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Subungual Melanoma: A Deceptive Disorder

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SUMMARY Subungual melanoma is an uncommon form of acral melanoma that arises within the nail bed. The incidence for acral melanomas is similar worldwide, but the proportion is higher in dark-skinned individuals. The subungual form represents about 2% of cutaneous non-sun induced melanomas in the western world, and up to 75% in Africans, 10% in Japanese, and 25% in the Chinese of Hong Kong. Up to 33% of subungual melanomas are amelanotic. Black pigmentation of the adjacent nail fold, termed Hutchinson's sign, may be a diagnostic clue. Non-specific features and symptoms along with a high incidence of amelanosis often lead to delayed diagnosis, disease progression, and a poor prognosis with challenging treatment options.

KEY WORDS: Subungual tumor, melanoma, acral lentiginous melanoma, nail disease, onychomycosis

INTRODUCTION

Subungual melanomas (SM) are uncommon malignancies of the nail which represent 0.7% to 3.5% of cutaneous melanomas diagnosed in the general population (1-3). SM is a distinct variant of acral melanomas, often with histology characteristic of acral lentiginous-type melanomas (4). The incidence of SM is similar for all ethnicities, although a higher proportion of acral lentiginous and subungual melanoma occurs in dark-skinned patients (5). Subungual melanoma survival rates remain poor when compared to melanoma of other parts of the body (6). Low survival rates are due to late detection. To facilitate early diagnosis, SM guidelines have been promulgated (1,7). Treatment of subungual melanoma remains surgical, with wide local excision and amputation as primary modalities.

HISTORY

The first clinical description of SM was made in 1834 by Boyer (8) in a 58-year-old man's fifth digit of the hand. In 1886, Hutchinson (9) described melanomas of the nail bed, which he referred to as melanotic whitlow due to its resemblance to herpetic infection of the hand. His initial description stated: "...Careful observation will find, at the edge of the inflamed nail, a little border of coal black colour, and this however slightly marked, must be allowed to make the diagnosis. I have seen at least half a dozen of these cases. Early amputation is demanded…" (9).

ETIOLOGY

SM, though rare, may occur in any patient worldwide. Overall, melanomas are a byproduct of

genetic and environmental factors, although sun exposure is unrelated in some forms (10). SMs have not been linked with sun exposure. In fact, the nail plate is a barrier to UVB radiation (5). SM may first be evident as a split nail, nail bed swelling, or crusty ulceration. Early literature has suggested that SM may be a direct result of trauma (11,12); however, the majority of analyses do not support such causation (2,13,14). One study showed a 20% incidence of nail injury within the 20-year period prior to SM diagnosis (6,15). In a cohort of Japanese patients, a history of trauma in the affected digit was present in up to 44% (7). A 2002 study maintains the possibility of injury as etiology factor, as trauma induced proliferation may mutate melanocytes (16). However, we believe that the relationship is incidental, with trauma serving to bring awareness to the affected digit (2).

EPIDEMIOLOGY

SMs are most commonly seen in people aged 50 to 70 years. Although the same incidence of melanoma exists among racial groups, dark complexion persons have a higher proportion of this subtype of melanoma since they have a lower incidence of sun-induced melanoma (5). SM accounts for 1% to 3% of all cutaneous melanomas in the white population, up to 75% of African melanomas, about 10% of Japanese melanomas, and 25% of melanomas in the Chinese of Hong Kong (4,17-20). Conversely, other forms of melanoma are more prevalent in lighter skinned populations and are related to sun exposure (4). The great toe or thumb are primarily affected in SM, accounting for 75% to 90% of cases (4). In one Japanese study, 19% of all diagnosed melanomas involved the nail (21). Several other studies in Japan have shown that melanoma in the acral regions, including the nails of the digits, remain the most common type (7). Acral melanomas have a slight preponderance of female over male cases (4).

CLINICAL MANIFESTATIONS

SMs arise from the nail matrix, but may involve other components including the proximal nail fold, nail bed, and hyponychium. They often begin as brown-black discolorations of the nail bed which may appear in the form of bands or streaks (Fig. 1). This discoloration will progress to thickening, splitting, or full destruction of the nail with pain, inflammation, discharge and pigmentary change possible in the surrounding areas (14). In a study by Takematsu *et al*. (7), 31% of SMs began as below nail pigmented streaks and became ulcerated or painful after several years. With disease advancing over many years, involvement of the eponychium and paronychium is common. The widening, dark, and longitudinal nail streak may initially be termed melanonychia striata, which when broad, darkly pigmented, or with blurred lateral borders merits special consideration of SM (22). Black pigmentation of the adjacent nail fold is an ominous feature, termed Hutchinson's sign. Unfortunately, 1/5 to 1/3 of SMs appear amelanotic, further challenging recognition (6,14,23).

SM, similar to other types of melanoma, has a biphasic growth pattern with horizontal and vertical components. Additionally, the tumor thickness is the most important prognostic factor for this disease (6). In one study, Clark levels for invasiveness were at Level IV or V in 33 of 49 patients at the time of diagnosis (17). This same study showed thicker SM of the toe than finger (mean 3.5 *vs*. 2.5 mm; *P*=0.005). Lymph node involvement may be clinically apparent in some SMs. An early study showed that 7 of 20 patients had ipsilateral upper extremity nodal involvement and 7 of 14 had ipsilateral groin involvement for primary SMs in those respective regions (2).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is wide for SM. Subungual pigmentation may be caused by fungal infection, subungual hematoma, foreign material, drugs, or systemic conditions. Other causes may be neoplastic, as in pigmented Bowen disease or benign melanocytic nevi (4,24). Table 1 outlines conditions that may resemble SM.

Table 1. Conditions resembling subungual melanoma

Subungual hematoma
Paronychia
Granuloma
Ethnic pigmentation
Onychomycosis nigricans
Glomus tumor
Benign nevus
Subungual exostosis
Mucous cyst
Subungual fibroma
Keratoacanthoma
Subungual squamous cell carcinoma
Pigmented basal cell carcinoma
Bowen's disease
Kaposi's sarcoma
Angiosarcoma
Dermatofibroma
Wart

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2008;16(4):236-242

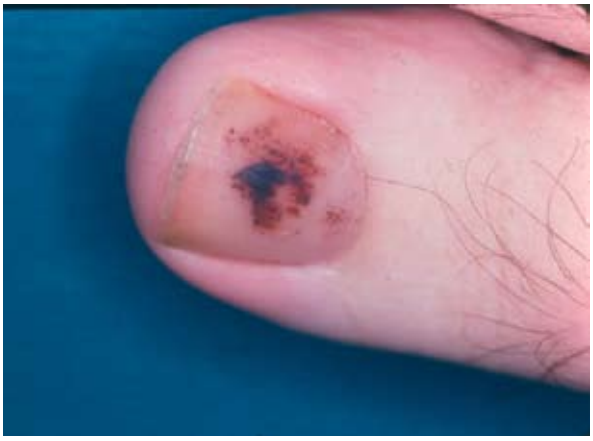

Figure 1. Subungual melanoma. (from ref. 4, with permission of Blackwell)

A principal task is to determine whether nail changes are of melanocytic or nonmelanocytic origin. This may be done with clinical and dermoscopic examination. Subungual hematoma and fungal infections tend to have homogeneous pigmentary distribution, whereas melanocytic conditions appear granular with cellular inclusions of melanin (24). Furthermore, subungual hematoma will appear with a reddish to reddish-black color depending on the time of the bleed. Bloodspots with a proximally round shape tapering to a filamentous end may be evident (24). It is wrong to exclude a diagnosis of melanoma if hemorrhage is present because secondary bleeds may still occur in SM (24). Fungal infections clinically suggesting SM include those caused by *Scytalidium dimidiatum* and *Trichophyton rubrum*, entities known to produce black pigmentation (25,26) (Fig. 2). Nail discoloration by epithelial hyperpigmentation may mimic SM when appearing as gray bands composed of homogeneous gray lines. Brown-black colored bands on the nail plate and regular linear patterns

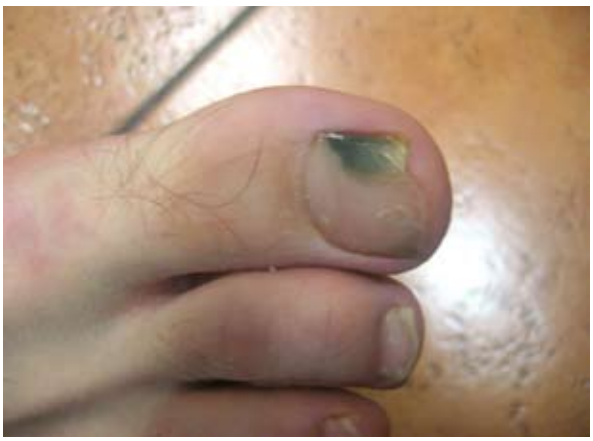

Figure 2. Black nail in a patient with onychomycosis.

Table 2. Systemic conditions resulting in nail pigment changes

Vitamin B12 deficiency
Folate deficiency
Cushing's syndrome
Addison's disease
Drug induced pigmentation – (azidothymidine, tetracycline, ketoconazole, sulfonomide, 5-fluorouracil, etc.)
Acquired immunodeficiency syndrome
Peutz-Jeghers syndrome

suggest melanocytic hyperplasia, whereas irregular patterns hint at melanoma (24) (Fig. 3).

Drug, hormonal, and nutritional causes of longitudinal melanonychia have been noted. In one small group of HIV patients, 67% on azidothymidine (AZT) treatment demonstrated such discoloration (27). Addison's disease, Cushing's syndrome, and hypothyroidism produce pigmentary nail changes (28,29). A bluish-black discoloration has been reported in vitamin B12 and folate deficient patients and is reversible with dietary supplementation (30).

The distinction between nevi of the nail matrix and SM must be made. A benign nevus may be identified in children and may be congenital. It is colored light brown to black and can have a pseudo-Hutchinson sign, in which banding pigmentation is visible through a translucent cuticle. Junctional nevi are more common than compound nevi in this condition, and the heavily pigmented nature of some nevi may simulate melanoma (24). In comparison, SM will often have a broader dark brown band with blurred lateral borders. Rapid growth leads to bands which are not parallel and hints at an ominous diagnosis (24).

Table 1 and Table 2 list more conditions to consider in the diagnostic work up of a patient with black nail disease.

Figure 3. Longitudinal melanonychia.

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2008;16(4):236-242

Table 3. Nail specific ABCDEF guidelines to assist in risk assessment of subungual melanoma

A	Age – peaks at 50 to 70 years old African, Japanese, Chinese, and Native American are dominant
B	Brown-black band often >3mm with irregular border
C	Change in size and growth rate, or failed improvement with adequate treatment of alternative cause
D	Digit – 1) thumb 2) big toe 3) index finger; usually only one affected digit
E	Extension of discoloration, Hutchinson's sign
F	Family history of melanoma

HISTOPATHOLOGY

SMs have a unique histopathologic profile due to the involvement of the nail unit. Major features include an increased number of melanocytes in the basal layer of the specimen. This layer is entirely full of pleomorphic melanocytes with bizarre nuclei. Many pagetoid cells, characterized by irregularly shaped nests of plump melanocytes, are present (7). Melanoma in situ has these aforementioned features but is devoid of stromal invasion. In many cases, melanin pigment will be found in the epidermis of the lower third of the nail matrix (31). Invasive nail melanoma will show higher melanocyte counts (2-3 times that of benign melanonychia), multinucleation, atypia, and florid pagetoid spread of melanocytes (31). Inflammation is also present in advanced melanoma unlike benign melanonychia.

Histology of SM may be consistent with superficial spreading (50%), acral lentiginous (67%), or sometimes both forms of melanoma.(31). Specifically, acral lentiginous melanoma (ALM) is a subtype involving the volar areas. It is characterized by acanthosis, elongation of rete ridges, and lentiginous proliferation of atypical melanocytes in the epidermis (7). Basal keratinocytes become replaced by cytologically malignant melanocytes in ALM. Histology demonstrates greater than 6.5 melanocytes/mm of basal layer length. Furthermore, lymphoid cells infiltrate the underlying dermis in ALM.

The Fontana-Masson stain, which identifies melanin, may be helpful in the diagnosis of melanoma, including SM. The immunostain Melan-A (monoclonal antibody A103 or MART-1), S-100, HMB-45, and NKI/C3 protein markers have similar utility. The S-100 marker is the most sensitive one (32). Unfortunately, such stains are not definitive, as 20%-33% of nail unit melanomas are amelanotic (1).

DIAGNOSTIC APPROACH

Frequently, 2-3 years pass before a patient seeks medical evaluation for a nail finding suggesting SM (7). Diagnosis is established by biopsy, though certain clinical features are indicative. A biopsy specimen should include part of the nail-bed, nail-plate, and nail matrix (6,33). A repeat biopsy may be warranted if the initial specimen is inconclusive. Nail specific ABCDEF guidelines are helpful in assessment and are outlined in Table 3 (1). Hutchinson's sign, or black discoloration of the proximal nail fold, is suggestive of SM with poor prognosis. This feature has inherent flaws, as it has no use in amelanotic melanoma. Furthermore, a Hutchinson's-like sign may be associated with Laugier-Hunziker syndrome, ethnic pigmentation, infection, or use of specific medications.

Clinical evaluation may include dermoscopy (34). It is helpful to closely evaluate any pigmented banding patterns and the free edge of the nail (24).The use of a gel, such as ultrasound gel as a type of immersion medium, decreases viscosity and fills any cavities while permitting the dermatoscope to stay on the nail plate without rolling off. Grayish homogeneous bands or thin gray lines evident with dermoscopy are suggestive of benign melanocytic hyperplasia or ethnic pigmentation. This phenomenon of epithelial hyperpigmentation without accompanying melanocytic hyperplasia is seen in a lentigo, drug-induced pigmentation, and ethnic pigmentation (24). Brown to black pigmentation in an irregular longitudinal pattern with nail plate erosion, Hutchinson's sign, and blood spots (seen in 5% of pigmented melanomas), are suggestive SM signs (35). The brown pigmented band, composed of multiple thin brown lines, can be regular or irregular and is caused by melanocytic hyperplasia in a nevus or melanoma (24). Dermoscopy of amelanotic melanoma of the nail may demonstrate remnants of pigment, linear irregular vessels, and erosion of the nail plate (35).

Additional assessment includes examination of axillary and inguinal lymph nodes, which may include use of computed tomography (36). American Joint Commission on Cancer (AJCC) staging, level of invasion, ulceration, and Breslow and Clark's levels should be determined as well (36). Specifically, classification of melanomas by Clark's levels can be challenging in the nail because of the unique anatomy. Modifications have been made

to overcome this obstacle. For example, Clark's Level V is defined as SM invasion to the underlying bone, as subcutaneous fat is usually absent (37).

PROGNOSIS

Prognosis is poor for SM, often due to the late stage at diagnosis. Five-year survival rates for the invasive type average around 40% (2,7). However, rates may be as low as 18% for five-year survival as shown by Feibleman *et al*.(38). A study of 49 patients showed less favorable outcomes for invasive SM of the toe when compared to the finger (40% *vs*. 72% 5-year survival) (17). Black Americans have a 3.5% lower survival rate than White Americans with SM (confidence interval 1.4-8.6) (36). The most significant factor influencing prognosis is the presence of lymph node involvement, emphasizing the value of a complete exam for these patients (17). Prognosis may also be impacted by gender, as studies have shown the majority of long-term survivors seem to be women (67% *vs*. 50% overall long term survival (39)). Mitotic rates of melanocytes may also be predictive of prognosis, in an inverse relationship to survival (38). Clinical thickness of the tumor also relates to prognosis. One study showed ≥4mm thick tumors resulted in an outcome of only 25% disease free survival at 2 years (17).

MANAGEMENT

Treatment options for SM, specifically early amputation, remain similar to those proposed initially by Hutchinson in the 1800s (9). Other modalities, such as laser surgery, have no definitive role in treatment. Appropriate surgical management involves wide local excision of the in situ form and often amputation when SM is invasive (17). Radial margins should be determined by the Breslow depth. A 1-2 cm margin is preferred in patients with a 2-mm deep invasive melanoma, however, due to the paucity of soft tissue in the nail, amputation must often be performed to accommodate the suggested margins (17). Additionally, nodal dissection is recommended in patients with clinically positive lymph nodes.

Conservative levels of amputation are safe and will not affect recurrence if negative margins are achieved (40). One 2003 study suggested that limited excision with three-dimensional histology had similar survival outcomes when compared to traditionally amputated patients (41). Another analysis also advocated a conservative digit sparing approach and showed no recurrence in 75% of patients at 6-year follow up (42). Mohs micrographic surgery to refine excision has been employed with some success (43). Brodland (44) showed 86% survival at 7.7 years in a small retrospective US study of Mohs micrographic surgery for nail melanoma. Such research represents the continued effort for newer treatment modalities to conserve a functionally precious part of the human anatomy (45,46). Aggressive amputation and digit sparing approaches such as Mohs microsurgery remain options mandating careful scrutiny individualized for each patient (44).

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