

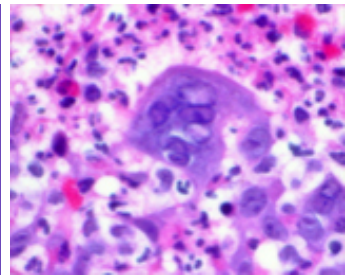


eLITERATURE REVIEW

eMedicalDermatology Review

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January 2010: VOLUME 2, NUMBER 3

Update on the Management of Nail Disorders



In this Issue...

In this issue, we take the mystery out of the diagnosis and treatment of nail problems, such as onychomycosis and nail psoriasis, encountered routinely in clinical practice. The vexing problems of when, where, and how to biopsy the nail matrix for longitudinal melanonychia and other nail tumors will be explored.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe how the unique structure of the nail unit plays a role in the pathophysiology and treatment of nail fungus and nail psoriasis.
- Evaluate various techniques used in nail surgery, including partial nail plate avulsion and matrix shave excisional biopsy for longitudinal melanonychia.
- Generate a differential diagnosis for longitudinal pigmented bands in the nail using history, clinical features of the pigmented band, and dermoscopy, to guide clinicians regarding when, where, and how to perform a nail matrix biopsy.

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COMMENTARY

The diagnosis and treatment of nail disorders is challenging, because common dermatologic conditions behave differently in the nail than in other skin locations. This is largely due to the unique anatomical structure of the nail unit. In addition, therapy must be directed toward the nail matrix, which is sequestered deep in the digit, or to the nail bed, which is blocked by an impenetrable nail plate. This concept becomes most evident when faced with the challenge of treating fungal nail disease. It has been estimated that 50% of all nail disorders are fungal in nature, and in some practices the number may be much higher. The article by de Berker (reviewed in this issue) outlines the epidemiology, clinical features, diagnostic measures, and current state of treatment options for this common but pesky nail infection.

Although less common than fungal nail disease, nail psoriasis is perhaps even more difficult to treat, and is distressing to both the physician and the patient. The clinical features of nail psoriasis depend on which part of the nail unit is affected. These range from mild pitting and onycholysis to severe dystrophy resulting in temporary nail loss, the consequences of which can negatively impact quality of life. The article by Jiaravuthisan and colleagues (reviewed in this issue) presents a review of nail psoriasis pathophysiology. Additionally, it summarizes the current evidence-based literature for the treatment spectrum of nail psoriasis, ranging from topical medications and intralesional injections to systemic medications, including biologics.



One of the most important decisions in managing nail diseases is determining when a biopsy or surgical procedure is appropriate. Nail surgery is helpful in diagnosing suspicious or ambiguous nail tumors and nail dystrophies, and in relieving discomfort associated with a painful nail problem. Often, it is impossible to clinically distinguish malignant from benign pigmented bands in the nail or a subungual verruca from an invasive squamous cell carcinoma. In such cases, a biopsy of the pigment-producing area in the nail matrix or subungual growth is mandatory. Many practitioners are reluctant to perform nail surgery because of the potential risk for permanent nail dystrophy. Fortunately, a few simple surgical techniques minimize this risk and almost guarantee a favorable outcome. Jellinek's paper on melanonychia (reviewed in this issue) outlines an algorithm for managing pigmented bands in the nails. The technique of shave excisional matrix biopsy is an ideal method for biopsying many pigmented bands. It allows for a large specimen to rule out melanoma but has a low risk for permanent nail dystrophy.

Recent advancements in the diagnosis of nail disorders are reviewed in the article by Richert and associates. A variety of imaging techniques can be used to help the clinician arrive at a diagnosis using nonsurgical methods, including specialized magnetic resonance imaging (MRI) and ultrasonography for nail tumors. Polymerase chain reaction (PCR) for rapid fungal organism identification allows for precise identification of fungal species from simple nail clippings in about 48 hours. Chemical analysis for detection of drugs and other substances in fingernails, such as gadolinium, can be helpful in certain conditions, including nephrogenic systemic fibrosis.

Diseases of the nail are challenging to diagnose and manage, and may be quite frustrating to patients and physicians alike. The articles reviewed in this issue provide excellent clinical guidance for some of the more common and challenging nail problems. Nevertheless, the need exists for continued research in the areas of fungal nail disease and nail psoriasis, in order to discover therapies with more favorable cure rates. Although excellent surgical nail techniques with good cosmetic outcomes have been well described in the literature, practicing dermatologists must become more familiar with these methods in order to better serve their patients.

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NAIL MATRIX BIOPSY AS A DIAGNOSTIC TOOL

Jellinek N. **Nail matrix biopsy of longitudinal melanonychia: diagnostic algorithm including the matrix shave biopsy.** *J Am Acad Dermatol.* 2007;56(5):803-810.

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This article provides an algorithmic approach to the management of longitudinal melanonychia, using clinical features and dermoscopy as diagnostic aids. Longitudinal melanonychia results from melanocyte activation or melanocyte proliferation in the nail matrix which appears as longitudinal pigmented bands in the nails. Melanocyte activation usually involves multiple nails and is caused by drugs, neoplasm, mycotic, systemic, traumatic, and inflammatory diseases. Melanocyte proliferation usually involves a solitary nail and is due to a benign melanocytic hyperplasia, nevus, or melanoma.^{1,2}

This article focuses specifically on when and how to biopsy the nail matrix to make or exclude a diagnosis of melanoma of the nail. Most established matrix biopsy procedures are associated with the risk for permanent nail dystrophy. The technique of nail matrix shave excisional biopsy was originated by Haneke. It involves visualizing the entire focus of pigment in the matrix, scoring around it, and excising it in a parallel fashion. This method removes the matrix epithelium and 3 to 4 mm of matrix connective tissue, but does not remove the full thickness of the matrix. This allows a broad area of the matrix to be sampled, while decreasing the likelihood of permanent nail dystrophy. Jellinek also includes a review of other biopsy techniques for evaluation of longitudinal melanonychia and nail bed tumors, and discusses strategies for preventing permanent nail dystrophy following biopsy.

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Several other techniques can assure a safe and efficient nail biopsy procedure. Partial nail avulsion allows for identification and removal of a lesion. Afterwards, the reflected nail plate is placed back on the wound to act as a protective dressing, minimize discomfort, and facilitate healing. Full-thickness longitudinal lateral excisions primarily result in a narrower but cosmetically acceptable outcome. The nail literature is extensively referenced throughout the paper, as well as clinical examples from the author's own practice.

The most important conclusions to be drawn from this article relate to the clinical management of longitudinal melanonychia. In individuals who have longitudinal melanonychia with suspicious features (eg, brown background, irregular bands, and micro-Hutchinson's sign), a biopsy should be performed based on the location of the pigment within the nail plate, as well as the width of the band. For lateral bands, a lateral longitudinal excision should be performed. Midline bands should be biopsied via a 3-mm punch or shave excision, with 1-mm margins for pigmented bands >3 mm in width. The shave excision is preferable for these wider bands, as it reduces sampling errors, allows a generous margin to minimize residual pigment, and reduces the risk for permanent nail plate dystrophy. If dystrophy of the nail plate or other features suggestive of invasive melanoma are present, a full-thickness matrix excision is indicated to ensure adequate sampling for calculation of Breslow depth. Furthermore, the use of end-on dermoscopy of the free edge of the nail plate can pinpoint the location of the pathology and guides the location of the biopsy to the proximal matrix (pigment seen in dorsal nail plate) vs the distal matrix (ventral nail plate pigment).

Jellinek has provided us with an excellent framework for working up longitudinal melanonychia, most importantly describing how to link size and location of the pigmented band to the appropriate biopsy technique. In addition, the author explains in detail the matrix shave biopsy, which is an excellent choice both for obtaining a diagnosis and for minimizing post-biopsy dystrophy. We encourage practitioners to consider using this technique rather than the punch biopsy for pigmented bands >3 mm. Hopefully, this will reduce the need for possible future repeat biopsies and prevent associated nail dystrophies as well.

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Figure 1: Shave Excision of Melanoma.



Figure 2: Replaced Nail Plate After Melanoma Shave Biopsy.

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Richert B, Lateur N, Theunis A, Andre J. **New tools in nail disorders.** *Semin Cutan Med Surg.* 2009;28(1):44-48.

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Dermatologists welcome noninvasive diagnostic tests that help to evaluate and treat nail tumors or provide clues about the nature of a nail disorder. In this article, Richert and collaborators describe ultrasound imaging with real-time spatial compound imaging, which allows for the localization of tumors, cysts, and even blood flow. Optical coherence tomography and high-frequency ultrasonography provide the opportunity for high-resolution visualization of the nail anatomy and pathology.³

Traditional procedures have limitations: Mycology fungal cultures performed for identification of the species of the organism can take up to 4 weeks and are associated with a high rate of false-negative results. Periodic acid-Schiff (PAS) staining of nail clippings can identify the presence of fungal elements, but does not provide information on the type of organism or whether the fungal elements are viable. With the use of PCR, fungal species can be identified from nail clippings in <48 hours, which helps the clinician begin treatment earlier.⁴

Clinical trials use patient self-assessment to evaluate the impact of a condition on quality of life. The burden of nail disease can be measured with such self-assessment tools as Naildex and NailQoL, which are reproducible and reliable measures for quantifying the impact of nail diseases.⁷

Many drugs and ingested chemical substances are detected in measurable amounts in the nail plate. The fingernails provide information on the internal and external exposure to many substances for the previous 6 months, and the toenails for up to 12 months.⁵ DNA, metals such as lead, arsenic and thallium, and nicotine all can be detected in nail clippings. The ability to detect gadolinium in high levels in the nail plate may be helpful in patients with nephrogenic systemic fibrosis.

Methods to aid in the diagnosis of nail pigmentation in longitudinal melanonychia include visual inspection, surgical sampling, and immunohistochemical study. Dermoscopy of the nail matrix and nail bed after nail plate avulsion has been used as an aid to diagnosis and for localization of the pigment in the nail prior to biopsy. Histopathology is the standard diagnostic method, but some nail melanomas are challenging. Several immunohistochemical markers, such as S-100 protein, HMB-45, and acral lentiginous melanoma (ALM), can be useful adjuncts, although the sensitivity markers may vary in different types of nail melanoma.⁶

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Jiaravuthisan MM, Sasseville D, Vender RB, Murphy F, Muhn CY. **Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy.** *J Am Acad Dermatol.* 2007;57(1):1-27.

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Up to 50% of all patients with psoriasis experience nail involvement, ranging from mild pitting to severe nail dystrophy resulting in temporary nail loss. Severe nail psoriasis has a negative impact on a patient's quality of life, with 93% considering it a cosmetic handicap and 58% believing that it interferes with their ability to perform their job.⁸ As with most nail diseases, the clinical features of the disease process are determined by the location of the psoriatic pathology. Pitting and crumbling are related to matrix involvement, whereas onycholysis and nail bed hyperkeratosis are both nail bed-driven. Involvement of the proximal and lateral nail folds and the hyponychium impacts the nail plate secondarily. Psoriatic nails are exacerbated by physical trauma and exposure to harsh substances, probably through a Koebner mechanism. First-line treatment involves prevention of potential trauma to the nails and the avoidance of allergens/irritants.

Medical treatment of nail psoriasis is dictated primarily by the severity of psoriasis in the nails and at other sites, and by the age and general health of the patient. A number of topical medications, intralesional injections, and systemic medications are available. The effectiveness of most topical preparations is dependent on penetration to the nail matrix. The mainstay of topical therapy is the use of potent topical corticosteroids in various vehicles, with or without occlusion. The potential for development of periungual atrophy with long-standing use of potent steroid preparations must be considered. Tazarotene 0.1% gel has demonstrated benefits in a double-blind trial.⁹ Other topical preparations, including cyclosporine 10% solution, clobetasol 8% nail lacquer,¹⁰ 5-fluorouracil (5-FU), and keratolytics, such as urea cream, have been used in small uncontrolled studies with variable success. Topical 5-FU has been reported to exacerbate the onycholysis associated with nail psoriasis if that agent is used, it is best to clip the onycholytic nail back to the point of attachment.

The use of steroid injections containing triamcinolone concentrations of 2.5 to 10 mg/cc has met with some success.¹¹ Several studies have been conducted comparing the location of the injection in the nail bed, nail matrix, and nail folds.^{12,13} Some of these deeper injections require local anesthesia with a digital block to maintain comfort.^{12,13} Deep injections into the nail bed and matrix have been associated with efficacy ranges of 36% to 100% improvement.¹⁴ In addition to atrophy, there is a theoretical risk for tendon rupture with chronic use of intralesional treatments. Psoralen plus ultraviolet A (PUVA) and Grenz ray treatments have both demonstrated temporary benefits in uncontrolled studies of nail psoriasis. Systemic medications may not be appropriate for most patients with psoriasis limited to the nails, but in small studies of cyclosporine (3.0 mg/kg/day) and acitretin 0.53 mg/kg/day significant clearing of the skin, nails, and joints was reported at 10 weeks.¹⁵ In an open trial of low-dose acitretin, clearing or moderate improvement in nail lesions was reported in 50% of subjects with nail psoriasis over 6 months.¹⁶ Methotrexate may be helpful for the treatment of nail psoriasis when it clears skin psoriasis, but no favorable trials with this medication have been described. Surgery is not considered a standard of care for the treatment of nail psoriasis, although there have been anecdotal reports of 40% urea paste helping thicken psoriatic nails.

Biologics are extremely helpful for psoriasis involvement of the skin and joints, but there are fewer large, controlled studies on their use for the nail psoriasis. The largest controlled studies are with infliximab^{17,18} and showed significant improvement in nails at 1 year.¹⁷ A few small, open-label reports have demonstrated improvement in nail psoriasis with the use of etanercept, alefacept, and ustekinumab.^{19,20}

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The authors provide an overview of nail psoriasis pathophysiology, describing how the clinical features reflect the portion of the nail unit that is most affected. Various treatment modalities are examined, beginning with first-line topical therapy. Intralesional therapy, physical modalities, and systemic drugs are discussed as treatment options for this chronic problem.

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FUNGAL NAIL INFECTIONS

de Berker D. **Clinical practice.** Fungal nail disease. *New Engl J Med*. 2009;360(20):2108-2116.

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The most common cause of nail infection is a fungus, affecting up to 14% of the population.²¹ The incidence of fungal nail infections increases with advancing age and other medical conditions, such as immunosuppression.²² Dermatophytes account for 90% of the fungal organism and *Candida* plus nondermatophyte molds comprise the rest.²¹

The clinical features of the various types of onychomycosis are related to the location at which the organism enters the nail unit. Distal subungual onychomycosis enters distally under the free edge of the nail plate, and is characterized by nail bed hyperkeratosis and extension of the disease proximally. Proximal subungual onychomycosis, on the other

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hand, begins under the nail proximally and progresses distally, usually as a subungual white patch. White superficial onychomycosis resides on the surface of the nail plate and scrapes away as a powdery substance. *Candida* onychomycosis occurs in chronic mucocutaneous candidiasis in which all the nails are dystrophic. *Candida albicans* is often cultured from onycholysis and paronychia, but it is debatable whether *Candida* is a primary cause of these conditions or simply a secondary invader. Psoriasis and lichen planus of the nails can masquerade as nail fungus, so it is customary to document the presence of the organism by KOH (potassium hydroxide) preparation, fungal culture, or histopathology with PAS staining of nail clippings. Tinea pedis preceding nail trauma, psoriasis, diabetes, and immunosuppression are all associated with an increased risk for developing onychomycosis. The recurrence rate is high in susceptible populations.

Treatments for onychomycosis range from no treatment to topical, surgical, and systemic therapies. Because of the anatomical constraints of the nail and the fact that onychomycosis is primarily a disorder of the nail bed, topical medications are not as effective as systemic agents. The only topical medication approved by the Food and Drug Administration (FDA) for the treatment of onychomycosis in the United States is ciclopirox 8% in a lacquer formulation, although amorolfine 5% and tioconazole 28% are available in other countries. Mycologic cure with ciclopirox 8% lacquer for distal subungual onychomycosis, applied daily for 48 weeks, has been reported at 28% to 36%, with complete cure (mycologic plus clinical cure) less than half of that.²³

Large randomized trials have demonstrated efficacy for the 2 FDA-approved oral medications for onychomycosis—terbinafine and itraconazole. A head-to-head trial of 508 subjects demonstrated a clinical cure at 72 weeks in 54% of the patients who took terbinafine for 12 weeks, and 60% after 16 weeks, compared with a clinical cure reported in 32% of patients taking pulse itraconazole 1 week per month for both 3 and 4 months.²⁵

When these patients were followed for 42 months after the study, the relapse rate was 25% to 30%. Common side effects included gastrointestinal upset, headache, and rash. A meta-analysis showed that 3.4% of terbinafine-treated subjects and 2.6% of itraconazole-treated subjects discontinued the respective drugs because of side effects. Patients with preexisting liver disease should not be treated with these agents, and liver monitoring at 4 to 6 weeks is recommended.²⁴

Surgery is usually not a first-line treatment for onychomycosis, but keeping the nails short and debriding diseased nails has proven helpful, especially in studies of topical medications. Occasionally, if a solitary nail is infected, avulsion of the affected nail is appropriate.

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SUBUNGUAL SQUAMOUS CELL CARCINOMA

Dalle S, Depape L, Phan A, Balme B, Ronger-Savle S, Thomas L. **Squamous cell carcinoma of the nail apparatus: clinicopathological study of 35 cases.** *Br J Dermatol.* 2007;156(5):871-874.

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Squamous cell carcinoma (SCC) of the nail is rare, although it is the most common malignant tumor of the nail unit.^{26,27} Diagnosis is often delayed by months to years because of the wide variety of clinical manifestations. Many patients are treated repeatedly for a different condition before a biopsy is considered. Dalle and colleagues conducted a retrospective review of 35 cases of SCC of the nail to clarify the clinical presentations, pathologic features, and appropriate surgical management of this disease entity.

Of the 35 cases included in the review, subungual SCC was the initial suspected diagnosis in only 29% of the cases, with the most common other initial diagnoses including onychomycosis (26%), verruca vulgaris (14%), and longitudinal melanonychia (14%). Most patients had been treated as such for years before SCC was considered in the differential diagnosis. The majority of cases occurred on the fingernails, and 50% of those were on the thumbnails. Only 11% of the cases were SCC in situ, with the majority of cases representing invasive SCC. Patients were treated with either limited surgical excision (LSE), wide surgical excision (WSE) with nail avulsion, or digital amputation (DA). Half of the patients treated with LSE relapsed, whereas only 1 of 20 patients treated with WSE relapsed. Of 6 patients treated with DA, 1 patient relapsed at the stub and eventually died of metastatic disease. Interestingly, all of the patients who relapsed after initial therapy had a depth of invasion >1 mm. The authors proposed that the depth of invasion be systematically recorded in all cases of nail SCC for this reason, and that tumors >1 mm in depth be followed closely. They also concluded that for medial SCC and for lateral SCC with >50% involvement of the nail surface, WSE is the most appropriate surgical therapy.

This article is the largest published case review of nail SCC to date, which is significant because the majority of literature on this disease entity has been centered around a single or a few case reports. Dalle and coworkers have provided us with an important comprehensive look at this disease. Their review highlights the commonality of inaccurate and delayed diagnosis, thus reminding us to always consider SCC of the nail when a seemingly simple case of onychomycosis or subungual verruca is not improving with standard therapy. They also present important information about relapse after therapy and suggest a more aggressive treatment for tumors with a depth of invasion >1 mm. Although such tumors are not commonly reported by pathologists, perhaps they should be in order to guide appropriate surgical management. The authors also comment on Mohs micrographic surgery as a possible therapeutic strategy for limited tumors but do not include any cases treated this way. Mohs surgery has been reported in the literature as providing definitive cure, with very low relapse rates for nail unit SCC without osseous involvement.^{28,29} The authors argue that Mohs surgery should be used only for limited lateral tumors, as this scenario provides the best chance of preserving the functional and aesthetic nail structures. Otherwise, they recommend WSE for invasive tumors and DA for those with osseous involvement. Although these therapies will provide low relapse rates, they do lead to significant nail dystrophy.

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Figure 3: Squamous Cell Carcinoma of the Nail, Prebiopsy.



Figure 4: Squamous Cell Carcinoma of the Nail, Excision.

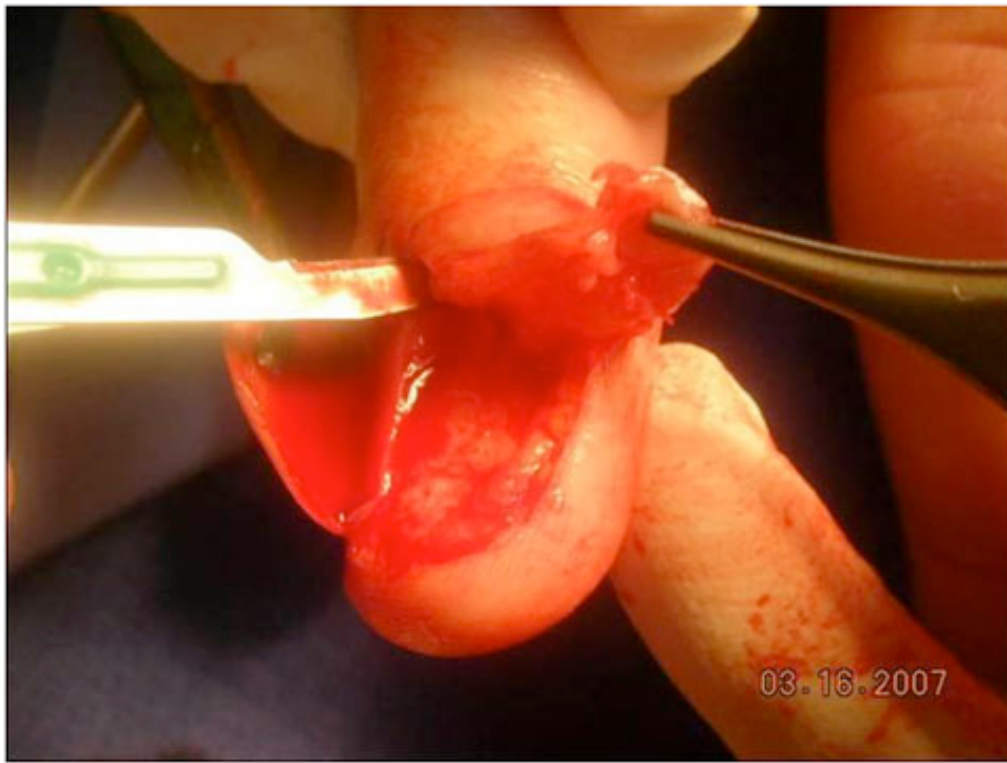


Figure 5: Squamous Cell Carcinoma of the nail , Excision.



Figure 6: Squamous Cell Carcinoma, Excision.

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