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NAIL DISEASE BEYOND ONYCHOMYCOSIS

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NAIL DISEASE BEYOND ONYCHOMYCOSIS

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Resumo

Introdução: A onicomicose é responsável por cerca de 50% das onicopatias, no entanto, existem outras causas, como as doenças cutâneas inflamatórias e infecciosas, patologias traumáticas e neoplásicas. O diagnóstico diferencial é muitas vezes desafiador porque as características clínicas podem ser similares, e, porque a mesma doença pode ter apresentações distintas dependendo da estrutura do aparelho ungueal afetado.

Objetivo: A presente dissertação tem como objetivo a revisão das etiologias mais comuns de onicodistrofia, para além da onicomicose.

Materiais e métodos: A metodologia aplicada consistiu na pesquisa de artigos científicos na base de dados bibliográfica *PubMed* e *IndexRMP*, tendo sido selecionados os artigos publicados entre janeiro de 2000 e dezembro de 2019. Os critérios de inclusão definidos foram os seguintes: artigos escritos na língua inglesa e portuguesa, cuja tipologia respeitasse estudos originais, revisões clássicas e revisões sistemáticas. Excluíram-se os artigos cujos estudos não foram realizados na espécie humana.

Resultados: As doenças mais comuns que podem mimetizar a onicomicose são as seguintes: Psoríase, Líquen plano, Alopecia Areata, Dermatite crónica, Infeções como verrugas virais e paroníquia, Manipulação e trauma provocado pelo calçado, Tumores benignos e malignos (exostose subungueal, quisto mixóide, fibroqueratoma, tumor glómico, queratoacantoma subungueal, doença de Bowen e carcinoma espinocelular e melanoma).

Discussão: Para se estabelecer o diagnóstico preciso e, conseqüentemente, prescrever o tratamento correto é fundamental conhecer as diversas onicopatias que simulam a onicomicose. A psoríase é a causa inflamatória mais comum de alterações nas unhas. A localização mais comum das verrugas são os dedos (nomeadamente, regiões periungueal e subungueal). Os tumores subungueais requerem uma avaliação por dermatologia, sendo necessário efetuar biópsia, para confirmação diagnóstica.

Conclusão: Esta revisão bibliográfica descreve a maioria das doenças que são relevantes no diagnóstico diferencial da onicomicose, pela sua prevalência e gravidade.

Palavras-chave: patologia da unha ou ungueal, onicomicose e revisão, e diagnósticos diferenciais, onicodistrofia

Abstract

Introduction: Onychomycosis is responsible for up to 50% of onychopathies, but other causes include inflammatory skin diseases, infections, trauma, and neoplastic processes. Differential diagnosis is many times challenging because changes of different etiologies may look similar, while the same disease can also have different presentations depending on which particular structure of the nail unit is affected.

Objective: This dissertation aims to review the most common causes of onychodystrophy beyond onychomycosis.

Materials and methods: The applied methodology consisted in the search of scientific articles in the database *PubMed* and *IndexRMP*. Articles published between January 2000 and December 2019 were selected and the inclusion criteria were articles written in the English and Portuguese language and those whose typology respected original studies, classic reviews, and systematic reviews. Articles whose studies were not carried out in the human species were excluded.

Results: The most common diseases that can mimic onychomycosis are Psoriasis, Lichen planus, Alopecia areata, Chronic dermatitis, Infections like viral warts and paronychia, Manipulation and Footwear trauma, and benign/malignant Tumors (subungual exostosis, myxoid cyst, fibrokeratoma, glomus tumor, subungual keratoacanthoma, Bowen's disease and squamous cell carcinoma, and melanoma).

Discussion: For establishing the precise diagnosis and, consequently, prescribing the correct treatment is crucial to know the various onychopathies simulating onychomycosis. Psoriasis is the most common inflammatory cause of nail changes. The most common localization of common warts are the fingers (usually the periungual and subungual skin). Subungual tumors many times need a biopsy and should be evaluated by a dermatologist.

Conclusion: This review describes most of the diseases that are relevant in the differential diagnosis of onychomycosis, either by their prevalence or by their severity.

Key-words: nail or unguinal pathology, onychomycosis and review, and differential diagnosis, onychodystrophy

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Glossary

Anonychia: total or partial lack of nail.

Beau's lines: deep grooved lines that run from side to side, on the nail plate's largest axis, on the fingernail or the toenail. They may look like indentations or ridges in the nail plate and represent an interruption of nail matrix maturation.

Chromonychia: discoloration of a nail.

Dorsal pterygium: a midline band that projects from the proximal nail fold, forming a 'v' shaped extension, that fuses with underlying matrix and adheres to the nail bed and causes loss of the nail plate.

Erythronychia: redness of the nail plate

Hutchinson's sign: pigmentation in the paronychia area suggesting subungual melanoma.

Leukonychia: completely or partially white nail.

Lunula: moon- or crescent-shaped whitish area at the proximal base of a nail and is the most distal visible part of the nail matrix.

Melanonychia: a band of brown-black discoloration due to melanin in a nail plate. Melanonychia may be transverse or longitudinal, single or multiple, due to melanocyte activation or proliferation.

Onychocryptosis: in-growing nail.

Onychodystrophy: refers to the various abnormalities in nail morphology caused by changes in the attachment of the nail plate or changes in nail surface or color.

Onycholysis: the abnormal lifting of the nail plate from the distal or lateral nail bed.

Onychomadesis: nail shedding (loss of nail) due to proximal detachment.

Onychorrhexis: longitudinal ridging and fissuring of the nail plate typically seen with ageing and diffuse nail matrix diseases.

Paronychia: literally means around the nail, and is an inflammatory process around the edge of a nail.

Pitting: tiny depressions or indentations in a surface plate.

Splinter hemorrhages: tiny blood clots that tend to run vertically under the nails.

Subungual hyperkeratosis: excessive reproduction of skin cells that accumulate between the nail and the nail bed.

Trachyonychia: rough sandpaper aspect to the surface of the nail(s) with excessive longitudinal ridging due to proximal nail matrix damage.

Introduction

The nail apparatus is constituted by the nail plate (a keratinized epithelium produced by the nail matrix), that emerges from the proximal nail fold and progresses distally, lying across and strictly adhering to the nail bed. **(Figure 1)** Processes that involve any of these regions may be responsible for onychodystrophy, a common cause for dermatology consultation.

Nail disease can lead to significant functional impairment, pain and esthetic damage. Familiarity with several common diagnoses and their appropriate evaluation can improve care of the patient with a nail disease.

Onychomycosis is responsible for up to 50% of all onychopathies, but the remaining causes include inflammatory skin diseases, other infections, trauma, and neoplastic processes. Differential diagnosis is many times challenging because on one hand nail changes of different etiologies may look similar, while on the other hand the same disease can also have different presentations depending on which specific structure of the nail unit is affected. The approach to a patient with nail changes includes a clinical history, as well as a thorough physical examination not only of the nails, but also a dermatologic and general physical exam. Finally, it is important to notice that not only the correct diagnosis, but also the treatment of nail disease can be difficult due to the low penetration of the topical products and the slow rate of growth of the nails.

This article discusses the most common causes of onychodystrophy beyond onychomycosis.

Materials and methods

We performed a literature search on *PubMed* and *IndexRMP* for relevant articles using the keywords: “nail” OR “ungueal”, AND “onychodystrophy”, “onychomycosis”, “psoriasis”, “lichen planus”, “alopecia areata”, “chronic dermatitis”, “viral warts”, “chronic paronychia”, “nail manipulation”, “footwear trauma”, “subungual exostosis”, “myxoid cyst”, “fibrokeratoma”, “glomus tumor”, “subungual keratoacanthoma”, “Bowen's disease”, “squamous cell carcinoma” and “melanoma”. Articles published between January 2000 and December 2019 were selected and the inclusion criteria were articles written in the English and Portuguese language and those whose typology respected original studies, classic reviews, and systematic reviews. Articles whose studies were not carried out in the human species were excluded. The articles were prepared based on the title and abstract, obtaining 487 for a full reading. Of these, it was possible to access its content in 262, having used 93 articles to prepare the dissertation.

Discussion

1. Onychomycosis

Onychomycosis is a fungal infection of the nails caused by dermatophytes, yeasts, or molds. It has a worldwide prevalence of 5,5%.¹⁻⁵ Well-known risk factors include advancing age, immunosuppression, diabetes, prolonged corticosteroid therapy, trauma⁶ and a history of tinea pedis.⁷ The nails of the feet are affected more frequently than the hands. Dermatophyte infections predominate in the feet, affecting in most cases the hallux. *Candida spp* infections are more prevalent on the hands and the risk is increased by the presence of microtrauma and the contact with water, especially in women. The diagnosis of onychomycosis is clinical, epidemiological, and laboratorial (mycological examination).

The most common initial clinical signs of onychomycosis are white/yellow or orange/brown, striae or patches of the nail plate (**Figure 2**). Other criteria include any or all: onycholysis, hyperkeratosis of the nail bed, subungual debris, and thickening of the nail plate. In longstanding or severe cases, there may be extensive onychodystrophy with nail plate thickening, crumbling, ridging, onychocryptosis, and partial or complete nail loss.

Onychomycosis is divided into 5 subtypes regarding the pattern of invasion. Distal lateral subungual onychomycosis is the most common and is characterized by distal onycholysis with subungual hyperkeratosis, nail plate thickening, and yellow to brown discoloration; progression is distal to proximal. In Superficial onychomycosis, usually seen in immunosuppressed patients, particularly in those with HIV, the fungus invades the upper surface of the nail plate translating clinically to superficial white patches that are easily scraped away with a blade. Proximal subungual onychomycosis is also associated with immunosuppression and is caused by the invasion from the undersurface of the proximal nail fold which then progresses distally, clinically presenting by diffuse patches or a transverse striate pattern. Endonyx onychomycosis is rare and is characterized by fungal invasion of the nail plate without infection of the nail bed. While the other onychomycosis subtypes are most caused by *Trichophyton (T.) rubrum* and *T. interdigitale*, endonyx onychomycosis is usually caused by *T. soudanense* and *T. violaceum*. Total dystrophic onychomycosis, the end stage of any of the onychomycosis sub-types⁸, may resemble both fungal and nonfungal nail conditions.⁸

Nondermatophyte molds such as *Scytalidium dimidiatum*, *Aspergillus niger*, and *Alternaria alternata* produce diffuse brown to black pigmentation of the nail plate.⁹ The dermatophyte *Trichophyton rubrum var. nigricans*, instead, causes longitudinal melanonychia in which the band is usually wider distally and narrowed proximally. Longitudinal melanonychia, due to benign melanocytic activation, may be caused by *Candida spp*, especially in patients with higher

Fitzpatrick skin types. However, it is important to notice that a biopsy should be obtained from any concerning melanonychia to rule out subungual melanoma. In addition, onychomycosis may coexist with other nail neoplasms, and therefore significant nail dystrophy or failure to improve with antifungal therapy, despite laboratory evidence of a fungal infection, should promptly obtaining a nail biopsy.¹⁰

Dermoscopy can be helpful to differentiate onychomycosis from both traumatic onycholysis and melanonychia.^{11,12} The most frequent pattern associated with a diagnosis of onychomycosis is a fringed proximal border in the area of onycholysis.¹² Another typical pattern is longitudinal striae, characterized by vertical streaks of different colors in the onycholytic area resembling an aurora borealis.¹² In cases of fungal melanonychia, dermoscopy may demonstrate linear bands that are rounded proximally and tapered distally.⁹

While history, physical examination, and dermoscopy are useful in diagnosing onychomycosis, mycological laboratory confirmation is necessary for definitive diagnosis and epidemiological characterization. Mycological testing is essential to avoid treatment failures, incorrect diagnoses, unnecessary side effects, and potential drug-drug interactions.^{13,14}

2. Skin diseases

2.1. Inflammatory

2.1.1. Psoriasis

Psoriasis is a common inflammatory skin disease (affects up to 3% of the general population) mediated by immunologic mechanisms, and the most common inflammatory cause of nail changes.^{15,16} It is caused by a polygenic predisposition in addition with environmental factors (such as infections, trauma, psychological stress, medications). Epidermal hyperproliferation characterizes the disease resulting in erythematous-squamous, sharply demarcated, skin plaques that typically involve sites such as knees, elbows, scalp and the intergluteal fold, followed by the nails, hands, feet, and trunk.

Although the most specific features of psoriasis are skin manifestations, about 40% of patients will have nail changes at any given time. Isolated nail involvement is not unusual (approximately 5% of patients, a situation that creates a diagnostic challenge). The fingernails are more often affected than the toenails.¹⁷ There are no differences concerning gender or age.¹⁸ Psoriatic arthritis with predominant involvement of the distal interphalangeal joints is associated with severe forms of unguis psoriasis.

Nail psoriasis has a significant impact on the patients, causing pain and discomfort, and leading to substantial functional impairment and mental stress. The severity of nail disease in patients with psoriasis does not correlate with the skin involvement but seems to have an increased incidence of psoriatic arthritis (several studies have described an incidence of up to 80%¹⁸⁻²⁰). They result from the close relationship between the nail and the enthesitis of the distal interphalangeal extensor tendon, one of the main enthesal compartments involved in psoriatic arthritis.

The most common presentations are psoriasis of the nail bed, nail matrix, and nail fold.²¹ All the clinical signs of nail psoriasis are not specific and may be found in several other nail diseases. The typical signs of psoriasis of the nail matrix are pitting, leukonychia, Beau's lines, red spots of the lunula, and crumbling of the nail plates. Pitting is the most common change observed (more than 60% of cases²⁰) and is characterized by small, irregular, depressions with a diameter less than 1mm, distributed along the nail plate. More than 20 pits are considered suggestive of possible psoriasis, while more than 60 are considered evidence of psoriasis. However, pitting is not specific, it can also be observed in other diseases such as alopecia areata or eczema. Leukonychia and loss of transparency (fewer common phenomena) are due to the involvement

of the midportion of the matrix. If the entire nail matrix is affected, a whitish, crumbly, poorly adherent “nail” is observed.

Parakeratosis affecting the nail bed manifests clinically (**Figure 3**) as subungual hyperkeratosis and distal onycholysis (the second most common signs of the nail psoriasis^{15,16,21}). An erythematous halo surrounding the onycholysis is a notable characteristic (mycotic onycholysis usually does not have this halo). The same process can also lead to an “oil drop” or “salmon patch”, a manifestation of exocytosis of leukocytes under the nail plate. The color results from the fact that the overlying nail plate prevents air from entering between the keratin layers, and thus it looks to be adherent. The space between the nail plate and the nail bed is frequently colonized by microorganisms, especially yeast or *Pseudomonas aeruginosa*, the latter of which causes greenish or nearly black discoloration. Splinter hemorrhages are another nail manifestation of psoriasis that is common, but not specific, involve the distal third of the nail plate and are the result of increased capillary fragility caused by minor trauma. Total dystrophy of the nail appears in a more advanced psoriasis stage and can even occur through complete destruction of the nail plate. Nevertheless, since many of these findings can resemble onychomycosis, and there seem to be an increased risk of onychomycosis in psoriatic nails, evaluation should always include proper fungal studies.^{16,22}

Psoriasis of the periungual region is characterized by paronychia.²¹ A psoriatic lesion in the undersurface of the proximal nail fold creates an abnormal cuticle leading to a separation of the proximal nail fold from the nail plate. This separation creates a paronychia characterized by an erythematous, inflamed proximal nail fold and ragged or absent cuticle. Like any chronic paronychia, maceration, and overgrowth of yeast under the proximal nail fold, can sustain the process. Paronychia, with critical onychodystrophy and even anonychia, can be observed in acrodermatitis continua of Hallopeau, considered by some as a variant of pustular psoriasis. This rare entity is defined by involvement of the nail folds of one or more fingers (sometimes the toes), commonly the thumb, with the formation of pustules on the bed and matrix that cause pain and discomfort. There may be shedding of nail plates.

There is still debate if nail psoriasis can be considered a risk factor for onychomycosis. In psoriasis patients, the most frequently isolated agents are molds and yeasts, which differs from the general population where the most frequent agents are dermatophytes.^{23,24} The fact that nail psoriasis destroys a physical barrier increases the risk for infection by non-dermatophytes. Nail psoriasis is frequently indistinguishable clinically from onychomycosis, and the differential diagnosis might be challenging. Although, it is important to note that the coexistence of the two entities can happen, and that both are common in the general population. Clinical observation of other areas of the body that are psoriasis predisposed (scalp, elbows, knees, gluteal cleft) and

negative KOH examination and fungus culture can provide clues to the diagnosis of nail psoriasis. The presence of psoriatic skin lesions is suggestive but is important to stress that psoriasis and onychodystrophy is not synonymous of nail psoriasis.

The most characteristic biopsy image is that of spongiform pustules with macroabscesses or microabscesses (subcorneal or intracorneal Munro abscesses) in association with the development of parakeratotic or orthokeratotic scales.

2.1.2. Lichen planus

Lichen planus (LP) is an idiopathic inflammatory disease of the skin and mucous membranes. LP occurs among 0.5 and 1% of the population. It can happen at any age but seems to be more often in the fifth and sixth decade of life.²⁵ Involvement of the nails is seen in 1% to 16% of patients. LP limited to the nails is uncommon, and when present, frequently involves the fingernails²⁶ and affects numerous nails. In a quarter of people with nail involvement, mucosal and skin lesions happen before or after the nail changes.

The four P's characterize classic LP: papules/plaques, purple, polygonal and pruritic. They are typically symmetric in distribution and occur mainly in the flexural surfaces of the forearms, wrists, and ankles. The papules/plaques are dry and shiny with a branny scale that forms fine, whitish streaks (Wickham's streaks), which allows a clinical diagnosis. In addition to the classic LP, many other variants occur much less frequently.

LP's pathogenesis and etiology are unclear, but the disease has been correlated with many environmental exposures, including medications, vaccinations, viral infections, and dental restorative materials. Is assumed to be an autoimmune disorder, mediated by cytotoxic T CXCR3 cells and plasmacytoid dendritic cells²⁷, there is also association with genetic factors, and exogenous factors such as described previously.²⁸

Clinical features of the nail apparatus are multiple and depend on which part is affected by the lichenoid inflammatory infiltrate.²⁹⁻³¹ It can quickly damage the proximal nail matrix, producing onychorrhexis, lateral thinning, and trachyonychia or pitting. If untreated, these can lead to scarring and eventually anonychia.

Approximately 20% of patients develop dorsal pterygium, considered highly suggestive of severe nail LP, and may be the only manifestation. It can occur in the central, lateral, or both areas. It is not associated with the duration of the illness and sometimes evolves quickly.³² In some patients, twenty-nail dystrophy may represent a variant of LP (which is more common in children). Other, less specific changes, than those mentioned, include yellow discoloration

(commonly in the toenails), onycholysis, subungual hyperkeratosis, and may be very difficult to differentiate from nail psoriasis or onychomycosis.^{15, 26, 28}

Dermoscopy changes can be helpful and are present in the nail matrix, nail bed, and perionychium.³³ Early manifestations include trachyonychia and pitting, while advanced disease usually shows lamina fragmentation, chromonychia, splinter hemorrhage, and onycholysis.³³

If only nail changes are present, the biopsy of the involved tissue can be necessary and shows classic LP histology - circumscribed, wedge shaped hypergranulosis, marked hyperkeratosis in the epidermis; irregular sawtooth-like acanthosis of rete ridges and subepithelial lymphohistiocytic infiltrate in band.

2.1.3. Alopecia areata

Alopecia areata (AA) is an immune-mediated disorder with a lifetime risk of 2%, characterized by non-scarring hair loss.³⁴ It may be restricted to one or more discrete, well-circumscribed round or oval patches of hair loss on the scalp or body (alopecia areata focalis [AAF]), or it may affect the complete scalp (alopecia areata totalis [AAT]), or even the entire body (alopecia areata universalis [AAU]). It is not possible to predict the natural course of the disease but is frequently benign. The hair regrowth spontaneously in 80% of patients in the first year, but relapses at any given time are frequent. One of the factors of poor prognosis is the presence of nail changes.³⁵

Although the etiology of alopecia areata is considered autoimmune, the pathogenic mechanism of nail changes remains unexplained. It has been suggested that since the nails are comparable in structure and growth to hair follicles, they may be influenced by a similar inflammatory reaction that is targeting the hair follicles.

The nails are affected in around 20% of adult patients and 50% of children.³⁶ The intensity of changes parallels the degree of follicle involvement. Incidence is much lower in patients with focal AA than in patients with AAT or AAU.^{37, 38} They tend to show simultaneously with hair loss, but occasionally can precede or succeed hair changes by months or years. They may persist even after hair regrowth.

The nail changes in AA are found within the proximal matrix, and are less pronounced in the distal matrix, and negligible in the nail bed. The most common are trachyonychia (**Figure 4**) and geometric pitting.³⁸ The pits are small, finer than in psoriasis, superficial, and regularly distributed in a geometric pattern, often in "rows of soldiers". Trachyonychia is more prevalent in children and most seen in men with AAT or AAU. It involves all 20 nails in 3.65% of patients who have alopecia areata and 15.4% of patients who have AAU. Punctate leukonychia, erythema

of the lunula (if onset is very acute), onychodystrophy, and rarely, onychomadesis (reported in acute onset of AAU) may also be seen. The nails also usually lose their shine. A rare sign that is strongly associated with alopecia areata is the so-called “spotted lunula” which is characterized by a spotty absence of the whiteness of the lunula. Because the nail changes occur in the context of follicle involvement, the diagnosis is made from clinical observation.

2.1.4. Chronic dermatitis

The term comprises several inflammatory diseases of different causes, including contact with irritants or allergy. The manipulation of chemicals is a typical cause. Clinically, it is exceedingly difficult to differentiate them because both have the same presentation and can happen together. Irritative or allergic contact dermatitis is more prevalent in manual laborers and women. In all types of dermatitis, if there is periungual tissue inflammation, it can lead to acute or chronic onychodystrophy. Nail changes are not extremely specific and should be evaluated in conjunction with the skin findings that frequently affect the digits, hands, or other areas of the body. The typical characteristics are Beau lines on the nail plate, thick pitting, subungual hyperkeratosis, onycholysis, roughness, furrowing, trachyonychia, and a decrease in nail growth. The proximal nail fold is typically thickened with chronic paronychia.³⁹ The cuticle then disappears by itself, and the proximal nail fold starts to separate from the underlying nail. The nail plate may become yellow due to the exudative phenomena characteristic of dermatitis. There can be accumulation of sensitizing substances under the nail and cause subungual dermatitis and onycholysis. The diagnosis is clinical and in the case of allergic contact dermatitis needs patch testing to determine the etiologic agents.

2.2. Infectious

2.2.1. Viral warts

Human papillomavirus (HPV) infections of mucosa and skin are prevalent and, usually, cause benign fibroepithelial papillomas or warts/verrucae (more common in childhood). Common warts are exophytic, hyperkeratotic, dome-shaped papules or plaques, caused by different HPV types (typically HPV-1, -2, -4, -27, or -57) that are weakly infectious. The most common localization are the fingers (usually the periungual and subungual skin), but also dorsal surfaces of the hands or in other sites prone to trauma such as the knees or elbows.²⁰ In the periungual skin, they most commonly are located on the lateral aspect of the proximal nail fold and spread across the dorsum of the fold. The involvement of the proximal nail fold may destroy the matrix,

leading to onychodystrophy.⁴⁰ Periungual verrucae can present as periungual hyperkeratosis, a keratotic subungual nodule with onycholysis, or as erythronychia.⁴¹ Most periungual warts in children resolve spontaneously. Subungual warts initially involve the hyponychium, growing slowly towards the nail bed and finally elevating the nail plate, which many times is not affected. Subungual warts are painful and may mimic a glomus tumor.

Picking, biting, and tearing the nail and nail walls are frequent habits in persons with periungual warts. This type of trauma is probably responsible for the spread of warts and their resistance to treatment. Periungual warts are frequent in nail biters, in whom they are multiple and involve multiple nails.

The diagnosis is clinical, and hyperkeratosis scraping leaves a capillary bleeding surface characteristic of papillomatosis. For subclinical presentations, dermoscopy can help in diagnosis.⁴² Histopathology shows projections of epithelial hyperplasia and keratinocytes with clear cytoplasm and irregular nuclei (koilocytosis).

Squamous cell carcinoma (SCC) can occur in or simulate a wart; thus, suspicious lesions require further evaluation.

2.2.2. Chronic paronychia

Paronychia is characterized by an inflammation of the nail folds (proximal or lateral), surrounding the nail, of a toe or finger. It can be divided in acute or chronic, with chronic paronychia being present for more than six weeks. Although both entities result from loss of the typical nail-protective architecture, they have different etiologies, leading to different treatments. Infections (bacterial or fungal) are responsible for acute cases and result from a breakdown of the protective barrier between the nail and the nail fold with subsequent entry of organisms.

Chronic paronychia is mostly due to irritants (represents a form of contact dermatitis)^{43, 44} and the most common include alkalis, acids, or other chemicals commonly used by dishwashers, housekeepers, bartenders, florists, laundry workers, bakers, and swimmers.⁴⁵ The condition is more prevalent in adult women, with continuous exposure to wet work and other irritants, and typically there are multiple digits involved (particularly the thumb and second or third fingers of the dominant hand), with involvement of one or more of the three nail folds (the more commonly affected is the proximal nail fold). The nail folds involved show edema without fluctuance, persistent erythema, tenderness, and absence of the cuticle. Recurrent episodes of discharge may be noted. Due to injury to the nail matrix, there may be changes noted in the nail plate surface such as Beau's lines.⁴⁶

Chronic paronychia usually has a prolonged course with superimposed, recurrent, self-limited episodes of acute exacerbation. Once the protective nail barrier is disrupted, repeated exposure to irritants may result in chronic inflammation. Although *Candida spp* and bacteria like *Pseudomonas aeruginosa* (**Figure 5**) can often be isolated from affected digits, they are believed to be secondary colonizers rather than a primary infection, and restoration of the normal barrier to infection through topical steroids has been shown to eradicate those most cases, and on the other hand systemic antifungals/antibiotics have been shown to be of little value.

The diagnosis of chronic paronychia is clinical, based on positive exposure history, symptom duration of at least six weeks, and clinical findings consistent with nail dystrophy.⁴³ If only a single digit is affected, malignancy, such as squamous cell carcinoma, must be considered.^{43,45}

2.3. Traumatic

2.3.1. Manipulation

Cosmetic manipulation (manicure or pedicure) increases the risk of infection and acute or chronic paronychia, usually caused by *Staphylococcus aureus* and *Pseudomonas spp*. In patients that manipulate the cuticle, horizontal parallel grooves in the nail can also be seen.

Habit tic disorder is a common self-induced disease, typically observed in adults and results from the habit of picking or pushing the cuticle backward.⁴⁷ The patient is usually unaware or unconscious of this practice. This is more of a habit, and there is typically no anxiety before the fingernail manipulation or any feeling of relaxation after the action. It is less often associated with psychiatric comorbidities such as obsessive-compulsive disease. The repeated external trauma to the nail matrix causes nail dystrophy.⁴⁸ The nail plate abnormalities are characterized by a central longitudinal linear depression circled by horizontal parallel ridges, explaining the name “washboard nails”. The cuticle is frequently detached, damaged, and can even be totally missing with loss of the adhesion of the proximal nail fold to the nail, leading to the exposure of the distal matrix and even hypertrophy of the lunula (“pyramidal lunula”). The nails can also lose their shine.⁴⁹ The most commonly digit involved is the thumb.⁴⁹ Once the cause of the problem is explained to the patient, the cure is simple, stop this habit leads to the spontaneous clearing of the nail.

2.3.2. Footwear trauma

Footwear controls stability and the consequent risk of trips, slips and falls by changing somatosensory feedback to the toes and ankle and adjusting frictional states at the shoe/floor

interface. Although the main purpose of the shoe is to protect the foot and guarantee propulsion, the female shoe design has been strongly determined by the demands of fashion over time and consequently compromising the normal functioning of the toes.

One prevalent cause of footwear trauma (that frequently simulates nail onychomycosis) is due to friction of the big toe against the shoe while walking, causing stress in the nail matrix and a perpetual onychodystrophy/fissuration of the wide margin of the nail plate. If the matrix is affected in a diffuse way, the nail plate can be partially or even entirely absent. The same process can also lead to a traumatic onycholysis, which is commonly bilateral, and frequently colonized by fungi and/or bacteria.⁵⁰ Other causes include defects in the ventilation mechanism design and the heel height of the shoe and common bone deformations of the foot that make it complicated for the foot to accommodate to the shoe.

When the trauma is acute, it leads to a subungual hematoma. In this case, a blood drain is beneficial to avoid compression on the matrix. Subungual hematomas are distinct from those in other cutaneous areas because the blood accumulates in the deepest nail plate layers. This fact explains why hematomas are progressively eliminated with nail growth, unlike melanoma cases.⁵⁰

2.4. Tumors

2.4.1. Subungual exostosis

Subungual exostosis (or osteochondroma) is the most frequent benign bony proliferation associated with nail anomalies.⁵¹ The lesions are located below or adjacent to the nail bed on the dorsal aspect of the distal phalanx, many times in the first toe.⁵²

It has an incidence of 0.003% in dermatologic consultation. It frequently affects children and young adults (presenting during the second or third decades of life) but has no gender predilection.^{51,53}

In most cases, it is a single lesion. It classically manifests as an elevation of the inner nail fold, associated by pain on pressure and is usually a small, hard, pink or skin-colored nodule that projects behind the nail's inner free edge. It may become hyperkeratotic or ulcerate.⁵⁴ It may increase in size over time, and this can cause lifting or deformation of the nail plate and cause slight discomfort while walking.

The exact pathogenesis of exostosis remains unknown, but it has been suggested that it represents reactive metaplasia precipitated by trauma. Also, chronic infections and irritation are recognized as causative factors.⁵⁵ The lesion starts as an area of increased fibrous tissue with

cartilaginous metaplasia that undergoes endochondral ossification and is transformed into trabecular bone. As the lesion matures and grows, the cartilaginous cap blends imperceptibly with the nail bed and becomes continuous with the underlying distal phalanx. This process is sustained until the lesion fuses completely with the distal phalanx.

The diagnosis is confirmed by radiologic examination⁵⁶, showing an exophytic lesion on the distal phalangeal bone. This should be done before any invasive procedure or biopsy. Histopathologic evaluation typically shows mature trabecular bone surrounded by fibrocartilage. The treatment is surgical.

2.4.2. Myxoid cyst

Digital myxoid cysts are collections of gelatinous material with viscous gross appearance in a cavity (pseudocysts) within connective tissue.⁵⁷ Typically they involve the lateral or dorsal aspects of the distal interphalangeal (DIP) joints and proximal nail fold. Less frequently it can be in the nail bed (8% to 30% of cases⁵⁷).⁵⁸ They are connected to the distal interphalangeal joint by a tract⁵⁷, and in the vast majority arise due to osteoarthritis and degeneration of the DIP joint capsule, leading to egress of joint fluid. The overproduction of hyaluronic acid from fibroblasts affected by trauma, arthritis and degenerative process is attributed to altered intraarticular pressure, osteophyte formation, or enzymatic action. The exact mechanism behind the formation of myxoid cyst is debated.⁵⁸ They can be classified based on 2 predominant independent mechanisms. The myxomatous (or superficial) type results from metaplasia of dermal fibroblasts leading to excess hyaluronic acid production. The other type is a ganglion or deep type that forms from leakage of hyaluronic acid through a pedicle connecting the involved joint and the pseudocyst.⁵⁸

They are the most common ungual tumor^{58,59}, occurring most frequently between the fifth and seventh decade of life and affecting women in a 2:1 ratio.⁵⁸

Clinically, they can be either solitary or multiple, and present as small, soft, skin-colored to translucent, dome-shaped, and fluctuant nodules, and rarely exceed 10 to 15 mm in diameter.

Nail changes can be an important clue due to compression of the nail matrix, and most commonly present as a longitudinal groove, that can be identified in approximately 75% of patients.⁵⁸

Due to the presence of an osteophyte at the DIP joint associated with the myxoid cyst (very suggestive of the diagnosis) plain films are usually the only image modality necessary. Ultrasound imaging is nonspecific, and although MRI can be diagnostic, it seldomly is required.

2.4.3. Fibrokeratoma

Classically, fibrokeratomas are acquired, asymptomatic, slow growing, oval or spherical nodules, with a hard or rubbery consistency, with a hyperkeratotic tip and a narrow base. They have a benign nature and develop spontaneously. Regarding growth, they may double or even triple their initial size. Most of lesions present in the periungual area, with the toes being most frequently affected. Periungual fibrokeratomas present as pink or skin-colored, fusiform-shaped papules originating from the proximal nail fold. They may compress the nail matrix leading to a longitudinal groove in the nail plate. Subungual fibrokeratomas (also called “dissecting ungual fibrokeratoma” because they divide the nail plate) grow underneath the nail plate, producing longitudinal erythronychia or onycholysis.

They typically present around adolescence, with their size and number progressively increasing with age. They can cause functional and cosmetic concern and pain.

When associated with Tuberous Sclerosis, they are called Köenen tumors (present in nearly 50% of patients), and in rare cases can be the only evidence of the disease. However, it is important to note that isolated periungual and subungual fibrokeratoma are also not rare in the general population.

2.4.4. Glomus Tumor

Glomus tumor is a rare benign soft tissue tumor, that arises from the neuromyoarterial glomus bodies (responsible for the regulation of the circulation and thermoregulation within the skin).⁶⁰ These structures are present in the reticular dermis, but are concentrated in the fingertips, and specifically in the nail.

Approximately 65 - 75% of glomus tumors present in the hand (they represent 1% to 5% of all soft tissue tumors of the hand⁶¹) and 50 - 65% are subungual. They have a female preponderance, presenting typically between 30 to 50 years of age.^{62, 63}

The typical presentation is the classic triad of paroxysmal pain with precise location and cold hypersensitivity. However, up to 23% may not show this triad.⁶⁴ The pain is severe, radiates proximally and is often aggravated by physical (e.g., compression) or thermal stimuli (especially cold). The patient’s symptoms typically exceed clinical signs. These lesions may not be clinically apparent or may only be seen through the nail plate as a small bluish to reddish-blue spot several millimeters in diameter, but rarely exceeding 1 cm, that does not blanch totally with pressure. A classical presentation (**Figure 6**) is longitudinal erythronychia that may be associated with a distal plate fissure. Half the tumors cause minor nail deformities, with ridging and fissuring being the most common.^{60, 65}

There are three clinical tests to diagnose: the “Pin love test”, where gentle pressure is applied to the nail with a clip to determine the point of maximal pain (that typically is severe); the “Hildreth test”, where a tourniquet is applied in the base of the finger and the “Pin love test” is repeated, this test is positive if the patient does not have spontaneous pain; and the “Cold sensitivity test”, where the pain should be reproduced when the finger is exposed to cold.⁶⁵

Advanced imaging is needed mainly in situations in which clinical findings are equivocal.

About 50% of subungual glomus tumors cause a depression on the dorsal aspect of the distal phalangeal bone, that can be seen on a radiographic study. On ultrasound they appear as hypervascular lesions⁶⁰, which is useful preoperatively to determine the size, location, and shape of the tumor.⁶⁰ Color doppler can be used to detect the blood flow (enhanced in glomus tumors) and it has a sensitivity and specificity of 100%, making it the diagnostic test of choice.⁶⁵ MRI is particularly good detecting soft tissue tumors, even with a small size (2 mm). Glomus tumors appear as hyperintense on T2 imaging, but its role in subungual glomus tumors is somewhat controversial, and although it shows a sensitivity of 90%, the specificity is only 50%.^{66,67}

2.4.5. Subungual keratoacanthoma

Subungual keratoacanthomas are a benign but rapidly growing tumor (it develops over a few weeks) of the nail bed that frequently leads to osteolysis (destruction) of the underlying bone. They have a more aggressive behavior than cutaneous keratoacanthomas⁶⁸ and rarely regress spontaneously.⁶⁹

They are extremely rare and usually affect a single digit (with a predilection for the first three fingers of the hand). It is more frequent in Caucasian⁷⁰, males (75%) and, mostly, older than 40 years.⁶⁹

The pathophysiology is not completely understood. The role of trauma (often reported) and oncogenic HPV have been suggested, but not confirmed.⁶⁸

Most cases present as a painful, nodular lesion with a characteristic central keratin-filled crater. The lesion can start as a small and painful keratotic nodule visible beneath the free edge of the nail, that grows rapidly to a 1 to 2 cm lesion, in 4 to 8 weeks, separating the nail plate from its bed causing partial onycholysis. Later it becomes a keratotic inflammatory nodule (pseudoparonychia), sometimes with a purulent exudate that includes keratin debris. The diagnosis should be suspected in the presence of a painful subungual mass that grows in a few weeks. Plain films show osteolysis, caused by pressure, with characteristic sharp limits. The main differential diagnosis is with subungual squamous cell carcinoma (mainly observed in older patients), that usually has a slow growth and seldomly shows osteolysis.⁷¹ When present, it has

ill-defined borders caused by direct bone invasion associated with periosteal thickening and reactive sclerosis. Additionally, immunohistochemical analysis of Ki67 expression can be useful for differentiating the two entities, with Ki67 being overexpressed in subungual squamous cell carcinoma compared with subungual keratoacanthoma.⁷²

There is a risk of bony destruction and recurrence when treatment or resection of the tumor is incomplete.

2.4.6. Bowen's disease and squamous cell carcinoma

Bowen's disease of the nail is a squamous cell carcinoma (SCC) in situ of periungual or subungual location that originates in the stratified squamous epithelium of the nail bed. Despite being uncommon, is the most common primary malignancy of the subungual area.^{73, 74} It usually affects the fingernails (probably due to the much higher sun exposure, when compared to the toenail, and the role of HPV) and is observed most often in middle-aged men.^{73, 75, 76} Thumbs of the left hand are most frequently involved.⁷³ It may progress to invasive SCC.

Some authors prefer not to use the term "Bowen's disease" for in situ epidermoid carcinoma happening under the nail plate, because it is not always easy to differentiate invasive from in situ carcinoma. And in fact, a biopsy specimen showing Bowen's disease does not exclude the possibility of invasive carcinoma in a different area of the lesion. The neoplastic process may occur in the periungual area as well as in the subungual tissues and most frequently originates in the nail folds.

The presence of HPV (usually -16, but also 31/33, 56, and 71)⁷⁷⁻⁸⁰ is a major risk factor.⁸¹ HPV has a strong association with SCC of the fingernails.⁸² In contrast, it has never been associated with SCC of the toenail.⁸³ Other risk factors are repeated trauma, ectodermal dysplasia of the nail bed, exposure to radiation and sunlight, chronic infection of the nail bed, arsenic, and immunosuppression.⁷⁴

Clinically, there is a slowly increasing periungual or subungual verrucous mass that may ulcerate and bleed; the tumor can cause onycholysis or nail plate destruction (partial or total nail loss is one of the most relevant clinical features). Onycholysis associated with oozing erosion or ulceration of a sometimes-crusty nail bed, periungual inflammation and swelling, lack of nail growth, discoloration, and localized pain (e.g., when the patient uses a keyboard) can be observed. Longitudinal melanonychia or erythronychia as well as pseudo-Hutchinson's sign have been seen in association with SCC. The presence of nodule formation, ulceration, or bleeding indicates that the carcinoma has become invasive.

The diagnosis is challenging and often delayed, and it can easily be misdiagnosed as an infection, for example.

In pigmented SCC, dermatoscopy may aid the diagnosis showing characteristic brownish points along imaginary lines. On the other hand, in nonpigmented SCC can see clustering, dot-like or glomerular vessels.⁸⁴

The definitive diagnosis can only be made if there is a high degree of suspicion and after performing a skin biopsy (the diagnostic test of choice). In fact, any chronic or recurrent nail damage that does not respond to the initial treatment should be biopsied.

Histologically it has total epidermal thickness dysplasia with (pagetoid) intraepithelial distribution of neoplastic keratinocytes.

In conclusion, as recognition of SCC of the nail is not easy (as they are frequently and recurrently interpreted as benign or infectious diseases), it almost invariably results in significant diagnostic delay, that leads to increased tumor extension at diagnosis. In fact, at the time of diagnosis, there is usually substantial local invasion, with the distal phalanx's involvement in 20% to 50% of cases.⁶⁶ Compared to cutaneous SCC elsewhere, SCC of the nail tends to become invasive more quickly, but metastases are uncommon. A recent review of the literature⁷³ showed a 1.6% rate of distant metastasis, 40% of which were fatal. Bone invasion happens in <20% of patients.⁸⁵

2.4.7. Melanoma

Subungual melanoma is an unusual variant of melanoma that arises from the nail matrix and frequently affects other areas of the nail unit (it accounts for 0.7 - 3.5% of all melanomas). It is by far the most lethal of the subungual malignancies, making it a critical differential diagnosis for any subungual lesion, independently of pigmentation. Sun exposure is not a risk factor for subungual melanoma, explaining why the incidence is equal among all ethnicities. There is also no difference in gender, and it occurs most commonly between 50 and 70 years.⁸⁶ It commonly involves the first finger of the dominant hand.⁸⁶ This tumor location supports the theory that repetitive microtrauma participates in the pathogenesis of subungual melanoma (more than 25% have a history of prior trauma).

Between the changes observed are subungual hyperkeratosis, brownish-yellow discoloration of the nail plate, and onychorrhexis. Hutchinson's sign is very suggestive of this neoplasia, however, it is important to keep in mind that this sign is not pathognomonic for subungual melanoma, because it can also be seen in benign lesions.

Although subungual melanoma can be amelanotic (about 25% of cases⁸⁷), approximately 70% begin as a single longitudinal pigmented band in the nail - longitudinal melanonychia.^{88, 89} Therefore, the diagnosis should always be considered when a single band occurs during adulthood without another plausible explanation. The band commonly increases and darkens over time (dark brown or black color), with blurred margins, a width superior to 3-4 mm and usually, there is progression of dark pigment into the proximal or lateral nail fold - the Hutchinson's sign (**Figure 7**).⁹⁰ This represents the clinical manifestation of the radial growth phase.⁹¹ During this phase, subungual melanoma spreads its pigment to the entire nail plate and adjacent tissues. Thus, when Hutchinson's sign is present, it is crucial to consider the diagnosis, but its absence does not exclude it. Also, when the band is wider proximally than distally is often characteristic of a rapidly growing melanoma.

The differential diagnosis of longitudinal melanonychia includes multiple benign processes that cause longitudinal pigmented bands in the nail, including melanocytic nevus of the nail apparatus (clinically, in nevi, there are usually brown points, which correspond to the transungual elimination of nevus cell nests), certain medications, subungual hematoma, and even as a normal occurrence in patients with deeply pigmented skin. Still, any solitary pigmented band that darkens, widens, or otherwise alters the nail plate needs to be evaluated and is the physician job to ensure that is not a melanoma.⁹²

Nail plate deformities can be present due to nail matrix injury, and therefore melanoma can present as a subungual pigmented lesion that might have ulceration and additionally can also have onycholysis and/or nail destruction. When the onycholysis is associated with oozing is a clue of an eroded or ulcerating tumor. In amelanotic melanomas, the presentation is of a non-pigmented nodule that usually bleeds and ulcerates, very much like a pyogenic granuloma, making the diagnosis challenging.

Subungual melanoma is also frequently mistaken as an infection. In cases of supposed infection with nail pigmentation, it may be important to perform a biopsy, if the process does not respond to treatment.⁹² Some non-dermatophyte fungi could produce soluble melanin, whose pigmentation begins distally and progresses proximally, usually creating a narrow wedge that is wider at the distal end. When bacteria cause the infection, pigmentation is usually peripheral or limited to onycholytic areas. In the case of *Klebsiella* and *Proteus* species, they are usually dirty - gray, in the case of *Pseudomonas aeruginosa*, greenish - black. They seldomly create bands of regular width and can be scraped off the nail surface.

Early diagnosis is made in only 20% of patients. An ABCDEF "rule" has been proposed to help in diagnosis. It looks at risk factors associated with subungual melanoma. These factors are designed to be used in combination and not isolated, as with more positive findings there is an

increase in the risk of the lesion being malignant: A) Age – peak incidence fifth to seventh decades; B) Black or brown color with band width of 3 mm or more; C) stands for Changes in the appearance of the lesion; D) Digit most commonly involved (fingers); E) Extension of pigment onto the proximal or lateral nail fold (Hutchinson's sign); and F) Family or personal history of dysplastic nevus or melanoma. Except for criterion F), these represent validated clinical criteria. Any lesion, associated with a concerning history or appearance, should undergo a biopsy, regardless of the number of positive criteria. This means that the most important step to diagnose a subungual melanoma is to consider the possibility when faced with adult-onset streaky nail pigmentation.⁸⁶ Only then are further diagnostic considerations made and tests performed.

Dermoscopic evaluation can be extremely helpful in differentiating between subungual melanoma and benign melanocytic pigmented lesions.⁸⁶ By dermoscopy, longitudinal melanonychia due to nail melanoma typically has blurred borders, non-homogenous pigmentation of the band, and nonparallel discontinued lines of distinct colors. Nevertheless, dermoscopy alone is not totally reliable for diagnosis, especially if the bands are black or the nails are thick. Furthermore, in nail melanoma, the lines are sometimes regular. Consequently, integration of the history, clinical appearance, and dermoscopic findings is necessary.⁹³ Dermoscopy also can be utilized to help in defining periungual skin involvement. However, for establishing the diagnosis of a subungual melanoma biopsy remains the gold standard.

If the histology analysis reveals melanoma, the biopsy of the nail matrix should be full thickness to define the depth of invasion. In the biopsy specimen, the cells are hyperchromatic, small, and hardly recognizable as atypical, and the pagetoid or dispersion pattern is usually absent. There are warning signs that reveal their extension into the squamous epithelium of the nail fold, which is clinically evident as a Hutchinson melanotic whitlow.

Between 12% and 33% of subungual melanomas are lymph node-positive on diagnosis. Prognosis is poor (historically, the 5-year survival is only 15% and the median survival is only 4.6 years⁸⁷), not just because of the frequent delay in diagnosis but also due to the aggressiveness and rapid development of metastases in this location.⁸⁸

3. Conclusions

Nail disorders are a frequent presenting complaint for both the primary care physician and the dermatologist. Nail diagnoses are extensive and involve inflammatory, infectious, and neoplastic conditions. Onychomycosis is a prevalent nail condition, and appropriate fungal studies should always precede treatment to confirm the diagnosis. For establishing the precise diagnosis and, consequently, prescribing the correct treatment is crucial to know the various onychopathies simulating onychomycosis. Subungual tumors need a biopsy and should be evaluated by a dermatologist. It is important to note that any chronic or recurrent nail damage that does not respond to the initial treatment should be biopsied.

This review describes most of the diseases that are relevant in the differential diagnosis of onychomycosis, either by their prevalence or by their severity.

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5. Appendix

5.1. Figures

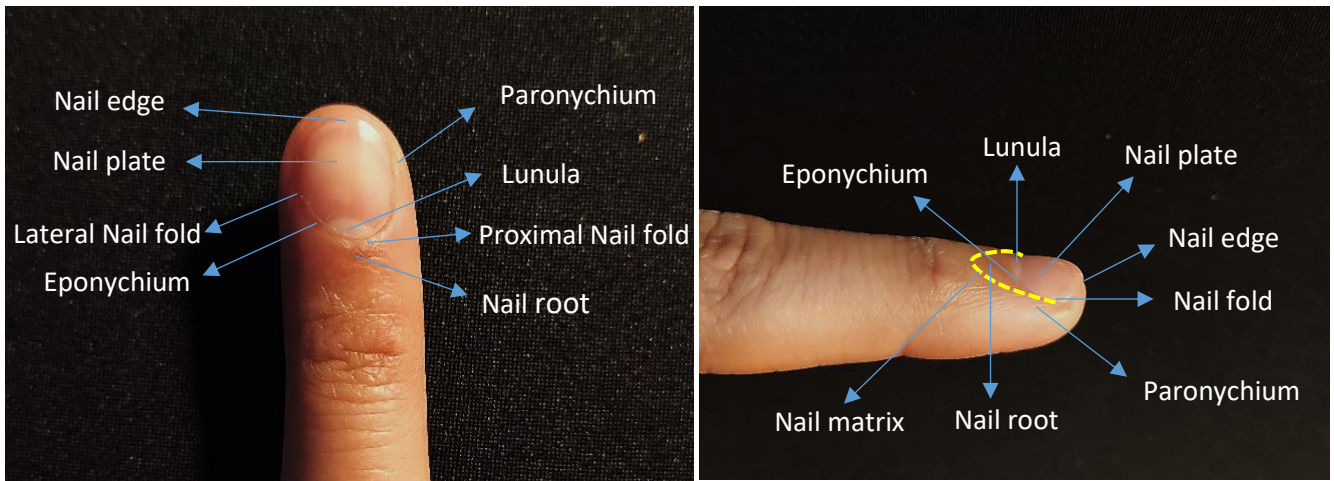


Figure 1 - Anatomical structure of the nail.



Figure 2 - Onychomycosis.



Figure 3 - Psoriasis.



Figure 4 - Alopecia areata.

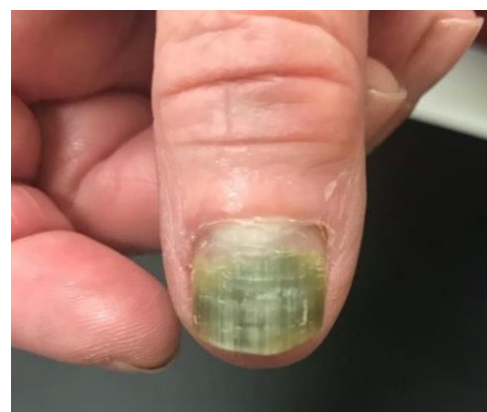


Figure 5 - Chronic paronychia
Pseudomonas aeruginosa.



Figure 6 - Glomus tumor.



Figure 7 - Subungual melanoma.