

The ABC rule for clinical detection of subungual melanoma

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Background: Subungual melanoma is a relatively rare disease with reported incidence between 0.7% to 3.5% of all melanoma cases in the general population. Unlike the significant improvement in the diagnosis of cutaneous melanoma, the diagnosis of subungual melanoma has shown little, if any, improvement over the years. The widespread adoption of the ABCDs of cutaneous melanoma has helped increase public and physician awareness, and thus helped increase the early detection of cutaneous melanoma; the same criteria cannot be applied to the examination of the nail pigmentation.

Objective: We reviewed the world literature on subungual melanoma and arranged the available information into a system for the identification of subungual melanoma. This system has to be thorough, easy to remember, and easy to apply by both physician and lay public. A case to illustrate the delayed diagnosis often encountered in the current evaluation of nail melanoma is presented.

Methods: A thorough review of the world literature on subungual melanoma was undertaken. The important findings of various studies and case reports were compared among themselves and the salient features were summarized. The information was then categorized under the easily recalled letters of the alphabet, ABCD, that have already become associated with melanoma.

Results: The most salient features of subungual melanoma can be summarized according to the newly devised criteria that may be categorized under the first letters of the alphabet, namely ABCDEF of subungual melanoma. In this system *A* stands for *age* (peak incidence being in the 5th to 7th decades of life and African Americans, Asians, and native Americans in whom subungual melanoma accounts for up to one third of all melanoma cases). *B* stands for *brown to black band with breadth of 3 mm or more and variegated borders*. *C* stands for *change in the nail band or lack of change in the nail morphology despite, presumably, adequate treatment*. *D* stands for the *digit most commonly involved*; *E* stands for *extension of the pigment onto the proximal and/or lateral nailfold (ie, Hutchinson's sign)*; and *F* stands for *family or personal history of dysplastic nevus or melanoma*.

Conclusion: Although each letter of the alphabet of subungual melanoma is important, one must use all the letters together to improve early detection and thus survival of subungual melanoma. Still, as with cutaneous melanoma, the absolute diagnosis of subungual melanoma is made by means of a biopsy. (*J Am Acad Dermatol* 2000;42:269-74.)

Pigmented lesions of the nail unit may be the result of a wide variety of causes, both benign and malignant. Among the possible diagnoses is subungual melanoma, the survival rate of which vastly improves with early detection. A case is reported here presenting with nail bed ulceration without Hutchinson's sign. The literature on subungual

melanoma is reviewed and a screening system is proposed, called the ABCDEF of subungual melanoma, aimed at aiding the early detection and management of high-risk groups.

CASE REPORT

A 68-year-old hypertensive Hispanic woman with hypercholesterolemia was referred to the dermatology clinic at the Columbia-Presbyterian Medical Center for evaluation of a painless nail ulceration on the right index finger. The ulceration, present for several months, was associated with intermittent bleeding, and preceded by a pigmented streak that had appeared in the same area 2 years previously. She had been treat-

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Fig 1. Right index finger of patient with subungual melanoma at presentation to dermatology after showing no improvement after antifungal and antibacterial tablets. Nail plate is eroded and replaced by hemorrhagic crust. Proximal and lateral nailfolds are swollen and erythematous.

ed with several courses of topical and oral antibiotics and antifungal medicaments without improvement. There was no family history of skin or nail cancer. Examination of the right index finger revealed a hemorrhagic erosion that replaced the entire nail plate, with periungual erythema and swelling. Nailfold pigmentation was absent (Fig 1). The rest of her fingernails appeared normal. Biopsy specimens were taken from the nail bed and nail matrix.

RESULTS

Histologic findings

The epithelium was ulcerated. Within the dermis were aggregates of poorly differentiated tumor cells containing golden brown pigment. The tumor cell studies were positive for HMB45 and S-100 protein and negative for cytokeratin, confirming the diagnosis of melanoma. Tumor thickness in these specimens, which represented a small portion of the lesion, was 1.5 mm.

Laboratory studies

X-ray examination of the right index finger revealed no abnormality. Work-up, including chest and abdominal computed tomography and positron emission tomography scans, revealed no evidence of metastases.

Clinical course

After the diagnosis of subungual melanoma was

established, the patient was referred to Memorial Sloan-Kettering Hospital, where a sentinel lymph node biopsy was negative. She underwent amputation of her right index finger at the proximal interphalangeal joint. On histopathologic examination, tumor thickness was 3.9 mm. The patient has been disease free for 2 years.

DISCUSSION

The patient presented with a painless ulceration of the nail plate. The differential diagnosis is substantial, and it is helpful for the clinician to group differential diagnoses into benign and malignant diseases.

Among the benign diseases that may present in this manner are trauma,^{1,2} subungual keratoacanthoma,^{3,4} pyogenic granuloma,^{2,5} paronychia,^{2,5,6} osteomyelitis,^{7,8} radiodermatitis,⁹ subungual epidermoid inclusions,¹⁰ and onychotillomania.¹¹

Among the malignant diseases that should be considered are squamous cell carcinoma,¹² Bowen's disease,^{3,13} epithelioma cuniculatum,^{14,15} basal cell carcinoma,¹⁶ porocarcinoma,¹⁷ bony metastases with secondary nail ulceration (most commonly caused by metastatic bronchogenic carcinoma),¹⁸ and malignant melanoma.

In the last decade, numerous studies have attempted to address the problem of subungual melanoma. Despite the apparent increase in attention to subungual melanoma, little progress has been made in the characterization of the diagnosis,

management, and prognosis since Boyer's first description in 1834¹⁹ and Hutchinson's in 1886.²⁰

Subungual melanoma is a relatively rare disease with reported incidences between 0.7% and 3.5% of all melanoma cases in the general population.^{2,21} It carries a poorer prognosis than cutaneous melanoma, with the 5-year survival rate ranging between 16% and 87%.^{1,2,5,21-26} The delay in diagnosis is reflected in the relatively small number of patients diagnosed with stage I (TNM [primary tumor, regional lymph nodes, and metastases] classification) subungual melanoma (20%), as compared with cutaneous melanoma (80%).²¹ Considering the current epidemic rise in the incidence of cutaneous melanoma,²⁷ an increase in the prevalence of subungual melanoma may be anticipated.

Several factors may be responsible for the delayed diagnosis of this tumor. First is the lack of a well-organized, easily remembered approach to the detection of suspect nail changes, such as is available for cutaneous melanoma. The easily remembered ABCD mnemonic, representing the first letters of the criteria embraced by the medical community in the approach to the patient with a pigmented skin lesion, has facilitated widespread education of both clinicians and the lay public. In turn, this has enhanced the early detection of suspect lesions, allowing for early evaluation and management. Today, some physicians use the ABCD criteria to review skin lesions with their patients, addressing the salient features they need to be aware of for self-examination, thus decreasing the frequency of office visits by allowing patients to follow their own lesions. This has resulted in 80% of cutaneous melanomas being diagnosed at stage I (TNM classification) with a 5-year survival rate of up to 100% reported in some studies.¹

The second factor that may be responsible for the late detection of subungual melanoma is its varied clinical presentation. Subungual melanoma is often misdiagnosed as onychomycosis^{1,5,6,12,14,19,21,28-32} or other benign diseases. In the first English-language description of subungual melanoma, Sir John Hutchinson remarked that it resembled whitlow, a fungal infection of the nail.²⁰ Other common misdiagnoses include subungual hematoma,^{5,21,33} pyogenic granuloma,^{5,33} warts,^{5,32} paronychia,^{1,5} ingrown toenails,¹² junctional nevi,^{5,23} vascular tumors,¹⁴ and squamous cell carcinoma.³³ A more detailed list can be found in the article by Bibbo et al.¹² The ease in misdiagnosing subungual melanoma often leads initially to inappropriate treatment and significant delays in appropriate management. Mean delays of 9 months^{33,35} and 23 months in 50%³⁵ and 41%¹ of the cases, respectively, have been reported, as with the patient in this article.

Table I. The alphabet of nail melanoma: Steps to keep in mind when examining nails for the presence of subungual melanoma

A	Age: Range 20-90 y, peak 5th-7th decades Race: African-American, Native American, Asian
B	Band (nail band): Pigment (Brown-Black) Breadth (≥ 3 mm) Border (irregular/blurred)
C	Change: Rapid increase in size/growth rate of nail band Lack of Change: Failure of nail dystrophy to improve despite adequate treatment
D	Digit involved: Thumb > hallux > index finger Single digit > multiple digits Dominant hand
E	Extension: Extension of pigment to involve proximal or lateral nail fold (Hutchinson's sign) or free edge of nail plate
F	Family or personal history: Of previous melanoma or dysplastic nevus syndrome

Third, the incidence of amelanotic melanoma in the nail unit was noted in recent series to be 14 of 38 patients²¹ and 5 of 25 patients,²⁶ with other studies quoting anywhere from 15% to 65%.^{5,26,36,37} This is in contrast to only 7% of cutaneous melanomas presenting as amelanotic.²¹ The lack of pigmentation in amelanotic melanoma further complicates an already difficult diagnosis, and in one series was found to be the most significant prognostic indicator of subungual melanoma.²¹

Fourth, the detection of nail melanoma during the radial growth phase has posed a significant challenge both clinically and histologically.³⁸ The presentation of the vertical growth phase almost always shows nail deformity characterized by nail thickening, destruction, and ulceration. The radial growth phase presents only with the continued growth of a pigmented nail streak, which in itself carries a large differential diagnosis.³⁹

A well-rooted misconception is Hutchinson's sign (periungual spread of pigment into the proximal or lateral nailfolds). This sign is regarded as an important indicator of subungual melanoma.⁴⁰ It has several inherent flaws, however. First, amelanotic melanoma, which lacks pigment, accounts for a relatively high percentage of subungual melanoma. Second, when present, Hutchinson's sign is not always associated with malignant melanoma, as in Laugier-Hunziker syndrome, ethnic pigmentation, use of certain medications, and others. In these instances, it is referred to as pseudo-Hutchinson's sign.^{39,41} Third, when it is associated with malignant melanoma, Hutchinson's sign is usually late presenting, heralding a poorer prognosis.

It is important to note that a poor prognosis for melanoma of the nail is not only a result of delay in diagnosis. It is also believed to be due to a more aggressive proliferative process.^{1,21} Subungual melanoma appears to metastasize earlier than cutaneous melanoma, and survival rates are much worse, stage for stage, and thickness for thickness.^{1,21}

Despite the rising incidence of malignant melanoma, its incidence in children remains uncommon.⁴²⁻⁴⁴ Recent epidemiologic surveys have shown malignant melanoma to occur in 0.8 to 6.3 cases per million in persons younger than 20 years, accounting for 0.2% to 2% of cutaneous and subungual melanoma, in all ages.³⁷ Although rare, malignant melanoma of the nail bed does occur in children, and should be suspected, particularly in the setting of longitudinal melanonychia (LM), melanonychia striata that has shown continued and rapid growth, eventuating in diffuse melanosis of the nail.³⁸ Other criteria similar to those used for adult subungual melanoma could be used as adjuncts for better assessing LM in children (Table D). In a recent study of 40 children (<16 years old) with LM, the single most common diagnosis was lentigo or nevus (together accounting for 77.5% of the cases).⁴⁴ None of the cases in the latter study represented a melanoma, although mild atypical changes were noted histologically in 2 of their cases. Color variegations, definition of the edges, width of the band, color of the band (black, brown, or light brown), and even the age of the patient (after the age of 1 year) at the time of onset of the LM were all nonpredictive of the histologic type of the lesion.⁴⁴ The authors of that article recommended that if their results are confirmed in a larger scale study, one should avoid performing biopsy of LM in children except when a rapid darkening in color or increase in width is observed.

The most common histologic diagnosis of a pigmented longitudinal band of the nail, in adults, is a benign melanotic macule^{45,46}; in children the most common histologic diagnosis is a junctional nevus.^{44,47,48} The histopathologic subtypes of subungual melanoma include lentigo maligna, superficial spreading, acral lentiginous, and nodular.¹² It is not certain whether these subtypes are an indication of differences in host resistance. In any event, subungual melanomas have biologic and histologic features similar to melanomas of the palms, soles, and mucous membranes, but different from those seen elsewhere. In large-scale analysis of the histopathology of subungual melanoma, acral lentiginous has been the single most common type.^{21,29}

Neither the histologic subtype nor the mitotic rate appear to have any bearing on survival.^{29,49} Breslow depth, and to a lesser extent the Clark level,

and presence of ulceration or bone invasion have been found to be the most important factors regarding prognosis. Although not uniformly agreed upon, the presence of vascular invasion and the mitotic rate have also been shown to be independent prognostic factors.²⁹ The relatively poor 5-year survival for subungual melanomas is reflected in the rather impressive mean Breslow depth of 4.7 mm at presentation.^{29,49}

Clearly, high mortality, lack of public and physician awareness, high frequency of delayed presentation, and prolonged periods of misdiagnosis, suggest the need for a uniform screening system. Such a system is already in place for cutaneous melanoma and is colloquially referred to as the ABCD's of melanoma. An analogous screening system for subungual melanoma is warranted and proposed here.

To facilitate widespread use of such a system, it is advisable to arrange it into a simple pattern, such as an easily recalled mnemonic similar to that in current use for pigmented skin lesions; namely, the ABCDEF of nail unit melanoma (Table D).

When first evaluating a patient, one commonly notes the age and race in the presenting complaint. Thus "A" represents the *age* of presentation and the most commonly afflicted races: African-American, Native American, and Asian. The Age of presentation has been reported to range between 20 and 90 years,^{2,21,35,37,45,49} with rare cases reported in patients as young as 12 months.^{38,42} For reasons that are unclear, although the peak incidence of subungual melanoma is in the fifth to seventh decades,^{2,6,26,35,46,49,50} the majority of benign pigmented bands appear in younger persons. Most of the latter histologically represent a melanotic macule.^{45,46} The incidence of cutaneous melanoma in dark-skinned people is significantly lower than in whites,²⁷ but subungual melanomas occur disproportionately more often in dark-skinned persons. Subungual melanoma represents 15% to 20% of all melanomas in African-Americans,³⁹ 10% to 31% in Asians,^{2,26,28,39,45} and 33% in Native Americans.⁵¹

The presenting complaint/physical finding is usually a pigmented nail band, which may have an extensive differential diagnosis.³⁹ The letter "B" is reminiscent of the nail *band*. The *band* most commonly is *brown* or *black*.^{51,52} During the examination, one should note the appearance of the *band*: its pigment shades, *breadth/width*, and *border*. The presence of variegated shades of brown and black or homogeneously black pigmentation,²⁸ a *breadth* of 3 mm or more,^{38,53} or an irregular or *blurred border* should raise the suspicion of melanoma.^{28,39,45,46,54}

The letter "C" stands for *Change*. A recent, sudden, or rapid increase in the size, comparable to the

radial growth phase,^{38,39} as well as lack of homogeneity of the pigment^{1,39} or change in the nail morphology,^{12,33,39} suggest onset of malignancy. A lack of change/improvement in the nail plate dystrophy, or ulceration despite appropriate treatment, behooves one to consider a diagnosis of subungual melanoma. It should be remembered that the benefit of pigmentary alterations may be lacking in cases of amelanotic melanoma.^{1,12,21,33,34,38,39}

The letter "D" represents the *digit* involved. Subungual melanoma most commonly affects the thumb, then the hallux or index finger.⁹ When involving the hand, it appears to be most commonly localized to the *dominant* one,¹ although some articles fail to find such a predilection.²¹ The involvement of a single digit with a pigmented band should raise much higher suspicion for subungual melanoma than when similarly pigmented bands involve multiple digits.^{1,33,39,54} This is especially important to remember because pigmented nail bands may be seen in as many as 100% of African Americans older than 50 years.

One cannot evaluate subungual melanoma without discussing Hutchinson's sign. This can be incorporated under the letter "E," which stands for extension of the brown or black pigment to involve the proximal or lateral nailfold.^{5,39,41} The extension of the pigment onto the free edge of the nail plate has also been reported as a clue for subungual melanoma.⁴¹

Finally, the letter "F" can remind us to inquire about the *family* and personal history of dysplastic nevus syndrome or previous melanomas because these would raise the suspicion for future malignant degeneration of nail melanotic macules.³⁹ If such a family or personal history is present, photography may be used to follow the progress of nail pigmentation.⁵⁵

It is hoped that by using a systematic approach to the evaluation of nail complaints, the awareness and sensitivity to the diagnosis of subungual melanoma will be raised, allowing statements such as "By the time subungual melanoma is diagnosed, approximately 15% are already metastatic"⁴³ to become a thing of the past.

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