Aged-Related Changes in the Nails

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Introduction

Nail changes and disorders are common among elderly individuals, and occur at different rates when compared to the general population. The nail apparatus ages intrinsically, resulting in certain characteristic clinical changes [1]. Conversely, nail disorders are acquired and arise from secondary pathologic processes. It is important for clinicians to be familiar with both categories and differentiate between the two.

Nail Changes in Older Adults

Classically, the clinical manifestations of the aging nail have been defined as changes in nail plate color, contour, linear growth, surface, and thickness [2]. These alterations likely result from a multifactorial process, including arteriosclerosis or impaired peripheral circulation, ultraviolet radiation, trauma, and faulty biomechanics [3].

In the normal nail, the color of nail plate is white immediately above the lunula, the visible and most distal aspect of the nail matrix, and pink in the portion overlying the nail bed [4]. In contrast, the nails of the elderly are often yellow, grey or white [4]. Such whitening of the nail plate overlying the nail bed is termed leukonychia, and may result from age-related changes of the nail matrix resulting in opacity of the nail plate (true leukonychia) or the nail bed (apparent leukonychia). With age, the lunula also significantly decreases in size, and may completely vanish [3–5]. Other specific well-described variations in nail plate color—including Terry's nails, half-and-half nails, and Muehrcke's lines—also occur in elderly individuals, though they are often associated with underlying systemic diseases [6–8].

Contour related nail changes vary between fingernails and toenails. With age, the longitudinal curvature of fingernails often deceases, resulting in a flat (platyonychia) or concave (koilonychias) nail plate [3, 4]. The latter condition is notably associated with many other congenital and acquired pathologic processes and thus is not specific for aging [9]. Nail clubbing also occurs in elderly individuals, however, is associated with underlying bronchopulmonary disease in the majority of all cases [9].

Increased transverse curvature of the nail plate represents the most common age-related change in toenails. Radiographic data confirm that this change directly results from progressive widening of the base of the distal phalanx and thus affecting the overlying nail matrix [10]. Consequently, as the proximal nail plate progressively flattens, the transverse curvature of

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the distal plate increases to compensate in a lever-like manner [10]. Such changes often result in the painful incarceration of the distal nail bed between the lateral aspects of the nail plate, a condition termed "pincer nail deformity" or onychocryptosis [10]. In addition to intrinsic aging, acquired pincer nail deformity is also clinically associated with various tumors of the nail apparatus, systemic medications (with β-blockers being the most common), underlying visceral and hematologic malignancies, end stage renal failure, and autoimmune disease [10–14]. Given the intrinsic distal nature of the location, conservative interventions are often favored initially for this condition, including mechanical thinning of the nail plate, chemical softening of the nail plate with keratolytics or acids, and trimming of the lateral aspects of the nail [10, 15]. Mechanical bracing of the affected nails using a technique termed orthonyx has also been attempted with encouraging results [16, 17]. Specifically, a memory alloy prosthesis is attached to the lateral aspects of the nail in order to exert pressure opposing the transverse nail curvature, thus flattening the plate [16, 17]. Surgical intervention is often required in cases recalcitrant to conservative therapies, with cauterization of the lateral matrical horns and dermal grafting under the nail matrix providing the most consistent, permanent results [10, 18, 19].

The rate of linear nail growth has been well demonstrated to progressively decrease with advanced age. The physiologic average rate of linear growth is 0.1 mm/day (3.0 mm/month) for fingernails and 0.03 mm/day (1.0 mm/month) for toenails until the age of 25, at which time this rate decreases approximately by 0.5 %/year [20]. Concomitant systemic disease and medications may also alter linear nail growth [3].

Onychorrhexis, or the superficial longitudinal ridging of the dorsal nail plate, represents the most characteristic age-related change in nail plate surface, and likely results from a disregulation in nail matrix keratinocyte turnover [21]. In some cases these ridges may also act as a nidus for plate to split distally, most often distal to the hyponychium. As such, affected individuals are frequently distressed by the cosmesis of these changes, even though there is no associated medical risk or functional impairment. Periodic nail plate buffing is considered the most effective therapeutic intervention, though caution is recommended in patients with preexisting age-related nail plate thinning or atrophy, as any mechanical manipulation may paradoxically increase the risk of nail plate splitting [4].

Nail plate thickness represents the distance between dorsal and ventral surfaces, and is determined by the length of the nail matrix. However, both environmental and systemic factors may also contribute to nail plate hypertrophy or atrophy. In general, toenails often thicken with age, while fingernails often become thinner [22]. Such changes may affect one or all of nails [22]. Specifically, the idiopathic thickening of an isolated nail plate is termed onychauxis, while thickening of all ten toenails is referred to as pachyonychia. In extreme cases, the nail plate may develop an ostraceous or "ram's horn-like appearance" (given the nail curvature and hypertrophy), termed onychogryphosis (Fig. 1). While these changes can occur on any of the digits, the hallux is most commonly affected. Treatment for nail plate hypertrophy is generally recommended to prevent self-injury and unintended excoriations, and typically entails either chemical or mechanical debridement [4]. Notably, mechanical debridement is often most successful when performed by a provider, as some elderly individuals may experience difficulty with the posturing and dexterity necessary. Complete avulsion of the nail plate without matrix ablation is a therapeutic alternative in refractory cases [4].

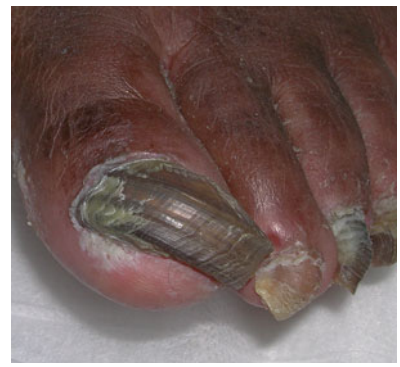

Fig. 1 Onychogryphosis

Common Nail Disorders in Older Adults

In addition to the intrinsic physiologic changes of the nail plate that occur with aging, nail disorders are common in geriatric populations. This high prevalence of nail disease in the elderly is multifactorial: impaired circulation, increased susceptibility of the nail apparatus to infection due to barrier defects, increased rate of cutaneous neoplasms, elevated prevalence of comorbid dermatologic or systemic disease, and medication use are all contributing factors [2].

Brittle Nail Disease

While largely a cosmetic concern, nail brittleness is a common complaint of elderly individuals, occurring in an estimated 35 % of individuals older than 60 years [23]. Typically, affected individuals complain of soft, easily torn or split nails, and a general inability to grow longer nails [4]. As described above, longitudinal nail splitting occurs commonly in the setting of intrinsic age-related onychorrhexis (Fig. 2). Onychoschizia—or the distal lamellar peeling and splitting of the dorsal aspect of the nail plate—also is common in the elderly, particularly women, as is trachyonychia—an opaque roughness affecting the surface of the dorsal nail plate.

Previously, brittle nails were believed to result from decreased water content. However, this theory has since been disproved, with emerging data now demonstrating no significant difference in water content between normal and brittle nails [24]. Instead, water binding capacity has been identified as the likely causative factor, as it is reduced by nearly one half in brittle nail plates [25, 26]. As keratin, keratin-associated proteins, and lipid-content all contribute to nail plate water binding capacity, an abnormality in one or several of these factors may underlie brittle nail pathophysiology [27, 28]. Environmental factors may also further exacerbate brittle nails clinically, though they are not believed to represent a causative factor [29]. Patients with brittle nails are advised to avoid repeated hydration and desiccation of the nail plates (which often occurs occupational settings) as well as exposure to dehydrating agents used in nail cosmetics, as these may damage intracellular corneocyte bridges and dissolving intracellular lipids, thereby further increasing nail plate fragility [29, 30]. Rarely, brittle nails may also represent a harbinger of an underlying dermatologic or systemic disease, including psoriasis, lichen planus, lichen striatus, alopecia areata, Darier's disease, peripheral arterial disease, arteriosclerosis, microangiopathy, Raynaud's disease, polycythemia vera, dyserythropoietic anemia, thyroid disease, hypopituitarism, gout,

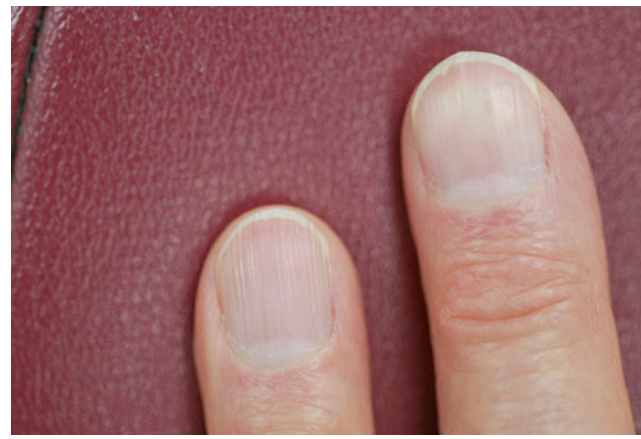

Fig. 2 Onychorrhexis

osteoporosis, diabetes, malnutrition and nutritional disorders, chronic renal failure, hemodialysis, osteomalacia, acromegaly, pulmonary tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, systemic amyloidosis, and various visceral malignancies—often in the setting of acrokeratosis paraneoplastica [31–36].

Treatment of brittle nails is often difficult given the multifactorial nature of the disease. As stated previously, environmental exposures may exacerbate any underlying nail disease, and patients should be advised to reduce frequency of prolonged contact with water, as well as detergents, cleaning solvents, and alcohol-based hand sanitizers [30]. For prolonged contact with water, cotton-lined latex gloves should be worn. Hydration of the nail plate is also essential and patients should be advised to apply a thick emollient to the entire nail plate and proximal nail fold after soaking the tips in lukewarm water for 10–20 min [37]. Urea and lactic acid have been reported as particularly effective, as both agents act to increase the water content binding capacity of the nail plate [30]. Nail cosmetics may be cautiously recommended, as once-weekly application of nail lacquer may limit exposure of water and other offending detergents, as well as reduce water vapor loss [38]. However, since acetone, and to a lesser degree acetate, dehydrate the nail plate and reduce the intrinsic lipid content, polish removers should be used on a very limited basis [38]. Cosmetic nail hardeners should also be recommended judiciously, as they contain toluenesulfonamide-formaldehyde resins, which induce additional cross-linking between nail plate keratin. While such bonds may help to stabilize weakened nails, overuse may result in accumulation of excess keratin cross-links, thus paradoxically decreasing nail plate flexibility and increasing brittleness [38].

More recently, two new prescription medications targeting brittle nails have been released. The first agent recently gained FDA approval as a medical device for the treatment of brittle nails, and consists of a hydrosoluble nail lacquer containing hydroxypropyl chitosan, *Equisetum avense* extract and methylsulfonyl methane, which is marketed under the trade name *Genadur*® (distributed by Medimetriks). In one study, daily applications of this agent significantly reduced longitudinal groves and lamellar splitting after 1 month [39]. The second agent, a 16 % urea polyurethane lacquer, marketed as *Nu-Vail*® (distributed by Innocutis) also recently gained FDA approval as a medical device for the treatment of dystrophic nails, and was found to demonstrate a 60 % improvement in clinical parameters after 6 months of daily use [40]. Biotin supplementation can also often recommended as a systemic agent for the treatment of brittle nails, as elevated doses have been suggested to upregulate the synthesis of lipid molecules in the nail matrix, thus facilitating binding between nail plate keratinocytes [41]. Typically, dosages of 2.5–5 mg/day are recommended, as one study demonstrated a 25 % increase in nail thickness and an overall decrease in lamellar splitting with this agent [41]. Tazarotene 0.1 % cream has also anecdotally been suggested as a possible therapy, though few data exist [42].

Onychomycosis and Its Treatment in Older Adults

Onychomycosis is defined as a fungal infection that affects one or more components of the nail apparatus, with dermatophytes, yeasts, and non-dermatophytes molds all recognized as causative pathogens [43]. While the prevalence of such infections is approximately 10 % in the general population, upwards of 40–60 % of individuals over 60 years of age are affected [44, 45]. This overrepresentation of onychomycosis in geriatric populations is likely multifactorial, with reduced peripheral circulation, slower nail plate growth, inactivity, relative immunosuppression, glucose intolerance, larger distorted nail surfaces, difficulty with routine nail care and hygiene, increased risk of nail injury, and increased exposure to pathogenic fungi all representing contributing etiologic factors [3, 46].

Onychomycosis has a number of well-described common clinical presentations [47]. Of these, distolateral subungual onychomycosis is by far the most common, and is frequently associated

with *Trichophyton* spp. (particularly *T. rubrum* and *T. mentagrophytes*). In this entity, the point of fungal entry is either the hyponychium or the lateral nail bed, resulting in the classic clinical presentation of distal onycholysis, subungual hyperkeratosis with an accumulation of subungal debris, and a thickened nail plate. Conversely, proximal subungual onychomycosis is the rarest clinical variant, and is most often associated with underlying human immunodeficiency virus infection [48]. *Trichophyton rubrum* is the most common causative organism associated with this condition [49]. As the infection originates at the proximal nail fold and spreads distally, clinically presenting as an opaque white discoloration of the proximal nail plate immediately overlying the lunula [43]. White superficial onychomycosis, a third clinical variant, involves the dorsal surface of the nail plate, and presents with coalescing opaque patches. The most common associated pathogen, *Trichophyton mentagrophytes*, contains enzymes capable of degrading nail plate keratins, so that affected areas appear crumbled and dilapidated [43].

Though many clinicians initiate treatment of onychomycosis based on clinical impression alone, this is not recommended as many other entities present with similar clinical findings. Pathologic diagnosis can easily be obtained through periodic-acid Schiff (PAS) staining of nail clippings or subungual debris, though it cannot reliably speciate the infecting organisms. Additionally, the pathologic diagnosis relies on the presence of branching septae; yeast forms alone do not confirm fungal infection of the nail apparatus [50]. Culture remains the gold standard for diagnosis, as it also identifies the pathogenic organism and allows antifungal sensitivity testing, though has a relatively low sensitivity of 53 % [51]. Accordingly, best practice guidelines dictate that both culture and PAS staining should be performed, as this combination yields a sensitivity of 96 % [51].

Treatment of onychomycosis in elderly populations has traditionally been difficult, primarily due to poor response, frequent relapses, and elevated associated risk profiles [3]. *Topical therapy definitively carries the lowest risk of toxicity, though has historically not been curative. Instead, topical treatments have often been employed as a palliative measures, preventing the spread of fungal infection to neighboring nails. Ciclopirox 8 % lacquer is the most well studied topical agent, demonstrating clinical cure in 5.5–8.5 % of all cases* [52]. *Urea 40 % gel has also been anecdotally recommended as an adjunctive agent, theoretically increasing cutaneous absorption of any topical antifungal preparation* [53]. *However, the recent FDA approval of two new topical agents for will likely affect the treatment algorithm for onychomycosis, particularly in elderly adults.*

Efinaconazole (Jublia® distributed by Valeant) is a new triazole antifungal topical solution that received FDA approval in June 2014 for the treatment of onychomycosis. Data from duplicate industry-sponsored phase III clinical studies demonstrated that 17.8 and 15.2 % of all study subjects attained a complete cure after 52 weeks of daily treatment [54]. *An additional 35.7 and 31.0 % of study subjects were also noted to have less than 10 % of nail plate involvement after completing the treatment regimen. The most common attributable adverse reactions reported during the preclinical studies were application site dermatitis (3.5 %), application site vesicles (2.0 %, 1.2 %), contact dermatitis (2.9 %, 1.4 %) and ingrowing nail (2.6 %, 1.9 %), though one subsequent smaller study suggests the ability of efinaconazole to induce delayed contact sensitivity may be limited* [54, 55].

Tavaborole (Kerydin® distributed by Anacor Pharmaceuticals), a first-in-class, boron-containing oxaborole broad-spectrum with antifungal activity against dermatophytes, yeast, and non-dermatophyte molds, also recently received FDA approval for the treatment of onychomycosis [56]. *In duplicate industry-sponsored phase III clinical trials, complete clinical cure was achieved 6.5 and 9.1 % of patients treated with tavaborole for 360 days* [57]. *An "almost clear nail" was also observed in an additional 26.1 and 27.5 % of study subjects. In both the phase II and phase III clinical trials, adverse events were infrequent and limited to cutaneous irritation* [57].

Regardless of the topical agent selected, the infected portion of the nail plate should be frequently debrided, ideally every 3–4 weeks [4]. Removal of the affected nail plate and subungual debris not only decreases fungal load, but also may increase topical therapy penetration [58]. While topical therapies carry a very low risk of toxicity, compliance with daily or twice daily applications can be difficulty for elderly individuals, particularly in the setting of limited mobility or other musculoskeletal or rheumatologic comorbidities [59].

Surgical or chemical nail avulsion represents an additional adjunctive therapy that best utilized in cases with lateral nail plate involvement [60]. The presence of a dermatophytoma—a subungual mass of densely packed fungal hyphae with poor antifungal penetration—is another indication for partial or complete nail debridement [60, 61].

Systemic antifungal therapy remains the gold standard for treatment of onychomycosis. Terbinafine, fluconazole, and itraconazole are the three agents most widely prescribed systemic antifungals. Due to the safety and efficacy concerns, older agents such as griseofulvin and ketoconazole are infrequently prescribed. Of the former three, only terbinafine and itraconazole are FDA-approved for the treatment of onychomycosis. Prior to the initiation of any systemic treatment regimen, the following factors should be considered: the patient's relevant past medical history, current medications, and the causative or suspected pathogen.

Terbinafine is a synthetic allylamine antifungal with fungicidal activity against fungi, dermatophytes, and some yeast forms through the inhibition of squalene epoxidase [62]. This agent is currently the drug of choice for treating onychomycosis, as it has been repeatedly demonstrated to have the highest rates of clinical cure and the lowest rates of recurrence [63–65]. Terbinafine is also highly lipophilic and persists in the nail plate for several months after discontinuation [62]. Terbinafine is dosed at 250 mg daily for 6 weeks for fingernail onychomycosis and 12 weeks for toenail onychomycosis. The data regarding the overall efficacy rate for terbinafine vary. Several meta-analyses suggest a clinical cure rate between 66 and 75 %, though early studies demonstrate rates of 38–54 % [65–69]. Adverse effects commonly attributed to terbinafine include nausea, gastrointestinal disturbance, dysgeusia, leukopenia, liver function abnormalities, and cutaneous eruption [43]. Rarely, terbinafine has been associated with fulminant liver failure, and thus, intermittent laboratory assessment of hepatic parameters is often performed. Terbinafine has few significant drug interactions, and can be co-administered statins, digoxin, warfarin, and many other medications commonly prescribed in elderly populations [43]. However, this agent is a potent inhibitor of CYP2D6, affecting the metabolism of numerous medications including many beta-blockers as well as donepezil, and thus, medication reconciliation and review is recommended prior to initiating therapy [70]. In older patients who may be on multiple medications (including hepatically metabolized drugs such as statins), pulse dose treatment consisting of 7 days a month for 4 months has been shown to reduce likelihood of transaminitis with only slightly lower cure rates [67].

Itraconazole is a synthetic triazole antifungal, and has a broad spectrum of fungistatic activity but potential side effects with older adults should be carefully considered [71]. Through the inhibition of ergosterol synthesis, itraconazole is able to inhibit growth of dermatophytes, *Candida*, and some nondermatophyte molds [71]. Similar to terbinafine, itraconazole is also highly lipophilic and persists in the nail plate for 6–9 months after discontinuation [71]. Two dosing regimens exist for itraconazole: daily treatment and intermittent (pulse) therapy. Daily treatment is dosed at 200 mg/day for 8 weeks for fingernail onychomycosis and 12 weeks for toenail onychomycosis. Pulse therapy, which is not FDA-approved for the treatment of toenail onychomycosis, consists of 400 mg/day for the first week of every month and lasts 2 months for fingernail onychomycosis and 3 months for toenail onychomycosis. As with terbinafine, the data regarding the efficacy of itraconazole vary, though most larger and head-to-head studies suggest terbinafine has a higher overall clinical cure rate than

either of the itraconazole dosing regimens [65, 66, 68]. Notably, itraconazole is absolutely contraindicated in patients with a past medical history of congestive heart failure due to its negative inotropic effect [72]. Other associated adverse reactions include nausea, gastrointestinal disturbance, telogen effluvium, hepatotoxicity, and cutaneous eruption [43]. Itraconazole is also a potent inhibitor of CYP3A4, and thus interacts with many medications. Those specifically mentioned in the associated FDA-mandated black box warning include: cisapride, midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol, lovastatin, simvastatin, ergot alkaloids, and methadone [73]. Given these associations and interactions, itraconazole is not typically a first-line agent in onychomycosis among elderly populations, though it has a definite clinical value in certain settings [74].

Of note, two published, peer-reviewed studies exist that specifically pertain to the treatment of onychomycosis in the elderly. The first—a single blind, randomized, non-industry-sponsored, prospective study—compared the efficacy of terbinafine and itraconazole in the treatment of onychomycosis [75]. In total, 101 individuals aged 60 years and older with dermatophytosis involving at least one hallux were enrolled. Half were treated with terbinafine 250 mg daily for 12 weeks, while the remaining individuals were treated with itraconazole 200 mg twice daily for 1 week per month for 3 months [75]. The resulting data demonstrated no significant difference in cure rates: the clinical cure rates were 62 % for terbinafine and 60.8 % for itraconazole [75]. Adverse events were noted in five individuals in the terbinafine treatment group and seven individuals in the itraconazole treatment group, all of which were mild and reversible [75]. The second study performed a subanalysis of patients 65 years and older from an open-label, randomized, multicenter study of adults treated with terbinafine or terbinafine and surgical nail debridement for onychomycosis [76]. Specifically, surgical nail debridement in the context of onychomycosis traditionally refers to the removal of all onycholytic portions of the nail plate, thus reducing the fungal load by eliminating the subungual debris [76]. The resulting data demonstrated that patients treated with both terbinafine and surgical debridement had higher rates of complete cure than those treated with terbinafine alone [76]. Additionally, the most frequently reported adverse events included nausea, arthralgia, and hypercholesterolemia, with three participants ultimately withdrawing due to a medication-related adverse effect [76]. Of the enrolled individuals 97 % of patients were concomitantly taking another oral medication throughout the course of the study: 64 % antihypertensives, 25 % antidiabetics, and 47 % lipid-lowering medications [76].

Lastly, various lasers and other light-based devices have been posited as a potential alternative therapeutic modality for onychomycosis, although their exact mechanism of action is unclear. Currently, the five devices are currently approved by the FDA for the treatment of onychomycosis, all of which are short-pulse neodymium-doped yttrium aluminum garnet (Nd:Yag) lasers [77]. Notably, all five devices only received approval for temporary increase in clear nail in patients with onychomycosis, not definitive treatment [78]. While the idea of laser treatment for onycomycosis seems promising, to date the data supporting the actual efficacy of this modality is mixed. One review of all relevant published studies pertaining to treatment of onychomycosis with the Nd:Yag reemphasized that while results were favorable, all studies were small and many poorly designed [77]. Furthermore, a more recent larger, randomized controlled trial found no significant difference in mycological culture or nail plate clearance [78].

Nail-Associated Neoplasms in the Elderly

Tumors of the nail unit can be classified as benign, malignant, or metastatic. While fibrous tumors are the most common neoplasms of the nail apparatus in the general population, digital myxoid cysts predominate as the most prevalent among the elderly [3, 79, 80]. These tumors have

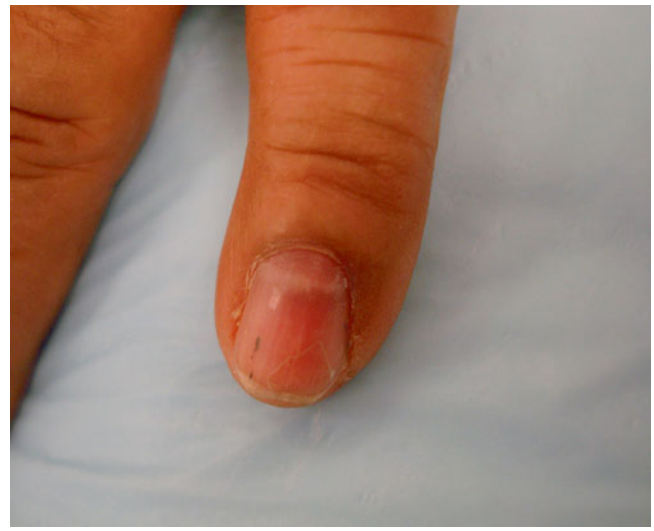

Fig. 3 Glomus tumor

many synonyms, including pseudomyxoid cysts, ganglion cysts, and digital mucous cysts, focal mucinosis, periarticular fibromas, and cutaneous myxoid cysts, among others [81, 82]. Digital myxoid cysts classically present as skin-colored to blue, smooth, translucent, dome-shaped papule located distal to the distal interphalangeal (DIP) joint, most commonly on the first three fingers [3, 81]. Histopathologically, these lesions are characterized by a deep focal mucinosis on acral skin without an epithelial lining. In over 80 % of cases digital myxoid cysts connect with the underlying DIP joint [83]. In cases where the lesion is located more distally and involves the proximal nail fold, the lesion may compress the underlying nail matrix and result in a longitudinal grove in the nail plate [81]. Generally, asymptomatic digital myxoid cysts are best observed clinically. For symptomatic or cosmetically bothersome lesions, surgical excision with ligation of communicating tract to the underlying joint is the gold standard for treatment [84]. Simple drainage of the lesions is a less invasive alternative for patients unwilling or unable to undergo surgery, though it is also associated with higher rates of recurrence [85].

Glomus tumors represent another common benign neoplasm involving the nail unit. While glomus tumors can develop at any site on the body, upwards of 75 % occur on the hand, most commonly on the fingertips [81]. Epidemiologically, over 90 % of cases occur in women, with an average age of 45 years [86]. Glomus tumors have two distinct clinical presentations: (1) a small red or blue macule on the nail bed that is visible through the nail plate (Fig. 3), or (2) longitudinal erythronychia—or a longitudinal erythematous streak that extends the length of the nail bed visible through the nail plate—with an overlying furrow in the nail plate and distal nicking [87]. The characteristic triad of associated pain, pinpoint tenderness and temperature (especially cold) sensitivity is highly specific in reaching a diagnosis [87]. Magnetic resonance imaging can be used to confirm the diagnosis in most cases. This imaging modality has the best capacity to assess the size and extent of the lesion and provides the highest sensitivity amongst all imaging modalities [88–90]. Surgical excision the primary treatment for these tumors, though some evidence suggests a recurrence rate of approximately 17 % [91]. Asymptomatic lesions can be monitored clinically, though further evaluation and biopsy are recommended if squamous cell carcinoma or amelanotic melanoma is in the differential diagnosis.

Squamous cell carcinoma is the most common malignant neoplasm affecting the nail apparatus [81, 87]. While epidemiologic data for this malignancy is limited, one retrospective study found a male predominance, with a peak incidence between 50 and 69 years of age [92]. Risk factors for subungual or periungual squamous cell carcinoma include: trauma, ionizing radiation, arsenic exposure, dyskeratosis congenita, and human papillomavirus (HPV) infection [92–94]. Specifically, HPV subtype 16 DNA has been identified by polymerase chain reaction (PCR) in 74 % of all reported cases [93]. The morphologic presentation of squamous cell carcinoma of the nail unit can be variable and may mimic a variety of benign conditions clinically, often delaying diagnosis and appropriate treatment [87, 95]. While subungual involvement is most common, tumors may also arise in the paronychial epithelium [87]. Subungual lesions typically present with onycholysis overlying a verrucous or hyperkeratotic mass or a frank ulcer (Fig. 4) [87]. The loss of any longitudinal portion of nail plate indicates involvement of the matrix. Periungual lesions classically present as painless, slow-growing, hyperkeratotic or verrucous, papules or tumors that may ulcerate or bleed [81]. Mohs micrographic surgery is the treatment of choice for all squamous cell carcinomas involving the nail unit as it has the highest cure rate [96]. Nonetheless, recurrences still occur in as many as 20 % of cases [93]. Long standing lesions may progress to involve bone in between 20 and 60 % of patients [81, 97]. In cases of bone invasion, amputation of the distal phalanx is recommended by most sources [95].

Melanoma of the nail apparatus is a relatively rare malignancy in individuals of Caucasian descent, accounting for 1.4–3 % of all melanomas in this group [99–101]. Notably, while the relative incidence of nail unit melanoma is significantly higher among populations of color—with rates reported between 17 and 25 %—the absolute incidence does not differ significantly between ethnic groups [102–104]. Data from several large epidemiological studies suggests that the peak incidence occurs at approximately 60 years of age, with no significant difference between the sexes [99, 100, 105–108]. Most cases of nail unit melanoma

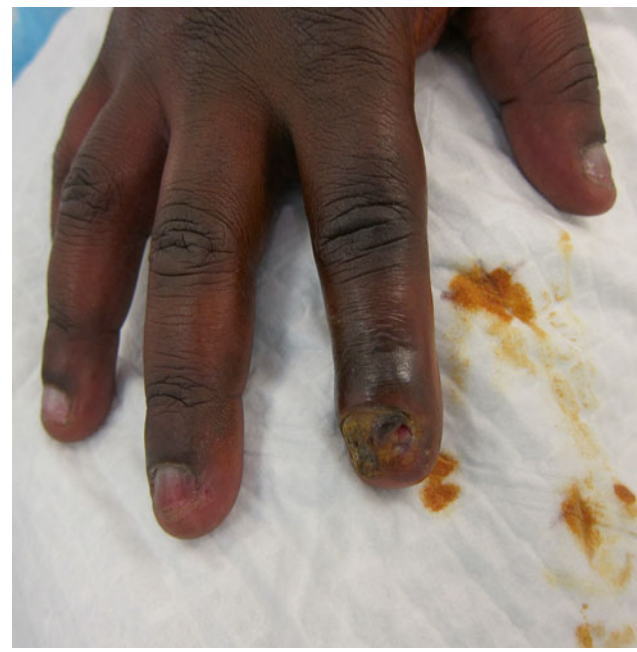

Fig. 4 Subungual squamous cell carcinoma

arise from the nail matrix, though tumors arising in the nail bed and lateral nail folds have also been reported [109]. The thumbs and halluces are most the most common sites, likely due to the increased proportion of nail matrix on digits, with no significant difference between left and right sides [103, 110]. The clinical presentation of nail unit melanoma largely is determined by the site of origin. Longitudinal melanonychia is the most common presenting sign and occurs in approximately 76 % of cases [111]. As longitudinal melanonychia may also result from benign lesions, the "ABCDEF rule" [Table 1] was developed to assist clinicians in identifying suspicious lesions requiring additional evaluation [112]. Hutchinson's sign—defined as pigment extension onto the proximal nail fold, lateral nail folds, or hyponychium—often represents the radial growth phase of melanoma arising in the nail matrix [113]. While Hutchinson's sign is by no mean pathognomonic for subungual melanoma, its presence almost always necessitates a biopsy. In addition to longitudinal melanonychia, other presenting signs include nail plate thinning and fissuring. It is important to note that upwards 20 % of nail unit melanomas are amelanotic, and thus only present with onycholysis or onychorrhexis affecting a solitary digit [114, 115]. Historically, amputation of the all or a portion of the affected digit was recommended for all cases of nail unit melanoma. However, these guidelines are now being reevaluated given the significant morbidity associated with the complete loss of a digit and the lack of evidence of a definitive survival benefit from amputation [116]. As such, some clinicians are performing wide local excisions such as degloving procedures for more superficial lesions [108].

Table 1 ABCDEFs of nail melanoma

A	*Age*: peak incidence at 60 years of age *Race*: *A*frican-*A*merican, *A*sian, Native *A*merican
B	*Band Pigment*: *B*rown-*B*lack *Breadth*: ≥3 mm *Border*: irregular, blurred
C	*Change*: rapid increase in size, growth of nail band *Lack of Change*: failure of dystrophy to improve despite adequate treatment
D	*Digit Involved*: Thumb, Hallux > index finger *Dominant Hand*
E	*Extension*: pigment extending to involve proximal/lateral nail fold, hyponychium, free nail plate edge
F	*Family or Personal History* of previous melanoma

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Conclusions

Increased age confers increased risk of nail-associated malignancy and timely biopsy is essential to early detection. Older adults are also more likely to use multiple medications, which have the potential to interact with common treatments for onychomycosis, a widespread condition in this population. Recent studies in the elderly population have begun to explore safer and more effective ways to treat onychomycosis.

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