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Seminars in Cutaneous Medicine and Surgery

Pigmented Lesions of the Nail Unit: Clinical and Histopathologic Features

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Probably the most common reason to perform biopsy of the nail unit is for the evaluation of irregular pigmentation, especially longitudinal melanonychia or pigmented bands. When narrow and solitary, these are usually the product of melanocytic activation/hypermelanosis, lentigines, or melanocytic nevi. Multiple pigmented bands are generally a benign finding, the result of melanocytic activation, as seen in racial pigmentation in darker-skinned patients, for example. In the context of an irregular, broad, heterogeneous or "streaky" band, the chief concern is the exclusion of subungual melanoma. Before assessing the histologic features of any such entities, it is important to understand the normal nail anatomy and melanocytic density of nail unit epithelium, as well as the type of specimen submitted, and whether it is adequate to undertake a proper histologic evaluation. The criteria for diagnosis and prognosis of melanoma of the nail unit are still evolving, and a variety of factors must be weighed in the balance to make a correct diagnosis. The importance of the clinical context cannot be overemphasized. There are also nonmelanocytic conditions to be considered that may produce worrisome nail discoloration, such as subungual hemorrhage, squamous cell carcinoma, and pigmented onychomycosis.
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Normal Anatomy of Nail Unit

Before embarking on evaluation of pigmented lesions of the nail unit, it is essential to understand the normal anatomy of the nail unit (Figs. 1 and 2). The nail unit includes the nail matrix, nail plate, nail bed, "sheaths" or cuticles, epithelial folds and grooves (framing), and the fibrocollagenous supportive tissues.[1-3] Histologically, the nail matrix epithelium consists of gently rounded ridges, called mamelons, which angle toward the tip of the digit, and become progressively flattened in transition to the nail bed epithelium. The proximal matrix produces the superficial aspects of the plate, and the distal matrix the remainder, with a small contribution from the nail bed, with the extent of its contribution a matter of controversy. These features explain how proximal matrix damage produces more obvious nail plate deformity, an important consideration in nail unit sampling.

The nail plate, composed of hard and soft keratins, is formed via onychokeratinization occurring in the keratogenous zone of the matrix, which has many similarities to trichilemmal keratinization. Keratinization is abrupt and occurs without a granular zone. The nail bed contains a thin epithelium, whose parallel longitudinal ridges (not rete) interdigitate in "tongue and groove" fashion with the underlying dermis. This pattern can only be appreciated when examining transverse "cuts" through the nail bed (from side to side), and is thus often not evident in longitudinal biopsies (Fig. 3). It is important to note that there is no distinct papillary or reticular dermis in the nail unit, nor are adnexa present except in the normal acral skin comprising the surrounding support tissue, including the nail folds and hyponychium. The distal portion of the proximal nail fold gives rise to the false cuticle. The specialized eponychial epithelium under the proximal nail fold gives rise to an important sheath, the true cuticle, adherent to the nail plate. There is little subcutaneous fat directly under the nail unit dermis, mostly periosteum and bone.

Melanocytic Density in the Nail Unit

One must also understand the normal density of melanocytes and their distribution at this site, which differs from other cutaneous sites.[4] In normal nail unit epithelium, the quantity of melanocytes is lower than in the skin. They also tend to be inconspicuous in normal matrix. Melanocytes may be found in a suprabasal position in the matrix, especially in the proximal matrix, where they are often located within the lower 2 to 4 cell layers. In the distal matrix, they are generally located in the first and second layers. As noted previously, the density of matrical

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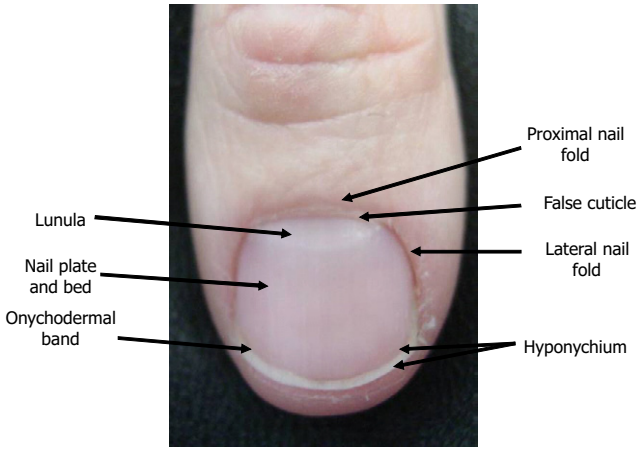

Figure 1 Anatomical landmarks of the normal nail unit.

melanocytes overall is less than elsewhere in the skin, that is, approximately 200/mm^2 compared with approximately 1150/mm^2, respectively. Normally, many of them do not actively synthesize melanin, especially those in the proximal matrix. In the distal matrix, however, approximately 50% synthesize melanin. Melanocytes in nail bed epithelium are even fewer (absent to 50/mm^2) and do not synthesize melanin.[4] This serves as an explanation as to why melanoma arising from the nail bed tends to be amelanotic, and thus a diagnostic difficulty.

From a practical point of view, it is important to have a grasp on the normal density of melanocytes along the basal layer, to be able to assess if there is a significant increase, suggesting a melanocytic proliferation. The melanocyte density is generally measured over a 1-mm interval at the epidermal-dermal junction of nail matrix or nail bed. In normal nails, the density ranges from 4 to 9 melanocytes (mean, 7.7) per 1-mm segment of nail matrix epithelium.[5,6] Normal matrical melanocytes are generally small, and some may display dendritic processes. As noted, they are often inconspicuous and are best highlighted via immunoperoxidase stains, including S100, HMB45, Melan-A, and MiTF. Melan-A, as a melanosome marker, can sometimes exaggerate the density of melanocytes especially in a heavily melanized nail melanocytic neoplasm. MiTF (microphthalmia transcription factor-1), being a nuclear stain, gives a more accurate assessment of density and location within the matrix (Fig. 4).[7,8] It is important to note that

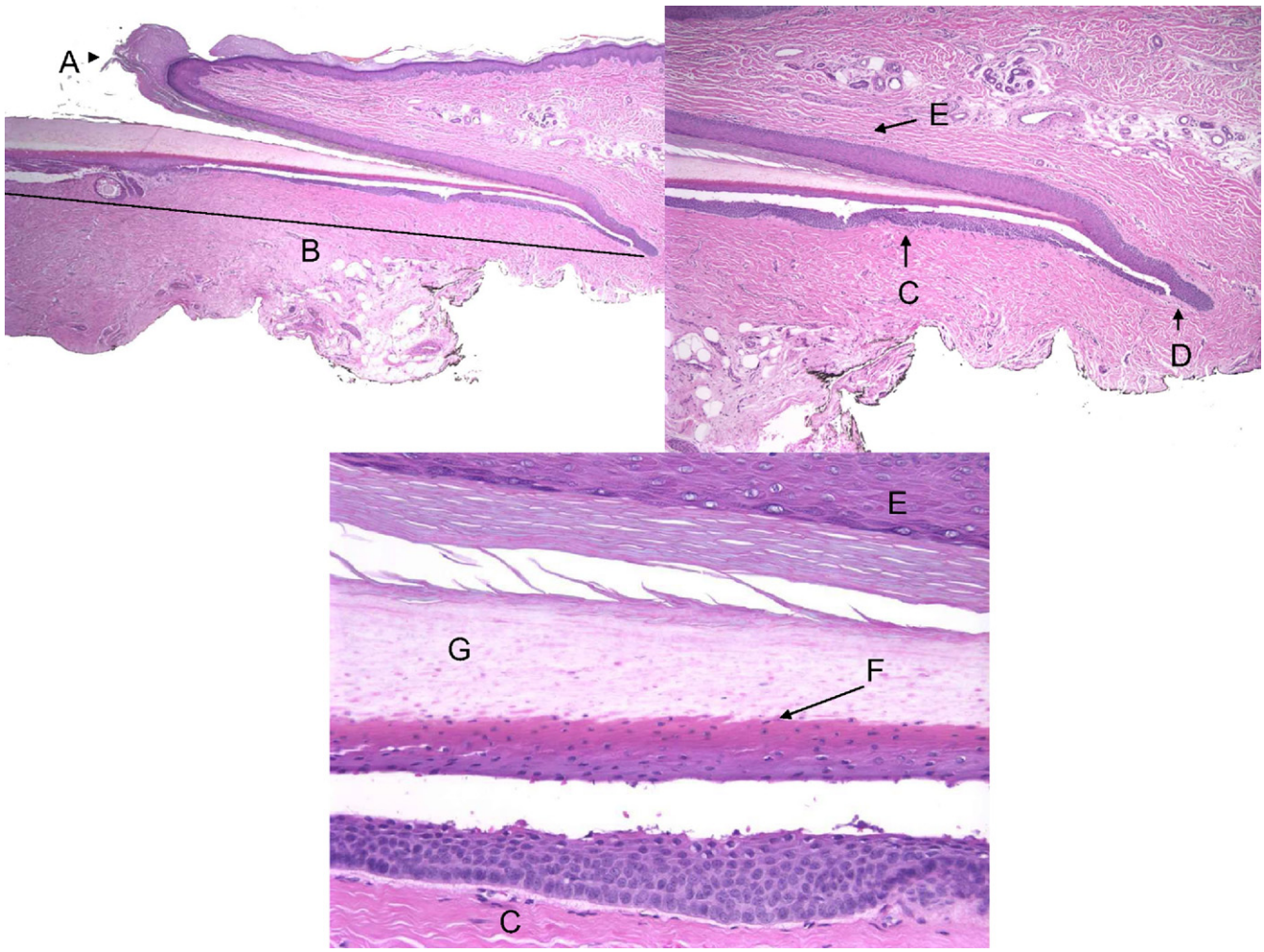

Figure 2 Histologic landmarks of the proximal nail unit. (A) proximal nail fold; (B) nail matrix (with incidental subungual epidermoid inclusions); (C) distal matrix; (D) proximal matrix; (E) ventral surface of proximal nail fold (eponychium); (F) keratogenous zone; and (G) nail plate.

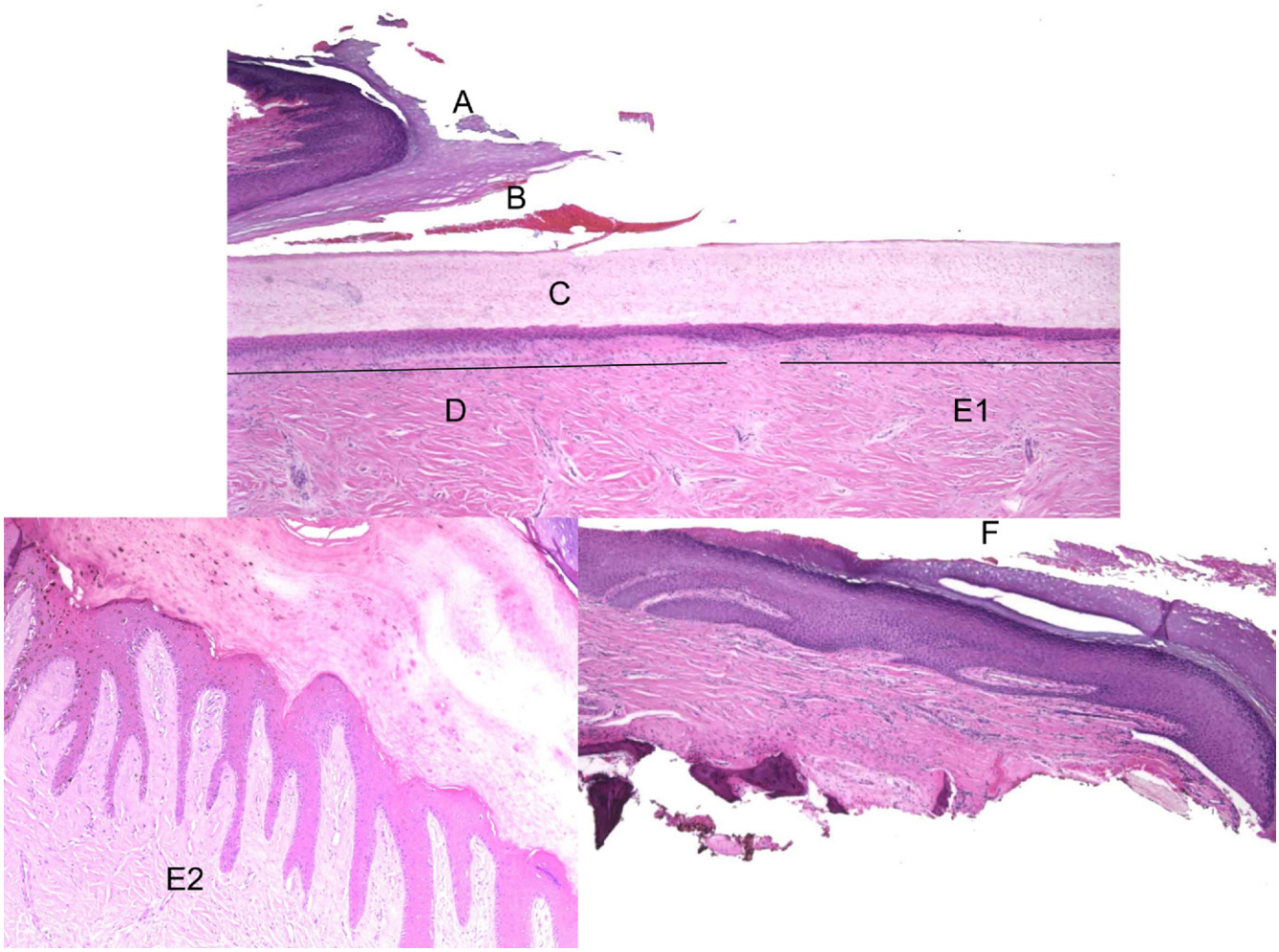

Figure 3 The distal nail matrix, nail bed, and hyponychium. (A) false cuticle; (B) true cuticle; (C) nail plate; (D) distal nail matrix; E1: nail bed; E2: nail bed in transverse section (with melanoma in situ); and (F) hyponychium (reverts to acral skin).

S100 immunostain should not be used, especially as a single stain, as nail melanocytes tend not to express this antigen reproducibly.

The Clinical Context

In addition to a basic understanding of the unique histology of the nail unit, one must also obtain as much clinical information as possible before attempting to evaluate any pigmented lesion of the nail unit. It is vital for this information to be given on any requisition form. Most pigmented lesions biopsied display longitudinal melanonychia or a pigmented band. Key clinical features useful in evaluating a pigmented band have been discussed in many publications,[9,10] and include those summarized in Table 1. If only one piece of information is given, the width may be the most helpful, just as the size of a pigmented lesion at any other cutaneous site is particularly informative. Demographic data, such as the age of the patient and the digit affected, are also important. For example, melanoma often arises in older patients, and the thumb and hallux are more commonly affected, as is the dominant hand.[9] It is helpful to know from where the pigment originates and its overall configuration. For example, if it does not involve the matrical zone, and is irregular at its free edge, subungual hemorrhage may be its etiology instead of a melanocytic proliferation. The findings on dermatoscopy may also be helpful in that regard.[10] A preoperative clinical photograph is the most helpful. However, if only a small punch biopsy is taken from the proximal portion of the band, a postoperative photograph may still contain valuable clues with respect to the remaining band.

Most examples of melanocytic activation, lentigo and nevus measure 3 to 5 mm or less in width, whereas melanoma tends to display a wider band (Figs. 5-9). A notable exception is a melanocytic proliferation in a young person that may be broad but still benign, sometimes displaying complete melanonychia.[10-12] Most lentigines and nevi display a band with a tan-to-brown hue. Bands caused by melanocytic activation may display a slightly gray hue. A benign band is generally also relatively homogeneous with respect to color and color intensity and has sharp edges. Most pigmented lesions producing melanin arise in the distal nail matrix. In general, there should be no periungual pigmentation (Hutchinson's sign).[13,14] Beware, however, the causes of pseudo-Hutchinson's sign, which are discussed in more detail in this article. One notable example consists of pig-

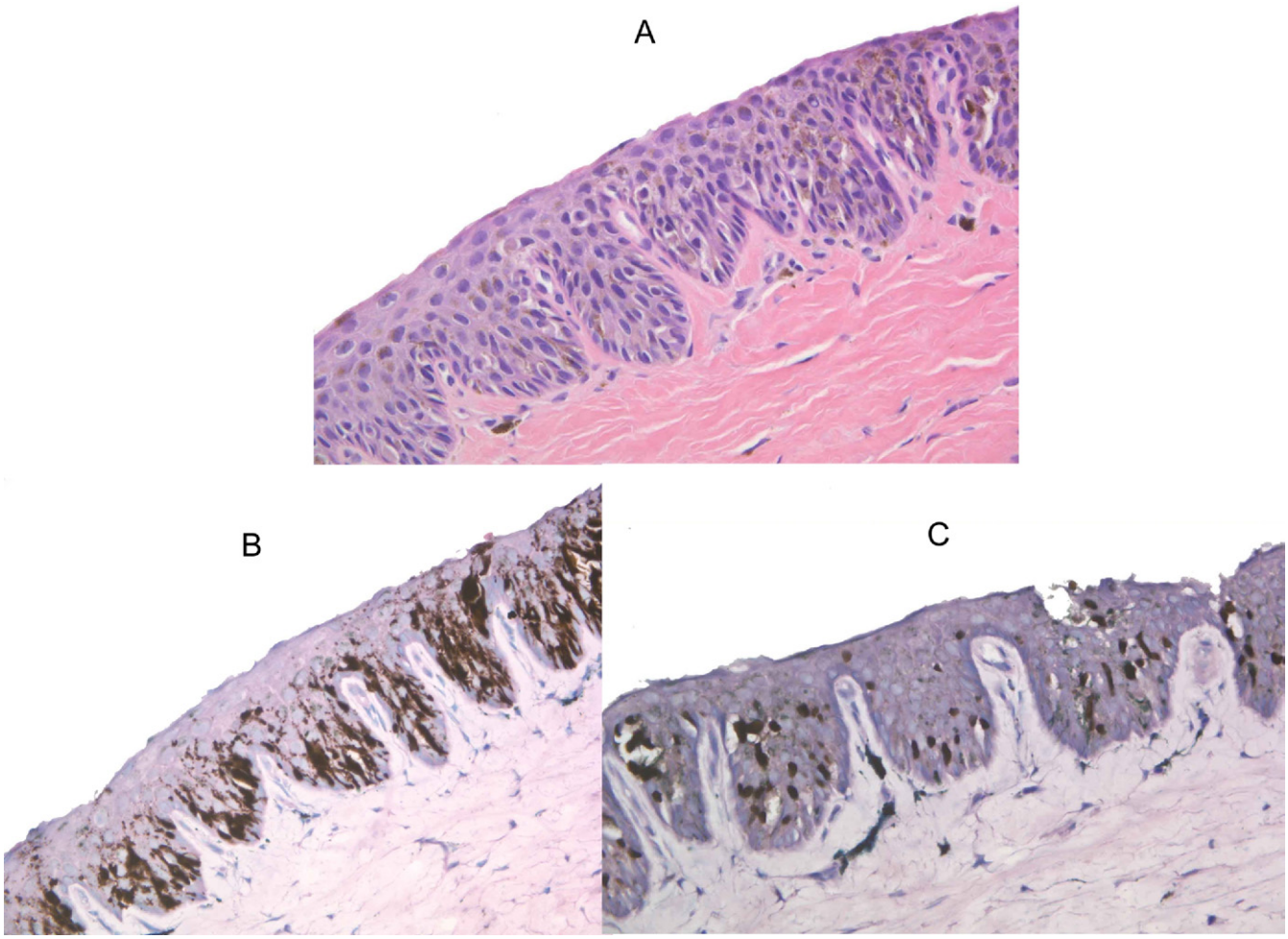

Figure 4 Immunohistochemistry in the evaluation of nail unit melanocytic neoplasms. (A) Melanoma in situ (hematoxylin and eosin, 400×); (B) Melanocytic density and distribution highlighted in Melan-A with Giemsa counterstain (400×); and (C) MiTF with Giemsa counterstain, highlighting melanocytic nuclei (400×).

mentation transmitted from a heavily melanized matrical lesion through the proximal nail fold, without actual extension of the melanocytic proliferation onto that area. This is generally confined only to the breadth of the pigmented band, however, and should not diffuse beyond it. Also, some benign melanocytic neoplasms may involve the periungual skin, in particular congenital nevi.[14] Approximately 75% of cases of melanoma present with longitudinal melanonychia, and most of these cases originate in the nail matrix. However, nail dystrophy may rarely be a presenting sign of amelanotic melanoma in situ.[15] In addition, amelanotic melanoma often originates in the nail bed where, as noted previously, melanocytes may not produce much melanin pigment.[4] Such lesions are often mistaken for granulation tissue/pyogenic granuloma, or an ingrown nail, and thus may escape diagnosis for a prolonged period as a result.

Biopsy Techniques and Tissue Submission

There are several biopsy techniques commonly used to sample pigmented lesions in this area, and a complete discussion of these is beyond the scope of this article but can be found in the references[16-18] and elsewhere. There are several general varieties of technique. A simple punch excision through the proximal nail fold to the matrix is fairly common. However, reflecting the proximal nail fold and removing the proximal nail plate to expose the matrix, with direct sampling of the apparent pigmented area, via punch, shave or other excisional techniques, may improve accuracy in sampling. An

Table 1 Key Clinical Information in the Evaluation of Longitudinal Pigmented Bands

Solitary or multiple bands
Width of the band
Homogeneity of the band
Lateral demarcation of the band (border)
Hutchinson's sign (periungual pigmentation)
Findings on dermatoscopy
Duration and any change over time
Which digit and which hand (dominant?) affected
Age of the patient
Any extenuating clinical history (drugs, pregnancy, baseline pigmentation, personal or family history of melanoma)

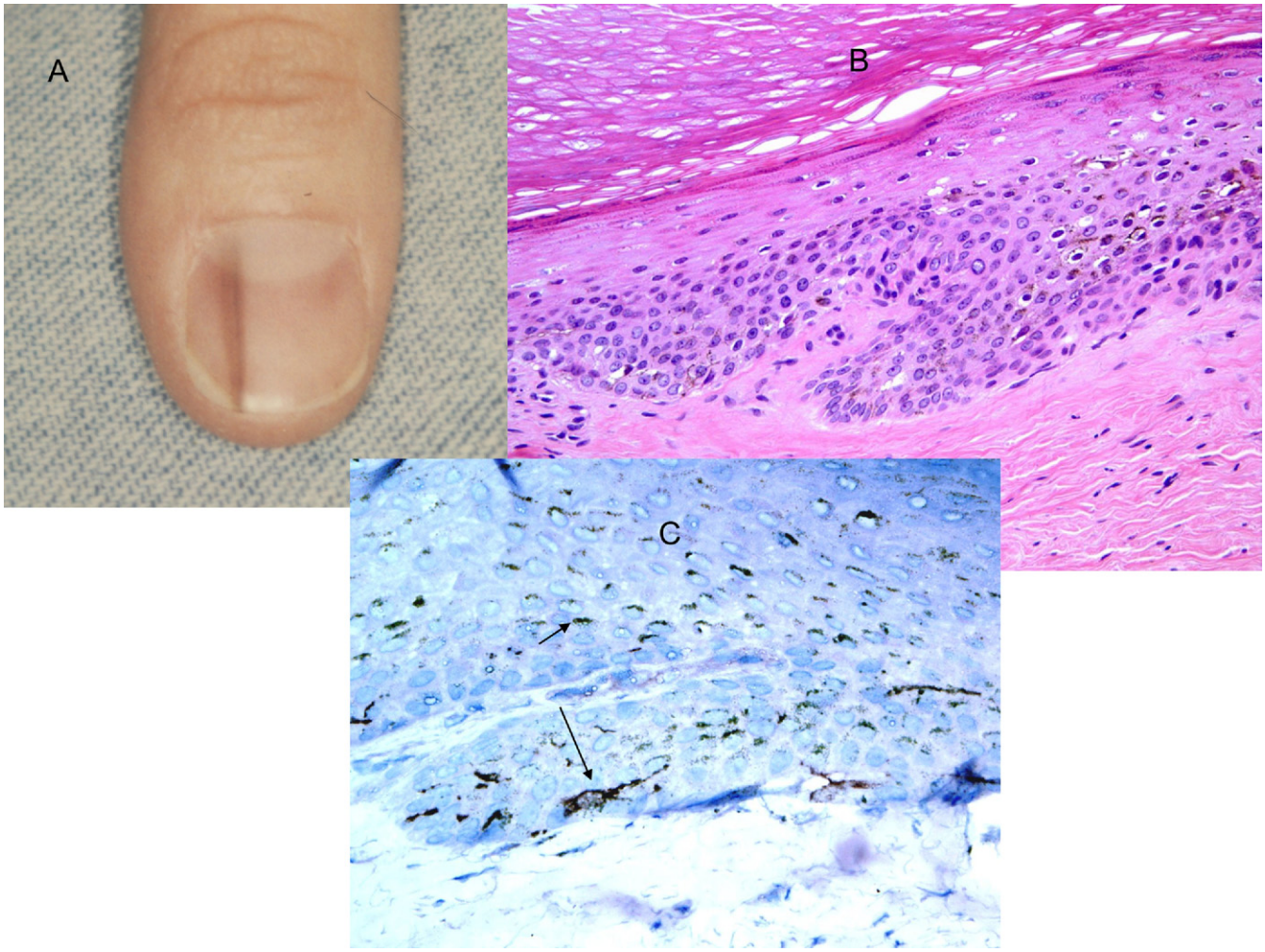

Figure 5 Melanocytic activation. (A) Clinical, gray-tan narrow pigmented band (Courtesy of Paula Vogel, MD); (B) Increased melanin in matrical epithelium, without an obvious increase in melanocyte density (hematoxylin and eosin, 200×); and (C) Melan-A with Giemsa counterstain, with melanocytes staining brown (long arrow), and melanin within keratinocytes staining a greenish hue (short arrow) (400×).

en-bloc longitudinal excision encompassing the full-length and width of the band is the gold standard, especially if lesions are laterally located, in which case this procedure produces a narrower but usually normal nail plate. Any of these techniques can cause a permanent nail dystrophy, although distal matrical sampling by shave technique tends to produce less, as the distal matrix contributes to the lower aspects of the nail plate. The proximal matrix contributes to the surface, and so sampling there produces greater likelihood of resultant nail dystrophy. Because most pigmented lesions do not arise from this zone, it may not be necessary to include it.

Complicating factors for the microscopic interpretation of such lesions include poor sampling of the tissue, producing crush and shearing artifact, and partial sampling. The tissue can also suffer from misorientation and resultant loss of epithelium. Care should be taken by the clinician in extracting the tissue, and the type of tissue submitted should be specifically designated (matrix, nail bed, nail fold, etc.) For example, if one submits only nail bed tissue, and most melanocytic proliferations originate in the nail matrix, the lesion of interest could be missed entirely. Ideally, the histology laboratory should also be acquainted with how best to handle such specimens, which may contain the hard keratin of the nail plate and may thus be difficult to section without adequate hydration, for example, soaking the paraffin block in water immediately before sectioning.

Histology of Pigmented Lesions of the Nail Unit

Melanocytic Activation (Hypermelanosis)

Melanocytic activation is probably the most common cause of benign melanonychia in adults as confirmed in some studies (Table 2).[11] This consists mainly of hyperpigmentation of the nail matrix epithelium without an obvious increase in melanocytes. Melanocytic density can be highlighted in immunoperoxidase stains, such as Melan-A or MiTF, and use of a red chromogen or Giemsa counterstain[19] is helpful in delineating the immunostain result in the midst of heavy melanization of keratinocytes. More subtle background pigmentation can be dem-

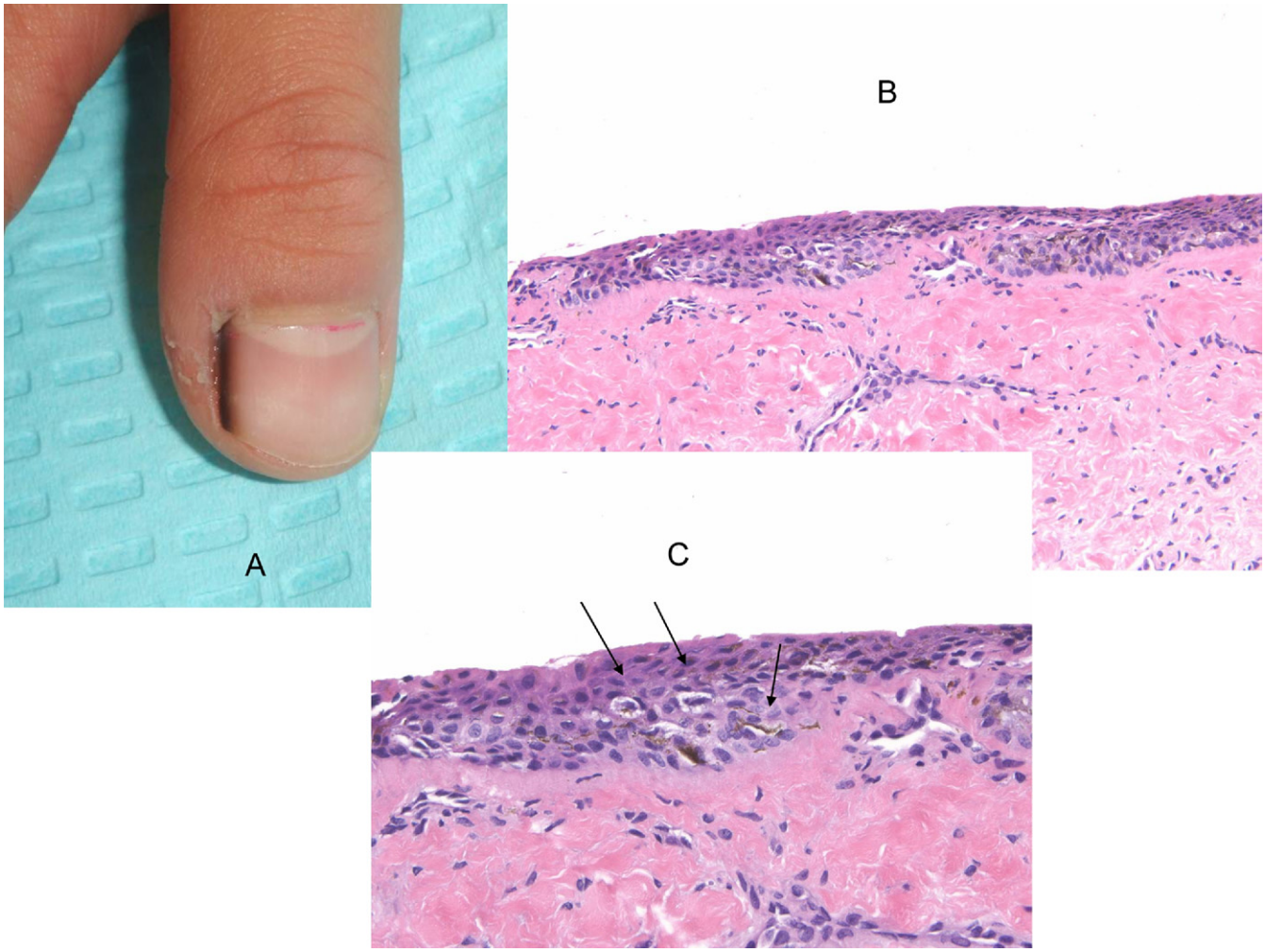

Figure 6 Lentigo. (A) Clinical, dark brown narrow band (Courtesy of Siegrid Yu, MD); (B) Increase in single melanocyte density (hematoxylin and eosin, 200×); and (C) Increased single melanocytes, with some also dendritic, arrows (hematoxylin and eosin, 400×).

onstrated in a Fontana stain, as interestingly, a longitudinal band may result even when the matrical pigmentation is rather limited histologically. The melanocytes in this setting are often dendritic, and there may be scattered melanophages (Fig. 5).

Lentigo (Melanocytic Hyperplasia)

The simplest melanocytic lesion of the matrix, as elsewhere on the skin, is the lentigo, also known as benign melanocytic hyperplasia. This has sometimes also been referred to by the confusing term melanotic macule. Some authors have used this designation also to refer to lesions compatible with melanocytic activation/hypermelanosis, or to a group of lesions, including both hypermelanosis and lentigo. As this term, when applied to lesions at other cutaneous sites, indicates a lesion containing hyperpigmentation of the basal layer but no increase in melanocytes, it is best avoided in this setting.

Lentigo of the nail unit consists of a slight to moderate increase in the number of single matrical melanocytes (10-31 cells/mm in one study),[4] without any demonstration of confluence. Dendritic melanocytes may be present. Cytologic atypia is absent or minimal (Fig. 6). Suprabasilar scatter of melanocytes should be only rarely observed and limited in extent. As in melanocytic activation, scattered melanophages may be present.

Melanocytic Nevi

Nail matrix nevi are probably the most common cause of melanonychia in children.[11,12] Nail matrix nevi are usually junctional and rarely compound. Most are of the "ordinary" type, although nevi with pigmented epithelioid melanocytes can be seen, and blue nevi[20,21] and Spitz nevi[22] have been rarely reported. The nail unit is a "special site," and nevi in this area can display unusual features, many of which are similar to those observed in acral nevi.[23,24] There is usually a lentiginous pattern of melanocytes in early lesions. The nests are often irregular and occasionally confluent, especially if the sections examined are longitudinal, and melanocytes may be present above the basal layer to a limited extent, particularly in children (Fig. 7).[12] Melanocytes should not be present in general in the superficial aspects of the nail matrix epithelium, as this is a worrisome feature seen more commonly in melanoma. Melanocytes can be larger and more hyperchromatic. Nevi, especially congenital nevi, may occasion-

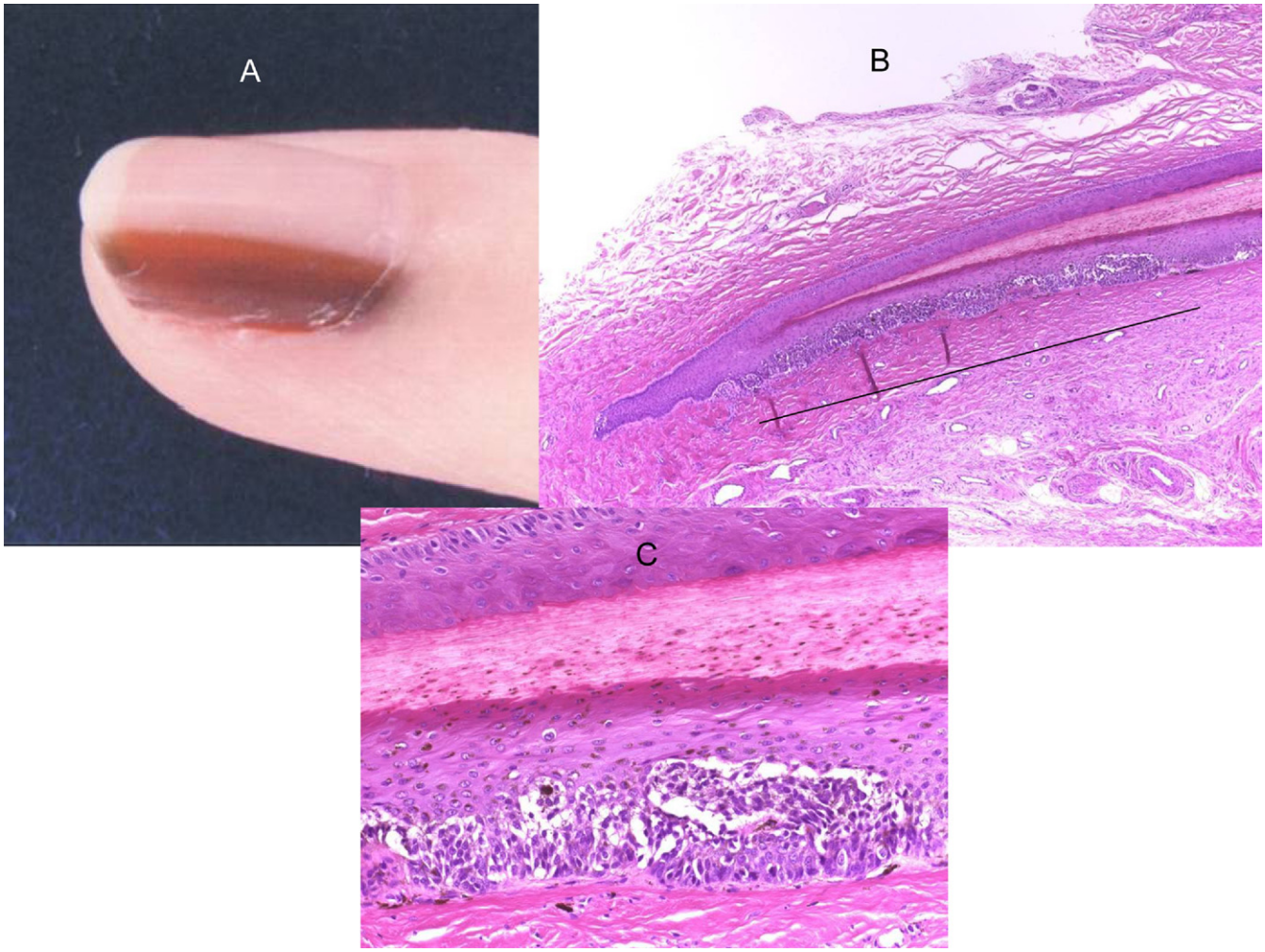

Figure 7 Nevus. (A) Clinical, dark brown narrow band, with pseudo-Hutchinson's sign at proximal nail fold/cuticle; (B) Melanocytes in nests, occasionally crowded, but in well-circumscribed array involving distal matrix, line (hematoxylin and eosin, 40x); and (C) Mainly nested, with rare melanocytes above the basal layer, and note melanin granules within lower nail plate (hematoxylin and eosin, 400×).

ally involve the periungual acral skin. Compound nevi often contain nests which are arrayed horizontally, perhaps a compressive effect of the hard overlying nail and relatively firm dermal tissue under the nail epithelium.

Nail Apparatus Melanoma (Subungual or Ungual Melanoma)

Although relatively uncommon, this tumor is highly dangerous. Compared with melanoma at other sites, it has a disproportionately higher mortality rate. The 5-year survival rate ranges widely from 16% to 87%, depending on the series, with 2 larger series in the 51% to 55% range.[25-27] It affects nonwhite patients with greater frequency than does conventional melanoma. The relationship with sun exposure for this subtype has not been elucidated. Most nail apparatus melanoma arises in the thumb and great toe (hallux), and digits on the dominant hand are also more often affected. It often presents in atypical clinical fashion, with nail dystrophy, and with or without abnormal pigmentation. This of course leads to late diagnoses and poor outcomes as a rule. In one larger study, the mean Breslow thickness at diagnosis was 4.8 mm.[25] It may arise in the nail matrix or less often the nail bed. When nail matrix melanoma presents as melanonychia (as it does in 76% of cases), it often produces a band wider than 3 mm, which has widened over time. A disturbing clinical finding is a band wider at the base than the distal edge of the nail, a sign of relatively rapid enlargement. However, in children this may occur in nevi.[10] The band is often irregular and not crisp at its lateral margins, and may be "streaky" or heterogeneous in color.

With time and involvement of the nail bed or periungual tissue, its irregularity becomes more obvious. Involvement of the proximal nail fold and sometimes the hyponychium (Hutchinson's sign, periungual pigmentation) is a fairly diagnostic clue, especially if the pigmentation is also irregular or diffuse. Often, Hutchinson's sign correlates histologically to melanoma in situ. Causes of pseudo-Hutchinson's sign should be kept in mind, including melanocytic nevi and lentigines, squamous cell carcinoma in situ, drug-induced pigmentation, trauma, radiation, racial pigmentation, malnutrition, and hemorrhage.[13] Nail plate thinning or fissuring is another concerning feature when seen concurrently with abnormal pigmenta-

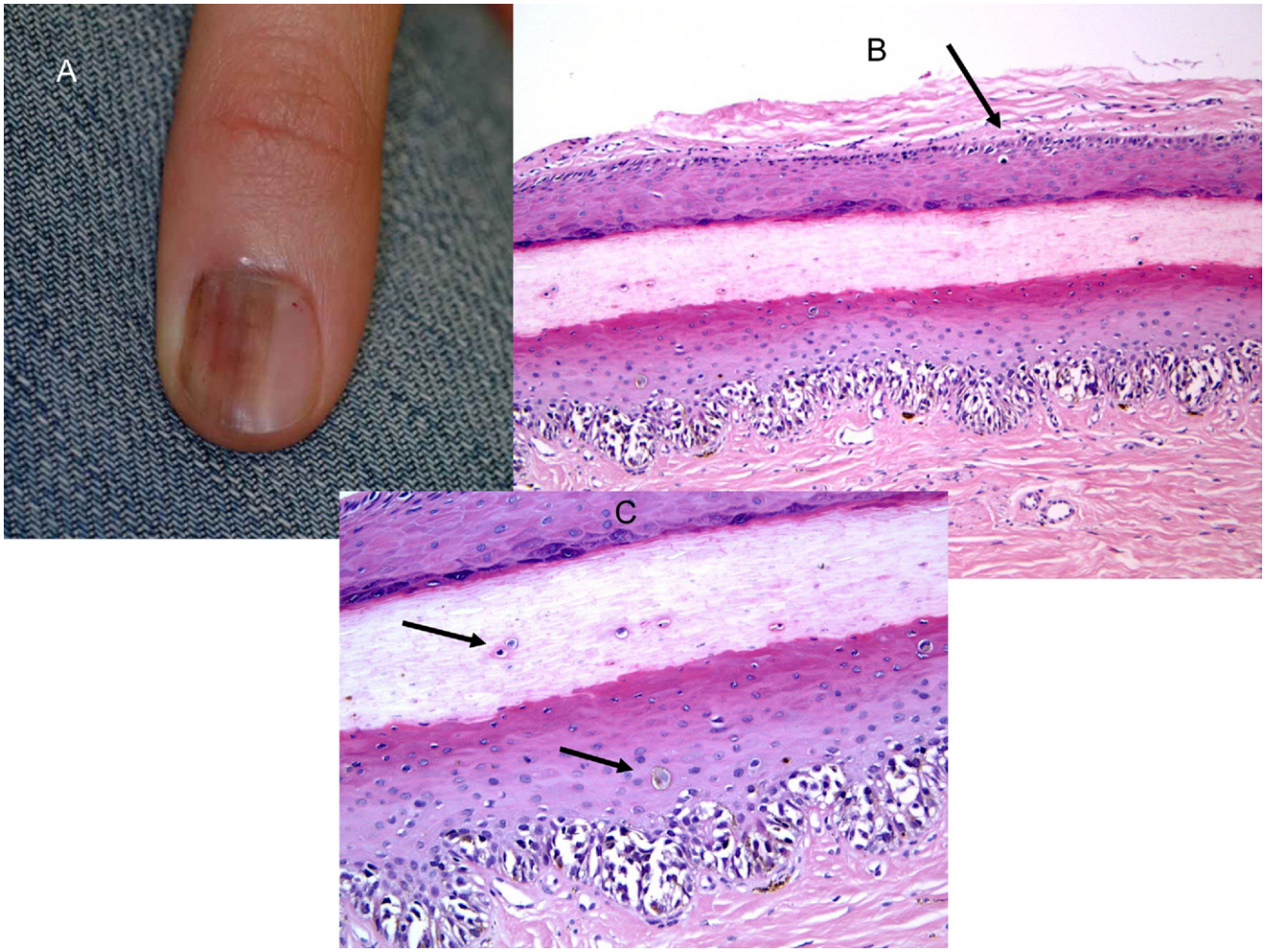

Figure 8 Melanoma in situ. (A) Clinical, a broader inhomogeneous band, with Hutchinson's sign at proximal nail fold (Courtesy of Jeffrey Sugarman, MD, PhD); (B) Confluence of atypical melanocytes, with involvement also of eponychial (ventral nail fold) epithelium, arrow, a correlate of Hutchinson's sign (hematoxylin and eosin,100×); and (C) Scatter of melanocytes within the upper matrical epithelium and visible within the nail plate itself, arrows (hematoxylin and eosin, 400×).

tion. If the tumor is allowed to progress, a nodule may develop, often with ulceration and nail plate destruction. Nail bed melanoma is often amelanotic and usually presents as a nodule, with associated onycholysis. An exceptional presentation of amelanotic melanoma in situ is roughening of the nail with distal splitting, mimicking lichen planus.[15] Desmoplastic melanoma of the nail unit has also been described.[28] Nail apparatus melanoma in children is exceedingly rare.[29]

Criteria for the diagnosis of nail unit melanoma are still in evolution, as are prognostic factors. Larger epidemiologic studies will be needed to address the latter. There is histologic discordance even among experts, and as such, a group of dermatopathologists with an interest in melanonychia has been formed as a subcommittee of the International Melanonychia Study Group, begun in 2007, to address these issues. Various criteria can be used to establish a diagnosis of melanoma, including poor circumscription, the density of single intraepidermal melanocytes, an irregular distribution of melanocytes, including confluence of nests, degree of suprabasal scatter, cytologic atypia, a lymphocytic infiltrate, and anisodendrocytosis (variation of dendrite size, also seen in acral melanoma).[6,27,30-32] (Figs. 8 and 9). Use of immunoperoxidase stains may be crucial to elucidating these features in some cases (Fig. 4). The ability to evaluate salient features also hinges significantly on the quality of the tissue submitted. In a recent study, the mean number of melanocytes in melanoma in situ was 58.9 per 1-mm interval along the epidermal-dermal junction (range, 39-136) compared with 15.3 (up to 31) for lentigo/benign melanocytic hyperplasia.[6] However, as evidenced in these data, the upper limit of density in lentigines is not far off from the lower end observed in melanoma in situ in some cases, and thus melanocyte density alone cannot be used to make a diagnosis of melanoma in situ. Confluence of single melanocytes may be observed, and there is usually a predominance of single cells over nests in early lesions. Suprabasal scatter that is marked and involves the superficial aspects of the matrical zone is cause for concern. It is thus crucial to examine any portions of nail plate for the superficial portions of the matrical keratogenous zone and nail bed, portions of which often remain attached to the nail plate

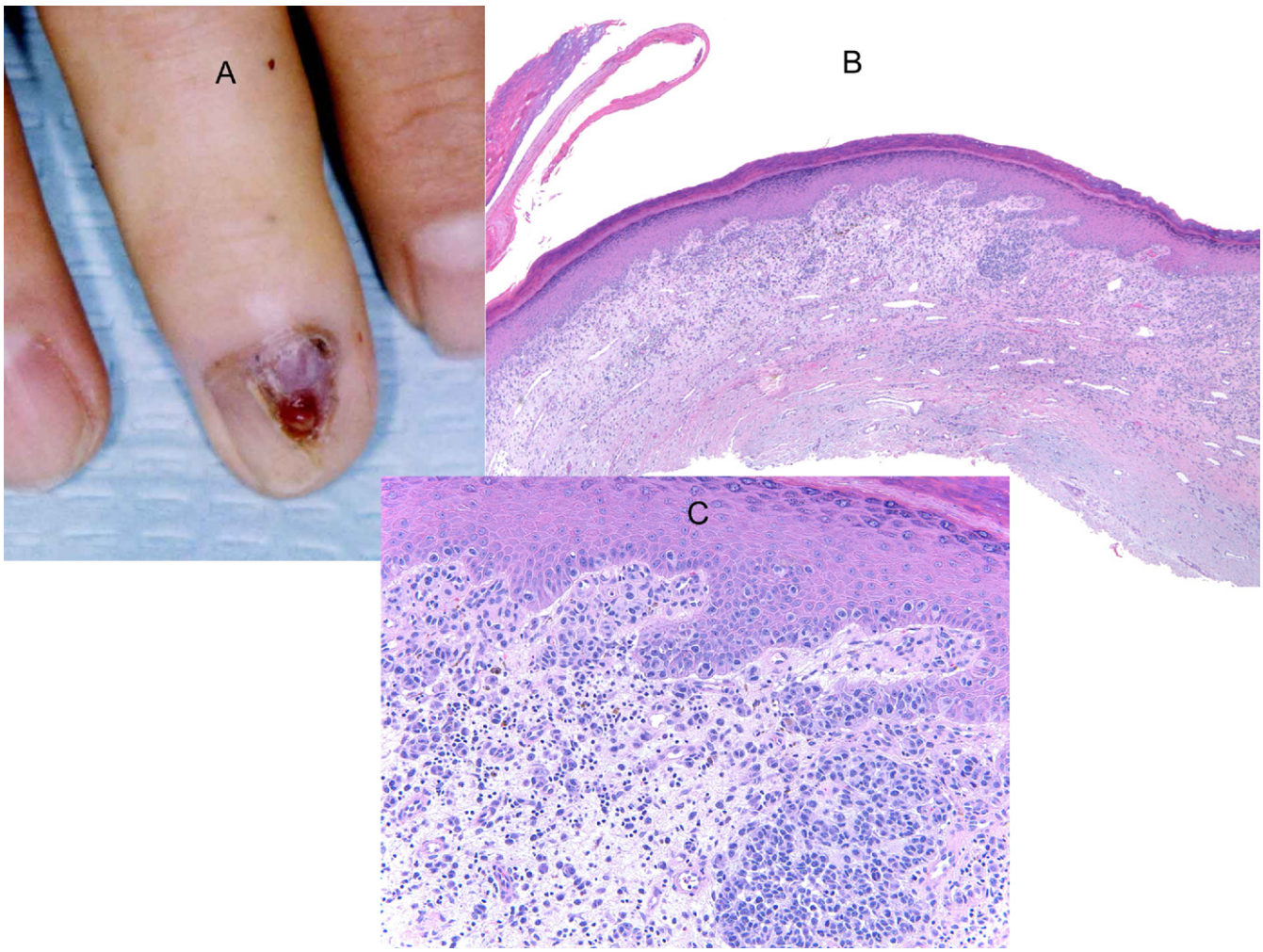

Figure 9 Invasive melanoma. (A) Clinical, a nodular tumor with discoloration and disruption of the nail plate, with a pyogenic granuloma-like appearance (Courtesy of Siegrid Yu, MD, PhD); (B) Involvement of nail matrix and bed with loss of normal epithelial architecture (now with formation of granular zone) and loss of nail plate (hematoxylin and eosin, 40×); and (C) Atypical melanocytes arrayed irregularly within the nail bed epithelium and within the dermis, without maturation with descent (hematoxylin and eosin, 200×).

when it is avulsed, as this may contain important diagnostic clues. Involvement of periungual or eponychial epithelium, as in Hutchinson's sign, is of course an indicator of poor circumscription (Fig. 8). Interestingly, cytologic atypia may not be marked in such areas.

Invasive nail unit melanoma displays many of the same features as that observed elsewhere on the skin. In addition to the findings noted in melanoma in situ at this site, the dermal component lacks adequate maturation, may display an irregular distribution of nests and syncytia, and may display an increased mitotic rate (Fig. 9). Neurotropism and lymphovascular invasion may occur. Unusual variants also found in nail unit melanoma include nevoid melanoma, as well as myxoid, chondroid, neuroid, and desmoplastic types.[28,32] Invasive melanoma of the nail bed is usually amelanotic, as noted above. In more advanced tumors ulceration and loss of the nail are frequently noted.

Diagnostic reporting of nail unit melanoma by the dermatopathologist can be somewhat challenging. Breslow thickness is reported in a manner similar to that at other cutaneous sites with a measurement from the most superficial epithelial layer visible, to the thickest portion of the dermal component. Normally, there is no granular zone in the nail unit, although one frequently develops in disease states, including melanoma. The correlation of thickness and prognosis may not be the same as for melanoma elsewhere.[27] Clark's anatomic levels cannot be established in the same manner. There is no distinct papillary dermis or subcutis in the nail unit proper, although these are present in periungual acral skin, and can be used in establishing conventional Clark's levels, if involved. Level V can be reported as involvement of the phalangeal periosteum or bone. Apart from general American Joint Committee on Cancer staging criteria, no other significant prognostic factors have been established firmly, especially with respect to the primary tumor characteristics,[27,31] and larger epidemiologic studies may better address those issues. Nonetheless, the author's recommendation is that the prognos-

Table 2 Causes of Nail Pigmentation

Melanocytic activation/hypermelanosis
Trauma
Medications
Racial pigmentation
Endocrinopathy
Pregnancy
Peutz-Jeghers and Laugier-Hunziker syndromes
Disruptions to the nail unit, including inflammatory and neoplastic conditions
Melanocytic proliferations
Lentigo
Nevus
Melanoma
Other
Nail hemorrhage
Pigmented squamous cell carcinoma
Pigmented onychomycosis

tic features commonly reported in cutaneous melanoma should be recorded for nail melanoma as well by the dermatopathologist.

Nonmelanocytic Causes of Nail Pigmentation

There are several conditions that may mimic melanonychia, and some nonmelanocytic neoplasms that can actually produce melanonychia. Several common entities in this group include subungual hemorrhage, pigmented squamous cell carcinoma, and pigmented onychomycosis.

Subungual hemorrhage usually produces an irregular area of discoloration, and less often a longitudinal band that may or may not originate at the proximal nail fold. It is one cause of pseudo-Hutchinson's sign. Its irregular edges and the presence of leukonychia may be a clue to its etiology, as is its natural evolution, that is, to grow outward with the nail. Nail dermatoscopy is a helpful way to confirm the diagnosis. However, pathologists are often asked to interpret portions of

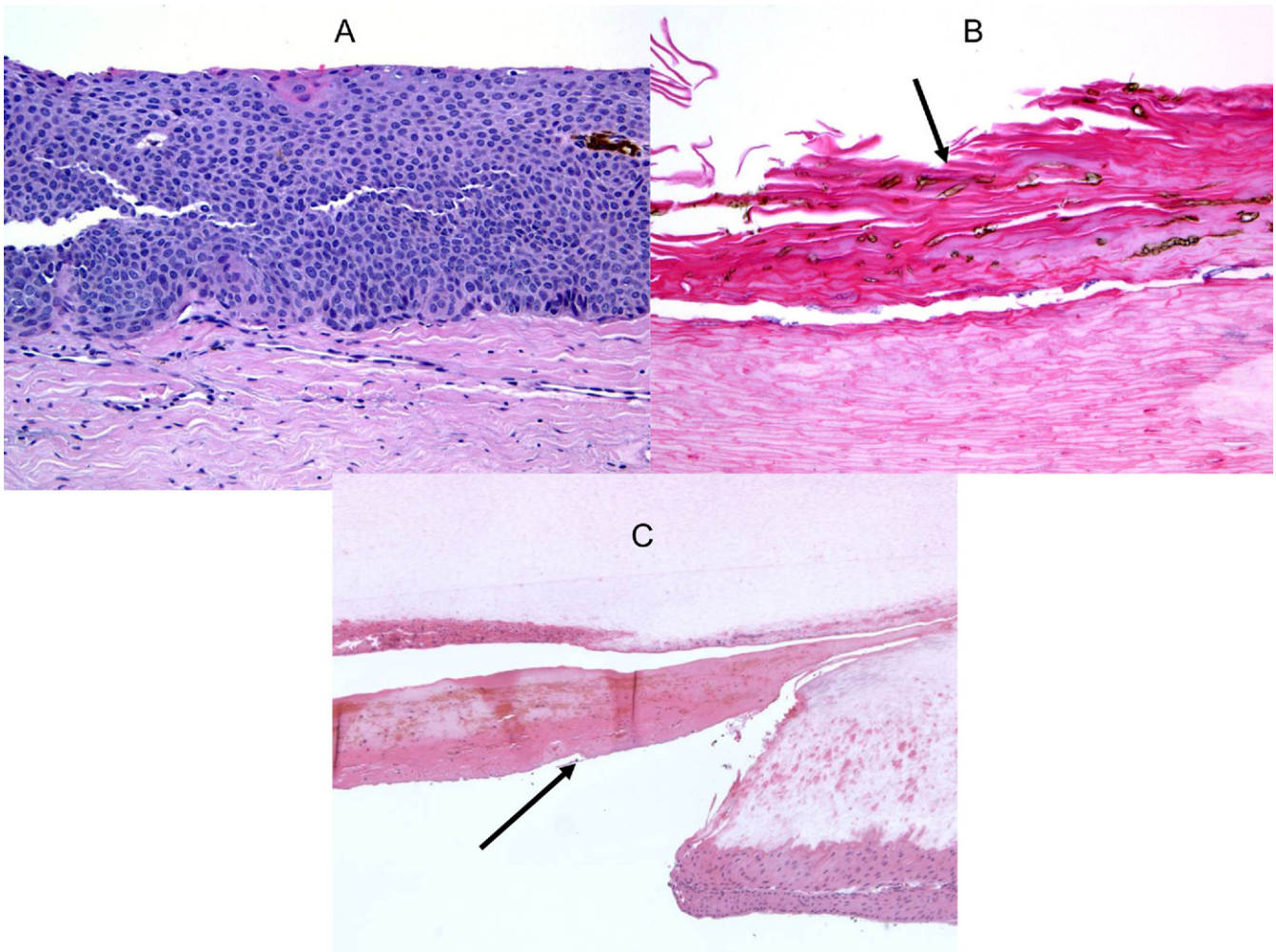

Figure 10 Mimickers of melanocytic causes of melanonychia. (A) Pigmented squamous cell carcinoma in situ, with expansion of the matrix by atypical and focally pigmented keratinocytes (hematoxylin and eosin, 200×); (B) Pigmented superficial onychomycosis, with pigmented hyphae containing melanin evident on the surface of the nail plate, arrow (hematoxylin and eosin, 400×); and (C) Subungual hemorrhage, with loculated erythrocytes under the nail plate, arrow (hematoxylin and eosin, 200×).

nail plate to distinguish between a melanocytic proliferation and hemorrhage (Fig. 10). When loculated subungual or intraungual erythrocytes are present, this usually poses no significant problem. However, if not, it can be helpful to stain for melanin with a Fontana stain, to exclude melanonychia. A common misconception is that conventional iron stains, such as Perls' stain, can be used to demonstrate iron/hemosiderin. However, because blood is present in an avascular space, the required enzymes needed to convert hemoglobin to hemosiderin, the latter of which is recognized by such stains, are not available, and thus these stains do not work in this context. Benzidine stain can be used to recognize hemoglobin, but it not widely used.[33] Another important aspect of this evaluation is that although hemorrhage may be confirmed, some nail neoplasms, including nail unit melanoma may be associated with hemorrhage. Conversely, melanin may enter the nail plate secondary to trauma, and thus hemorrhage and true melanonychia may be concurrent in that setting. Therefore, any suspected case of subungual hemorrhage should be clinically monitored to ensure that the area in question resolves as expected.

Pigmented squamous cell carcinoma may also produce longitudinal melanonychia (Fig. 10).[34] Pigmented onychomycosis, especially black superficial onychomycosis, is often the result of nondermatophyte dematiaceous molds, such as Scytalidium.[35,36] This also produces true melanonychia in a manner of speaking. The microorganisms stain with Fontana stain, as their cell walls contain melanin (Fig.10). As this diagnosis cannot be made without the nail plate, in any case of melanonychia in which nail matrix or bed biopsy is performed, the nail plate should always be submitted as well.

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