Radiological Imaging of Nail Disorders (PART II) – Radiological Features of Nail Disease

Abstract
We have seen that radiological techniques like digital x-ray, high-frequency ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI) have their unique roles in assessing a complex anatomical structure like the nail unit. Broadly speaking, USG and MRI help evaluate soft tissue components well; while, radiographs and CT scans help assess bony lesions better. In the second part of this review, salient radiological features of various nail disorders, as seen on these modalities are detailed. The radiological features mostly play a supportive role and help rule out differential diagnoses. However, in some diseases like retromychia and some nail tumors, radiological findings help clinch the diagnosis. The diagnostic features as well as the investigative modality of choice for a particular disease are highlighted based on the best level of evidence (LoE) available. This narrative review includes both infectious and non-infectious nail unit diseases, with special emphasis on nail unit tumors.

Keywords: Exostosis, glomus, nail psoriasis, onychomycosis, retromychia

Introduction
Radiological diagnosis of nail disease is a fast evolving field. Radiological modalities offer the advantage of being a noninvasive mode of investigation. Owing to the limited literature available on the topic, very few dermatologists and radiologists are aware of the radiological features of nail unit disorders. This is largely responsible for the limited usage of the radiological techniques in routine practice.

Through this review, we aim to collate and present the radiological features of nail disease, as visualized with various techniques. The aim is to highlight the technique of choice, wherever possible in these subgroups, so that nail disorders may be optimally evaluated.[1] The operating cost, level of skill/training required for interpretation of findings, and availability of the modality (especially in an emergency setting), need to be kept in mind while choosing investigations and interpreting results.[2] Patient considerations are equally important, especially because contraindications to radiation exposure or exposure to a magnetic field may exist. A well-founded nail diagnosis may often be based on a combination of clinical and radiological findings.

Methodology
A PubMed search pertaining to published articles using the keywords “radiology AND nail,” “radiodiagnosis AND nail,” “radiograph AND nail,” “CT and nail”, “MRI and nail”, “Ultrasonography AND nail” was done. The search yielded 6143, 10, 2494, 642, 615, and 6737 indexed articles, respectively, in English. The articles pertaining only to the “Nail Unit” in “dermatology” were shortlisted from the titles, and abstracts were then read. Articles were classified into review articles and clinical studies of various types. Full text versions of relevant articles, offering the highest level of evidence (LoE) were downloaded, based on the scheme proposed by Oxford Centre for Evidence-Based Medicine (OCEBM) in 2011 [Table 1].[3] The final data were analyzed and are presented in a narrative fashion.

Physical Nail Changes

Onycholysis
Onycholysis is distal separation of nail plate from nail bed resulting from multiple causes.
including trauma, onychomycosis, and nail psoriasis. On ultrasonography (USG), onycholysis is seen as an anechoic gap between nail plate and bed. Depending on the etiology, a thickening of nail bed may be appreciated, for example, in onychomycosis; or an increased vascularity in nail psoriasis.

**Onychomadesis**

Onychomadesis is proximal separation of nail plate from bed, which can be again multifactorial. However, an essential difference is that onychomadesis generally has a regrowing daughter nail. On USG, it is seen as a separation of the proximal nail plate into two portions. Thickened nail bed with reduced echogenicity, and an anechoic disruption of ventral nail plate, particularly near the proximal edge, is seen [LoE 5].[4] Thus, the proximal nail plate appears thickened and divided, especially if there has been a rapid regrowth, while distal part is often less echogenic.

**Subungual hematoma**

Bleeding underneath the nail plate can be a result of injuries, in which case, a distal phalanx fracture may be visualized on x-ray. On USG, acute hematoma is seen as an ill-defined hypechoic area. A subacute hematoma is also attached, as USG can assess the intensity of local inflammation, enthesopathy, and early development of psoriatic arthritis.[6]

Nail psoriasis USG findings include an increased thickness of nail plate, nail matrix, and nail bed [LoE 4].[6,7] Increased nail plate thickness has been found to positively correlate with duration of arthritis and number of involved joints. Other features include focal hyper-echoic involvement of ventral nail plate, loss of definition of ventral edge, wavy nail plate structure, with loosening of definition of ventral and dorsal plates. Activity of psoriatic onychopathy also correlates with USG-based blood flow evaluation. Regardless of coexistent nail changes, nail bed power Doppler (PD) signals are increased in psoriatic arthritis, suggesting an association with nail bed inflammation. Increased vascularity involving proximal to distal nail bed has been seen with active nail disease [LoE 5].[7,8]

USG also helps to differentiate nail psoriasis from onychomycosis. Moreno et al.[9] and Essayed et al.[10] evaluated various parameters including ventral and dorsal nail plate contours, interplate space, thickness of nail plate and bed, nail bed echogenicity, focal lesions, matrix thickness and length, distal phalanx periosteal surface, DIP joint space and contour, and distance between proximal nail plate and DIP joint. They concluded that USG nail measurements and characteristics can differentiate between psoriasis and onychomycosis [LoE 3] [Table 2].

**Table 1: Levels of evidence for clinical diagnostic studies as proposed by Oxford Centre for Evidence-Based Medicine in 2011**[3]

| Level of Evidence | Study Type |
|-------------------|------------|
| Level 1           | Systematic review of cross-sectional studies (Reference standard and blinding should be consistently applied) |
| Level 2           | Individual cross-sectional study (Reference standard and blinding should be consistently applied) |
| Level 3           | Nonconsecutive study OR Study without consistently applied reference standard |
| Level 4           | Case-control study OR Study with poor or nonindependent reference standard |
| Level 5           | Mechanism based reasoning OR Expert opinion |

Figure 1: Anteroposterior digital radiograph of a patient with nail psoriasis and psoriatic arthritis. Joint erosions, flexion deformity (arrows) at the inter-phalangeal joint of bilateral thumbs (R > L) and proximal interphalangeal joint of bilateral second, third, and fourth digits can be seen. A mild soft tissue swelling is seen in the right wrist (star)
MRI can help to detect enthesitis, enthesopathy, synovitis and bone marrow edema in cases with nail psoriasis and psoriatic arthritis [LoE 4].

**Connective tissue diseases**

Scleroderma-associated digital ischemia manifests as increased nail plate curvature, loss of distal nailfold, or even the nail plate. Radiographic changes include acro-osteolysis, calcinosis, flexion contractures, erosive changes, joint space narrowing, and subluxation. The frequency of these changes positively correlates with disease duration and internal organ involvement, more specifically acro-osteolysis correlating with interstitial lung disease [LoE 4]. Acro-osteolysis is more common in diffuse cutaneous (anti-Scl70 antibody positive) than limited cutaneous disease (anti-centromere antibody positive).

USG changes in scleroderma reveal irregularity, discontinuation, and thinning/thickening of nail plate. Edema of nail bed is seen as decreased echogenicity with reduction in vascularity on Doppler signals [LoE 4]. An increase in the nail bed matrix thickness has also been reported as a useful marker for scleroderma-related interstitial lung disease.

Systemic lupus erythematosus (SLE) with arthropathy can have typical radiographic changes including erosive arthritis, subluxation contractions, swan-neck deformity, and juxta-articular osteopenia [Figure 2]. Typical USG findings include edema-induced reduction in nail bed echogenicity and thickening or thinning of nail plate [LoE 4]. However, nail bed thickness is higher as compared to healthy controls. SLE has a predilection for thromboembolic phenomenon reflected by hypovascularity of the nail bed as seen on ultrasound Doppler (USD). This can lead to an irregular and discontinuous nail plate.

**Nail Infections**

**Onychomycosis**

This is a common nail infection, responsible for up to half of all onychopathies. The main USG findings include increased nail plate thickness, diffuse thickening and irregularity of nail plate lamellae [LoE 4]. Fusion of the nail plate lamellae and presence of posterior acoustic shadow within the nail bed is also seen. Presence of onycholysis with widening and thickening of nail bed, secondary to subungual hyperkeratosis, is often present. USG is useful in assessing treatment response in onychomycosis, with a normalization of nail structure and return to normal nail bed and plate thickness. Distinction between dorsal and ventral nail plate normalizes with treatment.

**Paronychia**

It is an inflammation of the nail folds, which may not always be infective. USG examination shows diffuse thickening of periungual folds with foci of increased echogenicity and intervening hypoechogenic areas suggestive of abscess (pus collection) [LoE 5]. Widening of the nail bed and nail matrix may often be noticed. Chronic cases may show a deformed nail plate architecture. Inflammation-driven increased periungual vascularity is appreciable on USD.

**Subungual warts**

It is a common periungual infection caused by Human Papilloma Virus (HPV), seen as slow growing keratotic

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**Table 2: USG differences between psoriatic onychopathy and onychomycosis**

| Psoriatic nail | Onychomycosis |
|---------------|---------------|
| Nail plate thickening present; but lesser than that seen in onychomycosis | Nail plate thickening with irregularity in lamellar structure is commonly seen |
| Nail bed thickening is present in many cases | Nail bed thickening is greater than that present in psoriatic onychopathy |
| Increased vascularity on USD | No increase in vascularity on USD |
| Higher PD signals at the nail bed and DIP joint | No PD alterations |
| More DIP alterations seen with structural damage in the DIP joint being common | No damage to DIP joint is seen |
| DIJ synovitis and erosions are present | No DIJ changes are seen |

USG: ultrasonography; USD: ultrasound Doppler; PD: power Doppler; DIP: distal interphalangeal; DIJ: distal interphalangeal joint
papules affecting distal (hyponychium) or lateral nail folds (perionychium). If nail matrix involvement is present, there is dystrophy of nail plate. On USG, wart appears as a hypoechoic fusiform eccentric lesion, hypovascular in nature. Thickening of nail plate and interplate space may be seen in cases with matrix involvement. A differential diagnosis to be considered in periungual location is Orf, caused by infection with Parapoxvirus. It generally appears 3 weeks after contact with animal fur, and is common in veterinarians or butchers.

**Tumors and Pseudo Tumors**

**Glomus tumor**

It is easily the most commonly discussed nail tumor in radiological literature. The choice of surgical techniques for glomus tumor excision depends on its localization, which is much aided by presurgical radiological mapping. MRI is considered the imaging study of choice, followed by contrast-enhanced CT.

On radiographs, bone erosion or an intrasosseous lytic lesion is visualized in less than one-third cases only, especially those with larger lesions of long-standing duration. On USG, glomus tumor appears as a nonspecific solid, hypoechogenic mass beneath the nail plate, which may be associated with erosion or scalloping of the underlying phalanx. A specific finding is hypervascular appearance on USD, due to a high-velocity flow in intramural shunt vessels. CT imaging can show the lesion, though soft-tissue details are very much limited. It is useful for demonstrating characteristic bony destructive changes, or when a satisfactory bolus of contrast has been administered. Without contrast, the lesion can be misinterpreted as other soft tissue tumors. High-resolution CT (HRCT) has been used for evaluation of glomus tumors of temporal bone.

MRI reveals glomus as a round, intense mass with intermediate or low-intense signals on T1-weighted images, and hyperintense signals on T2-weighted images. Gadolinium contrast images typically show a strong enhancement. MR angiography shows strong enhancement in arterial phase and increasing tumor blush in delayed phase. Solid glomus tumors, containing sparse vascular lumina are difficult to diagnose on MRI or MR angiography as they appear isointense with adjacent dermis on pre and post-gadolinium sequences. Diagnosis in such cases depends on visualization of a thin hypointense capsule, bone erosion, and matrix indentation. Mucoid tumors show mucoid degeneration of stroma, which appears hyperintense on T2-weighted images, with rim enhancement.

**Myxoid cyst**

Mucoid degeneration of connective tissue with metaplasia and proliferation of fibroblasts, leading to

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**Table 3: Radiological features of subungual glomus tumor**

| Radiograph | USG | CT | MRI |
|------------|-----|----|-----|
| The tumor is difficult to identify on radiograph | Lesion appears as a nonspecific, hypoechoic, solid mass, or may be anechogenic | May show the lesion without much soft-tissue details, thus may be confused with other soft tissue tumors | Vascular glomus tumors appear strongly hyperintense on T2-weighted images and MR angiography |
| Bone erosion may be seen occasionally involving the dorsal cortical surface of the distal phalanx, with or without a visible subungual mass | Associated with erosion of underlying bone in few cases | Useful for demonstrating characteristic bony destructive changes | There is avid enhancement in the arterial phase, as well as progressive enhancement in the venous phase due to intratumoral shunt vessels |
| Intraosseous lytic lesion may be seen at times, only a widening of the distance between the nail plate and bone cortex with a subtle soft tissue intensity may be apparent | Doppler imaging shows high-velocity flow in most, but not in all cases | Useful with contrast administration. Contrast enhancement helps to differentiate from nonvascular soft tissue tumors | Gadolinium contrast aids visualization |
| HRCT also used for evaluation of glomus tumors | Differential diagnosis of subungual hematoma | | MR angiography can help pick up lesion more easily |
excess hyaluronic acid, gives rise to myxoid cysts. They often produce nail deformity due to matrix compression.[23] A high incidence of postsurgical recurrence can be minimized by evaluating communication of the cyst with DIP joint, preoperatively.[21] USG reveals the cyst as a nonspecific, hypoechoic focal mass, difficult to differentiate from other subungual tumors. It is often successful in showing joint connection, if present on USD, myxoid cyst is seen as a round or oval shaped anechoic structure with posterior acoustic reinforcement and absence of flow. MRI can easily visualize the cyst as a well-margined, homogenous structure, which is hypointense on T1-weighted and hyperintense on T2-weighted images [LoE 4].[24]

At times, the clinical differentiation between a myxoid cyst and bony osteophyte may be difficult. USG is useful in such a scenario as osteophyte is seen as a cortical irregularity with posterior shadow cone; while a cyst is seen as an anechogenic tumor.[18] A hyperechogenic swelling in the same location suggests a solid tumor like epidermal or foreign body granuloma, gouty tophus, or a malignant lesion.[18]

**Giant cell tumor**

These tumors originate from the deep flexor tendon sheath. On USG, they appear iso-echogenic or weakly hypoechogenic. Though the tumor can make an imprint on the phalangeal cortex, the asymmetry of curvature is difficult to detect on USG.[18] Surgical planning is aided by preoperative USG localization.

**Onychomatricoma**

It is a rare benign tumor seen in middle-aged patients, characterized histopathologically by fibro-epithelial proliferation with projections arising from the nail matrix and growing within the nail plate. The clinical presentation comprises of a tetrad of xanthonychia, subungual hyperkeratosis, splinter hemorrhages, and longitudinal and transverse overcurvature of the nail plate,[25] with proximal nail plate having a funnel or Y-shaped appearance.

Except for nail plate and soft tissue thickening, much may not be visible on radiographs. However, on USG, a widening of nail matrix with a hypoechoic avascular mass can be seen deforming the nail plate. It contains echogenic foci corresponding to tumoral projections, along with irregularity and thickening of the nail plate.

High-resolution MRI shows characteristic features of onychomatricoma.[26] On T2-weighted images, the tumor appears as a hyperintense well-defined mass with filamentous extensions into the thickened nail plate.[26] Axial images show tiny holes filled with hyperintense filamentous tumor extensions in the thickened nail plate.

**Fibrokeratoma or Koenen’s tumor**

They are uncommon fibrous tissue tumors involving mostly toenails. A longitudinal groove on the nail plate is a frequent finding. On USG, they appear as hypoechoic, round to oval or fusiform lesions, with polypoidal morphology. They are hypovascular and eccentrically located in the nail bed.[4] On USD, there is hypovascularity of lesions except in angiofibromas that have an increased vascularity.

**Superficial acral fibromyxoma**

It is a rare, benign, soft-tissue tumor located in the periungual and subungual region in adults. It is located typically within the dermis or subcutis. On MRI, it appears as ill-defined heterogenous hyperintense soft tissue thickening [Figure 4a-c] [LoE 5].[27]

**Subungual exostosis**

It is a benign bone tumor involving distal phalanx, giving rise to pain and nail deformity. The differential diagnoses include osteochondroma, glomus tumor, verruca vulgaris, amelanotic subungual melanoma, etc. While exostosis has a fibrocartilaginous cap, osteochondroma has a hyaline cartilage cap.

Diagnosis can often be confirmed on radiographs, which show a well-defined trabecular bony outgrowth from the distal phalanx, with or without a defined cortex. “Coat hanger” exostosis appear to grow away from the nearby joint, and cortex and medullary regions maybe in continuation with that of phalanx from which the lesion projects. The cartilaginous cap may be partially or totally replaced by bone when the epiphysis of the parent bone closes.[28]

On USG examination, exostosis appears as a well-defined heterogeneous, hyperechoic lesion with calcification and distinctive fibrocartilaginous cap. USD shows hypovascularity. MRI is useful in characterization of the cartilaginous cap. Hyaline cartilage (osteochondroma) shows high signal intensity on T2-weighted images in
contrast to fibrocartilaginous cap (exostosis) which is hypointense.\footnote{23}

**Pyogenic granuloma (lobular capillary hemangioma)**

It is a common benign vascular tumor occurring in all age groups. Clinically, it appears as a solitary red mass with ulceration and bleeding in many cases. The most common cause of periungual lesion is drug intake.\footnote{29} Drugs including retinoids (acitretin, isoretinoin), taxanes, epidermal growth factor-receptor (EGFR) inhibitors, tyrosine kinase inhibitors, BRAF (proto oncogene B-raf) inhibitors, CD20 antagonists, and vascular endothelial growth factor (VEGF) inhibitors are known to cause such lesions. USG reveals a well-defined hyper-echoic mass with small hypoechoic foci \cite{31,32}. On USD, it appears as a hypervascular tumor with arterial waveform. MRI shows an isointense lesion on T1-weighted sequences, while it is hyperintense on T2-weighted images. Marked enhancement is typically seen after gadolinium enhancement.\footnote{30}

**Subungual keratoacanthoma**

Clinically, subungual keratoacanthoma (SAK) appears as a red scaly nodule, with rapid growth over a few weeks, and even destruction of underlying bone. A spontaneous regression may be present in few cases.\footnote{31,32} Radiographs show a crescent-shaped soft tissue mass, with a pressure-induced osteolytic defect. Sclerosis or periosteal reactions are often absent. On USG, SAK is seen as a well-circumscribed mass with mixed echogenicity and cortical bone erosion and posterior acoustic enhancement \cite{33}. MRI shows an intermediate intensity lesion on T1-weighted images and mixed signal intensity on T2-weighted images. Post gadolinium, fat-suppressed, T1-weighted images show a thin rim enhancement, corresponding to inflammatory changes. Central part of the tumor typically shows no enhancement \cite{34}. Radiologic imaging is often not able to differentiate between squamous cell carcinoma (SCC) and SAK.

**Subungual malignant melanoma**

Subungual malignant melanoma (SAM) is a distinct subtype of malignant melanoma histopathologically consistent with acral lentiginous melanoma. It presents with nail dystrophy, pigmentation of the nail and periungual soft tissue, split nail, or pigmented nail streak. USG is important for an accurate measurement of lesional thickness, which carries a prognostic significance akin to histological thickness \cite{4,39-41}.\footnote{42} USG can also detect angiogenesis and neovascularity within the lesion, which are the key factors in determining its metastatic potential.\footnote{36} While early stage SAM may have no USG evidence; larger lesions appear as solid, homogenous, hypoechoic, hypervascular masses.\footnote{21} Ill-defined hypoechoic areas in the periphery suggest peritumoral growth or infiltration. MRI appearance depends on the melanin content and hemorrhage within the lesion. Melanin has paramagnetic properties giving it a short relaxation time; thus, melanotic malignant melanoma appears hyperintense on T1 and hypointense on T2-weighted images. At the same time, amelanotic lesions appear hypointense on T1 and intermediate to hyperintense on T2-weighted images. A major source of confusion may be intratumoral hemorrhage, which is common in melanoma. High-resolution MRI can also facilitate accurate measurement of lesion thickness.\footnote{21,37,38}

**Squamous cell carcinoma**

Squamous cell carcinoma is a rare malignant tumor in the nail unit, which grows slowly, and causes bone invasion. Clinical features include onycholysis, nail bed erythema, and ulceration signifying advanced disease.\footnote{4,39-41} In such cases, radiographs may show bony erosion. On USG, SCC appears as an irregularly marginated, heterogeneously hypoechoic mass with internal vascularity.\footnote{21} Bony erosions, if present, may also be seen. USG may show low resistance and pulsatile flow within the lesion. MRI shows a lesion that is hypointense on T1-weighted and hyperintense on T2-weighted images, with ill-defined infiltrative margins. Heterogeneous contrast enhancement is characteristic. Cortical erosion of adjacent bone suggests tumor invasion. However, it may be difficult to differentiate radiologically from periosteal reaction and marrow edema seen in many cases \cite{33}.\footnote{42}

**Miscellaneous Conditions**

**Ingrown nail**

Ingrown nail is a commonly encountered condition in practice where preoperative radiography is recommended to rule out underlying bony outgrowth. USG shows a diffuse thickening of the nailfold with an increased echogenicity and vascularity suggesting inflammation.\footnote{43}

Pincer nail is a special subtype, often associated with osteophytes. Pang et al. recommended periodic radiographic assessment to detect early osteomyelitis in pincer nail patients with chronic inflammation or repetitive pyogenic infections.\footnote{44}

Harpoon nail is an ingrown variant where a nail spicule pierces and grows under distal periungual tissue. High-frequency USG is useful in confirming this diagnosis as it demonstrates a hyperechoic spicule under the subcutaneous tissue of nail fold, in continuation with the ingrowing nail plate. This is surrounded by a hypoechoic inflammatory halo with or without an increased vascularization. USD may show periungual or subcutaneous, hypoechoic or anechoic collections with hemorrhagic or purulent content.\footnote{45}
Congenital malalignment is another ingrown variant, shown to have a thickening of distal joint ligament on MRI. This is associated with the clinical bulge, giving clues toward pathogenesis of this condition.[46]

**Retronychia**

Retronychia diagnosis is greatly helped with USG. The condition is associated with embedding of proximal nail plate into the proximal nail fold. There is halted nail growth with chronic proximal paronychia. USG can support the diagnosis of unilateral as well as bilateral cases of retronychia, with well-defined diagnostic criteria having been developed [Table 4] [LoE 4].[47] A simultaneous presence of three major USG criteria is needed for the diagnosis of unilateral retronychia. Bilateral retronychia requires at least two criteria (with one of them being the presence of hypoechoic halo surrounding the origin of nail plate) for diagnosis.

**Onychogryphosis**

It is an acquired nail deformity resulting from poor blood circulation, diabetes, tight fitting shoes, anatomical anomalies like hallux valgus, old age, or repeated minor trauma. The nail plate becomes opaque, yellowish-brown, grossly thickened, elongated and partly curved. USG findings support the diagnosis revealing features like increased thickness of the dorsal and ventral nail plates, with essentially normal nail matrix or bed.[17]

**Subungual foreign body**

This is often an acute indication for radiological evaluation. Suspected foreign body may need to be ruled out in chronic cases as well. Digital radiographs can help with radio-opaque foreign bodies only. USG is a more versatile investigation in this scenario, as it is dynamic and can pick up even radiolucent foreign bodies.[18] USG helps preoperative localization of foreign body, whether single or multiple. It also allows evaluation of joint space if an extension of inflammation is suspected. PD of the joint in slight hyperextension helps to assess associated synovitis. Though MRI can show more details, it is not recommended if there is no clarity regarding the magnetic property of the unknown foreign body. Additionally, MRI is rarely accessible in emergency.[18]

**Leprous onychopathy**

Nail involvement tends to be variable for lepromatous vis-à-vis tuberculoid disease. Nail changes are more common with lepromatous disease, probably due to the role of more causative factors including neuropathy, trauma, vasculopathy, and drugs used. Reported changes include anonychia, onychogryphosis, brachyonychia and onychorrhexis in lepromatous (LL) and borderline lepromatous (BL) patients with grade 2 deformities; while subungual hyperkeratosis, Beau’s line, brown–black pigmentation, longitudinal melanonychia, and Terry’s nails signify active disease. Though no correlation of nail changes has been done with radiological changes, periostitis and "licked-candy" appearance accompany these changes on radiographs.[48-50]

Table 5 summarizes the radiological investigation of choice for various nail unit disorders.
Conclusion

Radiological investigations including digital radiographs, USG, CT, and MRI help evaluate nail unit disorders in detail. Of these, the investigation of choice often depends on the differential diagnoses being considered, availability of the modality, and patient considerations. USG of nail is rapidly evolving in recent times and proving to be a truly versatile modality. Radiological imaging has been found especially useful in evaluation of DIP, entheseus, suspected subungual foreign body, nail unit tumors, cystic swelling, or retromyonychia. A familiarity with radiological features of nail disease helps in arriving at a nail diagnosis in a noninvasive manner.

Author contributions

CG and SB have equally contributed to the design of the manuscript, writing of the manuscript and are accountable for all aspects of the work. AV and DJ offered critical comments and did corrections to the draft. All authors are responsible for ensuring accuracy and integrity of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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