)

1. Postinflammatory hyperpigmentation

An increase of melanin in the basal layer of the epidermis induces brown pigmentation. An increase of melanin in the papillary dermis induces purplish slate-grey pigmentation.

Melanosomes produced in epidermal melanocytes are transferred to epidermal keratinocytes and then partially phagocytized in dermal macrophages (melanophages) under normal conditions as shown in a schematic figure (Fig.10).

An increase in phagocytized melanosomes in dermal melanophages is found in many inflammatory diseases and may be associated with epidermal hypermelanosis. The result is a purplish slate-grey pigmentation of the skin.

This condition often exhibits focal damage to basal cells and melanocytes, and is designated as incontinencia pigmenti histologica. Such a condition is present in Bloch-Sulzberger syndrome (incontinencia pigmenti) or as symptomatic incontinence in lichenoid tissue reaction, that is, lupus erythematosus, lichenoid drug eruption, prurigo pigmentosa or a poikilodermic state (Table 3).

Prurigo pigmentosa (Fig.11) was first reported by Nagashima et al. in 1971.16 Prurigo pigmentosa is an inflammatory dermatosis characterized by severely pruritic, erythematous papules that resolve leaving a reticulated, mottled, hyperpigmentation (Fig.12). Most reported cases of prurigo pigmentosa have developed in Japanese. However, a white American with prurigo pigmentosa was recently reported.17

The histologic features (Fig.13) of the papular lesions in prurigo pigmentosa are 1) intercellular and intracellular edema with lymphocytic infiltration in the epidermis and 2) liquefaction degeneration of the basal layer. Mild to marked pigment incontinence and mild perivascular lymphocytic infiltration are observed in the reticulated, pigmented area.16 Differential diagnosis includes confluent and reticulate papillomatosis, acanthosis nigricans and tinea versicolor.

Subepidermal melanophages in most cases of postinflammatory hyperpigmentation are rarely found without obvious basal layer derangement. The pigment is usually retained in dermal melanophages for many months and thus it remains after all other evidence of active diseases, such as lichen planus, lupus erythematosus, or fixed drug eruption, for example, has disappeared.

Dermal and/or epidermal inflammation induces an increase in melanocytic activity and may induce an increase in melanosome phagocytosis by keratinocytes and by macrophages. As a result, pigmentation occurs. Darkening of the skin after mild inflammation is due to a direct or
Table 3. Post-Inflammatory Hypermelanoses (slate-grey, purplish-grey)  
(Incontinentia Pigmenti Histologica)

- Fixed drug eruption
- Lichenoid drug eruption
- Female facial melanosis (Riehl’s melanosis)
- Macular amyloidosis
- Friction melanosis
- Lichen planus
- Lichen striatus
- Dermatomyositis
- Lupus erythematosus
- Mycosis fungoides
  (Parapsoriasis en plaque)
- Prurigo pigmentosa
- Ashy dermatosis (erythema dyschromicum perstans)
- Incontinentia pigmenti (Bloch-Sulzberger syndrome)

Fig. 11 Clinical features of prurigo pigmentosa, 18-year-old woman.

Fig. 12 Close up view of Fig. 11.
indirect effect of chemicals and chemical mediators on melanocytes. Many experiments on inflammatory chemical mediators stimulating melanization in epidermal melanocytes have recently been performed. And the role of chemical mediator and vitamin D3 in inflammatory skin diseases and the correlation of UV exposure with the skin on the melano-nization of melanocytes and postinflammatory pigmentation have been discussed.

From the observation that normal human epidermal melanocytes become swollen and more dendritic when they were cultured with arachidonic acid metabolites, vitamin D3 or histamine, which are found in increased amounts in inflammatory skin, are thought to play a role in the induction of postinflammatory hyperpigmentation.\(^{18}\) Hyperpigmentation in the skin lesions of urticaria pigmentosa is quite likely to be induced by the chemical mediators, histamine, prostaglandins and leukotrienes, which are released from mast cells.\(^{2}\)

Prostaglandin E2, which causes a large increase of melanocyte density in mouse skin, also enhances melanogenesis in melanocytes.\(^{19}\)

2. Ashy dermatosis, erythema dyschro-micum perstans

Ashy dermatosis or erythema dyschomicum perstans (Fig.14) was originally described by Ramirez in 1957.\(^{20}\) Subsequently, many cases have been reported throughout the world.

Some of the lesions begin as erythematous macules which then gradually change to slate-grey in hue. However, in most cases these slate-grey, ashen-colored macules are recognized as pigmented macules in the beginning. When lesions erythematous in the beginning become pigmented macules later, a postinflammatory mechanism may be considered.

The macules are flat and each macule is nail-sized, though some of the macules may gradually enlarge in size and may coalesce.

Ashy dermatosis is an acquired generalized condition with nail-sized, ashen-grey, slate-grey, or purplish-grey macules due to the presence of melanophages in the dermis with or without hyperpigmentation of epidermal basal and suprabasal layers.

3. Macular amyloidosis

Common sites of macular amyloidosis are the upper back, hip, chest, breast, neck, arms, thighs, shins, and buttocks. Typical cases exhibit slightly pruritic, symmetrically distributed, purplish-grey brown macules which show up in a rippling pattern (Fig. 15). These macules, however, are easily dismissed as postinflammatory pigmentation because of their inapalpability; they are ignored by patients inasmuch as they are often asymptomatic, or are noted only for their cosmetic significance.

In macular amyloidosis, amyloid deposits are limited to the papillary dermis and are fewer than those in lichen amyloidosus, although the
Fig. 13 Light microscopic features of papular lesion in prurigo pigmentosa. Lymphocytic infiltration into the epidermis and in the upper dermis with some melanophages in the upper dermis. HE stain.

Fig. 14 Clinical features of ashy dermatosis, 42-year-old man.

Fig. 15 Clinical features of macular amyloidosis, 61-year-old woman.
pattern of amyloid deposits in the papillary dermis is very similar to that found in lichen amyloidosus. In macular amyloidosis, amyloid deposits in the dermis are variable, whereas pigment incontinence is a constant feature in all cases with macular amyloidosis. Amyloid deposits are detectable in some, but not all, dermal papillae over the macules. Pigment incontinence is always observable. By electron microscopy, amyloid substances and melanophages are found in the upper dermis. Amorphous materials composed of fine granules and fine wavy filaments can be identified in the epidermal basal layer and beneath the epidermal basal lamina. These materials are not amyloid but rather appear to be degenerated keratin. Macular amyloidosis seems to be induced by long-term contact with fabrics or in towels that irritate the skin.

Mild damage to the epidermis can cause keratinocyte degeneration and subsequent leakage of degenerated keratin and incontinence of melanin into the dermis. Amyloid deposition may or may not occur as a result of chronic irritation or inflammation of the skin.\textsuperscript{21}

4. Friction melanosis

The pigmentation in friction melanosis shows a rippling pattern (Fig. 16) and is especially noticeable on prominent portions of the skin such as on the neck, clavicular regions, high back, upper chest, upper arms, and hips, but it is absent in skin folds.\textsuperscript{22}

Magna-Garcia et al.\textsuperscript{23} reported young Latin women with an idio-pathic form of hyperpigmentation of the clavicular zone. Pathologic findings of these affected areas consisted of focal to extensive necrosis of the epidermis, focal junctional cleavage, melanin deposition in the epidermis and melanophages in the dermis. The authors felt that friction from clothing or from scrub pads made of sedge against clavicular protuberances was fundamental in pathogenesis.

Histologically, melanophages are constantly observable in the upper dermis with or without hyperpigmentation of epidermal basal and/or suprabasal layers. No amyloid deposits are detectable.

Friction melanosis is induced by long-term rubbing or contact with fabrics in clothing or coarse towels that irritate the skin. If any amyloid substance is deposited in the pigmented skin of "friction melanosis", the skin lesion should be regarded as macular amyloidosis. Therefore, friction melanosis should be histologically differentiated from macular amyloidosis and also from female facial melanosis if the pigmented lesion is seen on the face or neck.

B. Increased number of active dermal melanocytes (melanocytic)

1. Acquired dermal melanocytoses

Acquired blue-brown, purplish-grey or blue-grey macules are often observed on the face, trunk or upper arms of middle-aged or aged women,
Fig. 16 Clinical features of friction melanosis showing a rippling pattern, 25-year-old woman.

Fig. 17 Clinical features of pigmented macules on the forehead, cheeks and alae nasi in acquired dermal melanocytosis, 49-year-old woman.

Fig. 18 Clinical features of reticular pigmented macules on the forehead in acquired dermal melanocytosis, 69-year-old man.
and only rarely of men, in Asiatics.

Although these macules are clinically similar to nevus of Ota, female facial melanosis, or Riehl’s melanosis, they usually appear in the fourth or fifth decade of life and are not observable in ocular and mucosal membranes.

Most pigmented macules consisting of blue-brown and/or slate-grey small or reticular or large patches occurred bilaterally on the forehead, temples, eyelids, cheek, or nose (Figs. 17, 18, 19) and rarely on the frontal and parietal regions of the scalp.

Histopathologically, actively melanin-producing dermal melanocytes are found scattered in the upper and middle portion of the dermis without disturbing the normal architecture of the skin (Fig. 20).

This pigmented disorder has been designated as nevus of Ota-like macules or acquired dermal melanocytosis of the face. Pigmentary changes of this disorder are limited to the face, and the scalp in most cases as shown in a schematic figure (Fig. 21).

Hori et al. reported late-onset blue macules on the shoulders and upper arms or back associated with progressive systemic scleroderma (Fig. 22). Hidano and Kaneko reported late-onset blue macules on the face as well as on extremities and designate them as acquired dermal melanocytosis of the face and extremities.

The histology of these cases is the same as that of nevus of Ota-like macules of the face which show actively melanin-synthesizing dermal melanocytes, bipolar or oval in shape, scattered in the upper to middle portions of the dermis.

These macules usually appear after the age of 20 and increase in size and in intensity of color with advancing age.

Therefore, these reported cases are regarded as acquired dermal melanocytosis. The pathogenesis of these macules may be attributed to the migration of hair bulb melanocytes, to the reactivation of preexisting dermal melanocytes, or to the manifestation of latent dermal melanocytosis, which may be triggered by dermal inflammation, by the atrophy or degeneration of the epidermis and/or dermis by aging, or by some other causes.

REFERENCES

Fig. 19 Clinical features of pigmented spots on the cheek and ala nasi in acquired dermal melanocytosis, 29-year-old woman.

Fig. 20 Light microscopic features of pigmented macule in acquired dermal melanocytosis. Melanin-bearing bipolar cells (dermal melanocytes) are observed scattered in the dermis. Masson-Fontana stain.

Fig. 21 Schema of distribution of pigmented macules in acquired dermal melanocytosis of the face.

Fig. 22 Clinical features of late-onset blue macules associated with progressive systemic sclerosis, 33-year-old woman.
22. Hori Y, Takayama O: Circumscribed dermal melanoses: classifi-