MELANONYCHIA AS A DIAGNOSTIC CHALLENGE

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Summary: Melanonychia involves black-brown discoloration of the nail plate and nail matrix epithelium caused by melanin accumulation. Etiologically, we distinguish simple melanocyte activation and melanocyte proliferation. Melanocyte proliferation can be benign (such as lentigo and nevus) and malignant (subungual melanoma). Although they have similar clinical characteristics, their prognoses are significantly different. The paper presents two cases of melanonychia. In the first case, a 13-year-old boy had linear black-brown discoloration of the nail plate of the index finger of the left, non-dominant hand. There was no nail plate dystrophy, periungual pigmentation, or bleeding. Medical and family histories were unremarkable. Onychoscopic examination diagnosed a nevus of the nail plate. In the second case, an adult woman had linear brown discoloration of the nail plate of the thumb of the right, dominant hand. The discoloration had discreetly irregular edges without signs of nail plate dystrophy, periungual pigmentation, or bleeding. Medical and family histories were unremarkable. After onychoscopic examination, longitudinal excisional biopsy was indicated, establishing the diagnosis of lentigo. Careful history taking, physical examination, onychoscopic examination, and ultimately biopsy with histological examination allow for determining etiology, as well as for an early diagnosis of subungual melanoma as the most important precondition for successful disease treatment.
Key words: nail, discoloration, nevus, lentigo, melanoma.

INTRODUCTION

The term "melanonychia" derives from the Greek words "Melas," meaning black or brown color, and "Onyx," meaning nail. It is characterized by black-brown discoloration of the nail plate and nail matrix epithelium caused by the accumulation of melanin. It can affect one or more nail plates, both on the hands and feet. It predominantly presents as a longitudinal black-brown streak starting from the matrix and extending to the free edge of the nail plate. Less commonly, the discoloration affects the entire nail plate or manifests as a transverse band.

The black-brown discoloration is caused by the accumulation of melanin produced by melanocytes in the nail matrix. Differentiation includes simple melanocyte activation, benign, and malignant melanocyte proliferation. Melanocyte activation can be induced by iatrogenic agents, pathogenic microorganisms, nutritional deficits, and trauma. Additionally, it can be present in certain physiological conditions, abnormalities of the nail plate or periungual tissue, dermatological conditions, tumors, systemic disorders, and syndromes. Melanocyte proliferation includes lentigo, nail matrix nevus, and subungual melanoma.

Melanonychia in childhood is rare. In adults, its prevalence varies (from 0.8% to 23%). Diagnosis is based on history, physical examination, onychoscopic examination, and biopsy with histological examination. Treatment depends on the etiology and nature of melanonychia.

CASE REPORT

During a systematic examination of a 13-year-old boy, a single black-brown, linear discoloration was observed on the index finger of his left, non-dominant hand (See Figure 1). There was no nail plate dystrophy, periungual pigmentation, or bleeding. The onset time of the change could not be determined. The boy was healthy, and his medical and family history were unremarkable. On onychoscopic examination, brown-black, parallel, longitudinal lines were observed on a brown background. The hyperpigmentation of the nail bed was visible through a thin cuticle and the distal part of the proximal nail fold. A diagnosis of nail matrix nevus was made, and regular follow-up by a dermatologist was advised.

During a follow-up examination of a 59-year-old female patient, a single melanonychia of the nail plate of the thumb of her right, dominant hand was observed. It was a brown, linear, uniformly pigmented, clearly demarcated discoloration with discreetly irregular edges from the proximal nail fold to the free edge of the nail plate. There were no signs of trauma, nail plate dystrophy, or bleeding. The change had been present for several months without altering in size or pigment intensity. The patient, a homemaker and non-smoker, had cardiomyopathy, irregular heart rhythm, high blood pressure, type 2 diabetes, and high cholesterol levels. She was on continuous therapy with 200mg of amiodarone, 4mg of acenocoumarol, 20mg of enalapril, 1000mg of metformin, and 10mg of rosuvastatin. On onychoscopic examination, brown-black longitudinal lines of varying width were visible through the cuticle and proximal nail fold on a brown background. A longitudinal excision biopsy was indicated, revealing an increased number of heavily pigmented melanocytes without signs of atypia in the basal epidermis. Thus, a diagnosis of nail plate lentigo was made, and the patient was advised regular dermatologist check-ups..

Figure 1. Nail matrix nevus

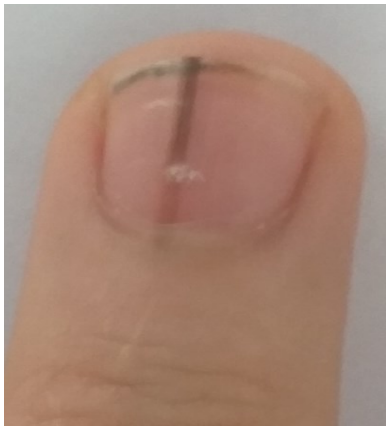
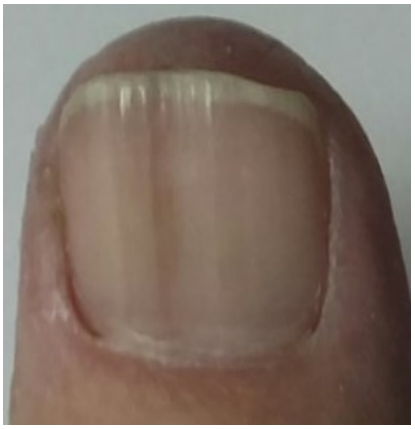


Figure 2. Lentigo of the nail matrix



DISCUSSION

Melanonychia implies nail pigmentation caused by simple activation of nail matrix melanocytes, either benign (lentigo or nail matrix nevus) or malignant (subungual melanoma) proliferation of the same [1].

Simple melanocyte activation (melanocyte stimulation, functional melanonychia) involves increased melanin production in secondarily activated melanocytes without an increase in the number of melanocytes [4].

Melanocytes are physiologically activated in ethnic melanonychia and pregnancy [7]. Ethnic melanonychia is predominantly present in individuals with darker pigmented skin types IV, V, and VI [1,7]. Its prevalence varies from 1% in Caucasians, 10%-20% in Asians, to 77–100% in African Americans [7]. It is most commonly found on the thumb and index finger of the hand and the big toe [1,7]. It often affects multiple nail plates, and its width increases with age [1,7]. Melanocyte activation during pregnancy involves several nails on the hands and/or feet [1]. It may disappear or persist after childbirth [1].

Melanocyte activation caused by drugs is often accompanied by skin and/or mucous membrane pigmentation [1]. Its form is variable (transverse or longitudinal stripes, solitary or associated) [1]. The majority of transverse melanonychias are caused by drugs [1]. Often, the changes involve several nails and fade partially or completely upon discontinuation of the drug [1,3]. Melanonychia can be caused by antiretroviral drugs (lamivudine, zidovudine), antimalarial drugs (mepacrine, amodiaquine, chloroquine, quinacrine), anticancer drugs (cyclophosphamide, doxorubicin, hydroxyurea, busulfan, taxanes, capecitabine, cisplatin, bleomycin, daunorubicin, dacarbazine, 5-fluorouracil, methotrexate) as well as simultaneous use of antiplatelet and anticoagulant drugs [1,2,3].

Melanocyte activation can also be induced by metals (arsenic, thallium, mercury), biological agents (clofazimine, infliximab, psoralen, phenytoin, fluconazole, cyclines, ketoconazole, phenothiazines), ultraviolet therapy, electron beam therapy, and conventional radiographic therapy (used in the 1950s and

1960s) [1,3]. The same effect is produced by henna, tobacco, potassium permanganate, tar, and silver nitrate [1].

Fungal melanocyte activation occurs as a result of onychomycosis, fungal infection of the nail plate [9]. So far, at least 21 different species of fungi that can cause fungal melanonychia have been described [9]. Its form is variable [1]. Dermatophytes (Scytalidium dimidiatum) form longitudinal stripes, yeasts (Candida albicans, Candida humicola, Candida parapsilosis) and molds (Trichophyton rubrum, Alternaria, Exophiala) form diffuse discoloration [9,10]. With eradication of the causative agent, the appearance of the nail plate usually normalizes [10,11]. The recurrence rate ranges from 10% to 50% [11].

Melanonychia can also be caused by gram-negative bacteria, including Pseudomonas aeruginosa, Escherichia coli, and Proteus mirabilis [1,12,13]. Immunocompromised states and working in a moist environment are risk factors [1]. Longitudinal stripes with a wider proximal edge or diffuse discolorations starting from the junction of the proximal and lateral nail folds and spreading irregularly along the medial edge are present on the nail plates [1].

The human immunodeficiency virus (HIV) predisposes to melanonychia (diffuse discoloration, multiple longitudinal or transverse stripes on multiple nail plates) accompanied by hyperpigmentation of the mucous membranes, palms, and soles [14].

Dark brown discoloration of the nail plate is observed in malnutrition (predominantly protein deficiency and vitamin D deficiency) [1,15]. It is also present in the absence of vitamin B12 (often found in vegetarians) due to decreased glutathione concentration and subsequent inhibition of tyrosinase, the main enzyme of melanogenesis [16].

Repeated local trauma caused by uncomfortable footwear, occupational trauma, onychophagia, onychotillomania, or carpal tunnel syndrome can activate nail matrix melanocytes [1,13]. Traumatic melanonychia is often accompanied by periungual signs of trauma [1]. Nail matrix melanocytes are often activated in a variety of inflammatory conditions and skin tumors, including Lichen planus, chronic paronychia, psoriasis, amyloidosis, chronic radiation dermatitis, Hallopeau acrodermatitis, myxoid pseudocyst, localized scleroderma, onychomatrix, subungual linear keratosis, Verruca vulgaris, subungual fibrous histiocytoma, Bowen's disease, basal cell carcinoma, subungual fibrous histiocytoma [1,13,14].

Multiple dark brown stripes or diffuse discoloration on multiple nail plates on the hands and feet are observed in Addison's disease, Cushing's syndrome, hyperthyroidism, acromegaly, alkaptonuria, hemosiderosis, hyperbilirubinemia, and porphyria [1]. Melanocyte activation is also present in the host reaction against transplantation (Graft versus host disease, GVHD) [1]. Laugier-Hunziker, Peutz-Jeghers, and Touraine syndromes are characterized by multiple dark brown stripes on the nail plates accompanied by pigmented mucous membrane macules on the lips and oral cavity [1,3]. Laugier-Hunziker syndrome occurs sporadically in white adults aged 20 to 40 years [1,3,18]. It does not have systemic manifestations or malignant potential [1,3,18]. Peutz-Jeghers and Touraine syndromes are predominantly present in children and are inherited in an autosomal dominant manner [1,3,18]. They are associated with intestinal polyps and an increased risk of gastrointestinal and pancreatic malignancies [1,3,18].

Melanocytic hyperplasia involves an increase in the number of melanocytes within the nail matrix [19,20]. We distinguish lentigo, nail matrix nevus, and subungual melanoma [19,20].

Lentigo and nail matrix nevus are benign changes [20]. Lentigo is melanocytic hyperplasia in the absence of melanocytic nests, usually present in adults (9% of longitudinal melanonychias in adults) [1,20]. Nail matrix nevus contains at least one melanocytic nest [19,20]. It accounts for 12% of longitudinal melanonychias in adults and 48% of longitudinal melanonychias in children [1]. We distinguish congenital and acquired nevus [20]. In children, especially under the age of 3, it is difficult to determine whether the nevus is congenital or acquired, considering that nail matrix nevus in the early stage can present as a colorless stripe [20].

In situ and invasive subungual melanoma belong to malignant melanocytic hyperplasias [3]. Subungual melanoma is a rare form of melanoma (1-3% of melanomas) [1]. The incidence varies among different races (from 10% to 25%), with higher incidences observed in Asian countries including Japan, China, and Korea [1]. There is no significant difference in incidence by gender [20]. The peak incidence is between the ages of 50 and 70 years [20]. Subungual melanoma is usually localized on the thumb, big toe, and middle toe [20]. In 38%-76% of cases, longitudinal melanonychia represents the first manifestation of the disease [20].

The medical history includes gender, age, occupation, hobbies, previous trauma, medical history, family medical history, continuous therapy, time of onset of melanonychia, location of melanonychia, color and width of the pigment strip, nail pain and/or bleeding, and nail deformity/brittleness [20]. In pregnant women, it includes a history of pregnancy and the relationship between pregnancy and the onset or progression of melanonychia [20].

The physical examination requires careful assessment of all twenty nails, skin, and mucous membranes [3]. During this examination, it is necessary to determine the following:

- Is one or more nails involved?
- Does one nail differ from the others (if multiple nails are involved)?
- Is the discoloration present on the surface, within, or beneath the nail plate?
- Is the discoloration linearly oriented?
- Is the discoloration wider or darker proximally?
- Is the discoloration associated with nail plate dystrophy (abrasion, splitting, cracking), periungual pigmentation, and bleeding?
- Is the discoloration accompanied by changes in the skin and mucous membranes? [1,3]

In the identification of subungual melanoma, the "ABCDE" (from English: Age, Nail band, Change, Digit involved, Extension, Family) rule established in 2000 by Levi and colleagues is applied (Table 1.) [20]..

Table 1. ABCDEF rule of identification of subungual melanoma

A	Age		From 50 to 70 years of age (Predominantly in African Americans, Asians, and Native Americans)
B	Stripe	Color	Black-brown band
		Width	Bands with a width of ≥3 mm
		Edges	Band with irregular or blurred edges
C	Change	Stripe	Sudden or rapid change in band size
		Nail	Change in nail morphology
D	Involved fingers	Finger	Thumb > Big toe > Index finger
		Hand	Dominant hand > Non-dominant hand
		Multiplicity	One finger > Multiple fingers
E	Extension		Extension of pigmentation to the cuticle, proximal or lateral nail folds (Hutchinson's sign), or free edge of the nail plate
F	Family and personal medical history		Family and personal history of melanoma or dysplastic nevus

Nail plate onychoscopy (with handheld dermoscope and digital videodermoscope) enables differentiation between melanin and non-melanin pigmentation (subungual hematoma, pigmentation caused by exogenous substances) [1,20]. Subungual hematoma is characterized by beads of varying sizes and colors (ranging from bright red to brown or black) depending on the depth and duration of bleeding [1]. It is important to note that subungual bleeding does not exclude the presence of subungual melanoma [1]. Additionally, Hutchinson's sign (extension of pigmentation into the cuticle, proximal, or lateral nail folds) of subungual melanoma and pseudo-Hutchinson's sign (hyperpigmentation of the nail bed visible through the thin cuticle and distal part of the proximal nail fold) should be distinguished [20,21]. Onychoscopic patterns of melanocyte activation, benign, and malignant proliferation have been convincingly confirmed in scientific research (Table 2) [1,20,22].

Table 2. Onychoscopic characteristics in relation to the cause of melanonychia 1

CAUSES OF MELANONYCHIA	ONYCHOSCOPIC CHARACTERISTICS
Melanocyte activation	Involvement of several nails. Homogeneous grayish background with regular gray lines.
Benign melanocytic proliferation	Brown background with brown-black longitudinal lines of identical color and width, with regular spacing (parallel).
Malignant melanocytic proliferation	Multicolored background with brown to black longitudinal lines of irregular width and spacing (loss of parallelism).

Intraoperative onychoscopy of the nail bed and matrix allows direct visualization of the changes in the nail bed and matrix [1]. Additionally, it facilitates determining margins and complete excision of the lesion [22].

Biopsy represents the gold standard in the diagnosis of subungual melanoma [6]. The type and location of the biopsy are determined by the morphological characteristics of melanonychia [1]. Histologically, subungual melanoma is characterized by asymmetry, infiltrative edges, significantly increased number of melanocytes in the basal layer (up to 39-136/mm), tendency to form compact aggregates in the suprabasal layers, presence of cytological atypia, and inflammatory processes [13]. Malignant melanocytes are multi-nucleated with large, atypical nuclei, exhibiting increased mitotic activity (Table 3).

Table 3. Histological characteristics in relation to the cause of melanonychia1,23

CAUSE OF MELANONYCHIA	HISTOLOGICAL CHARACTERISTICS
Melanocyte activation	Increased deposition of melanin in the epidermis without an increase in the number of melanocytes
Lentigo	Increased deposition of melanin and an increase in the number of individual melanocytes in the basal epidermis with the absence of atypia
Nevus	Increase in the number of individual melanocytes, irregular or slightly confluent melanocyte nests in the basal epidermis with the absence of atypia
Atypical melanocyte hyperplasia	Proliferation of melanocytes with mild cytological and architectural atypia
Melanoma in situ	Proliferation of melanocytes with significant cytological and architectural atypia, melanocytic fusion, and pagetoid spread
Invasive melanoma	Proliferation of melanocytes with significant cytological and architectural atypia, invasion beyond the epidermis

Treatment of melanonychia depends on the underlying cause [1]. Treatment of associated systemic or regional diseases, cessation of harmful medication use, avoidance of trauma, treatment of infections, or correction of nutritional deficiencies may result in regression of melanonychia [1]. Benign causes of melanonychia do not require treatment [23]. Treatment of subungual melanoma involves wide local excision of the nail or amputation of the finger [23].

CONCLUSION

Melanonychia represents a complex clinical entity whose etiology is often not easily determined. Simple activation of the nail matrix melanocytes, lentigo, nevus, and subungual melanoma have similar clinical characteristics, but their prognoses vary significantly. Careful medical history, physical examination, onychoscopic examination, and ultimately biopsy with histological examination allow for early diagnosis of subungual melanoma as a fundamental goal and precondition for successful treatment of the disease.

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