Symposium-Nails-Part II

Nails: Diagnostic clue to genodermatoses

Arun C. Inamadar, Aparna Palit

Department of Dermatology, Venereology and Leprosy, Sri B.M. Patil Medical College, Hospital and Research Center, BLDE University, Bijapur, Karnataka, India

Address for correspondence:
Dr. Arun C. Inamadar, Department of Dermatology, Venereology and Leprosy, SBMP Medical College, Hospital and Research Center, BLDE University, Bijapur - 586 103, Karnataka, India.
E-mail: aruninamadar@rediffmail.com

ABSTRACT

Nails are cutaneous appendages mostly involved in mechanical functions. However, nails may reflect presence of various systemic disorders evidenced by alteration of their shape, size, color or texture. Genodermatoses are multisystem disorders with cutaneous involvement. Many of the genodermatoses present with nail changes and some of these may be the clinical pointers to the diagnosis. Diagnostic clues to various genodermatoses derived from nail findings have been discussed.

Key words: Genodermatosis, nail patella syndrome, pachyonychia congenita, yellow nail syndrome

INTRODUCTION

It is customary to consider nail as an ornamental body part helpful in finer grip functions of hands and feet. However, appendageal structures like nail and hair may be as good reflectors as skin for presence of many systemic disorders. Cosmetic appeal of well manicured nails is undeniable; at the same time their efficacy as a diagnostic tool is well known.

Genodermatoses are conglomeration of cutaneous and systemic signs and symptoms and some of these disorders present with nail involvement. Nails may be the primary site of affection in some genodermatoses whereas in others it is merely part of a syndrome. In majority of the genodermatoses nail changes are nonspecific but in combination with other cutaneous and systemic features these may point to a probable diagnosis.

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Nail involvement in genodermatoses may be categorized in to three groups for better understanding and diagnosis [Table 1];

1. Genodermatoses with characteristic nail changes
2. Genodermatoses with significant nail involvement
3. Genodermatoses with nonspecific nail changes

GENODERMATOSES WITH CHARACTERISTIC NAIL CHANGES

Few genodermatoses present with characteristic nail changes which predominate the clinical picture. When encountered with such nail changes, these disorders merit the first diagnostic consideration.

Pachyonychia congenita

Thick, yellowish brown-colored nails present at birth or developed during neonatal period with or without natal teeth are pointers to the diagnosis of pachyonychia congenita (PC). Dystrophy of all the twenty nails is a feature common to all the three variants of PC, but other features may be variable. Upward angulation of the distal free edge of the thickened nail plate (progressive distal thickening) is a distinct feature[1] and helps to differentiate it from other disorders with thick nails. Recurrent

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Table 1: Some of the genodermatoses with nail involvement[1,10,17]

Categories	Genodermatoses	
Genodermatoses with characteristic nail changes	Pachyonychia congenita	–
	Nail-Patella syndrome	–
	Yellow nail syndrome	–
	Porphyrias	Congenital erythropoietic porphyria, erythropoietic protoporphyria, porphyria cutanea tarda
	Neuro-cutaneous syndromes	Tuberous sclerosis complex, Osler-Weber-Rendu syndrome, ataxia telangiectasia
	Disorder of keratinization	Darier's disease
Genodermatoses with significant nail involvement	Disorder of keratinization	Trichothiodystrophy, Mal de Meleda, Scleroatrophy of Huriez, Olmsted syndrome, Bazex's syndrome
	Mechano-bullous disorders	EB simplex, Junctional EB, Recessive DEB
	Poikilodermatous disorders	Kindler syndrome, Dyskeratosis congenita
	Congenital immunodeficiency	Congenital mucocutaneous candidiasis
	Disorder of pigmentation	Incontinentia pigmenti
Genodermatoses with non-specific nail changes	Ectodermal dysplasia	—
	Disorders of pigmentation	Cronkhite-Canada syndrome, Peutz-Jeghers syndrome, Laugier-Hunziker syndrome, LEOPARD syndrome
	Poikilodermatous disorder	Rothmund Thomson syndrome
	Disorder of keratinization	KID syndrome, other ichthyosis, and palmo-plantar keratoderma
	Neurocutaneous disorders	Neurofibromatosis type 1
	Metabolic disorders	Fucosidosis, Erythropoietic protoporphyria, acrodermatitis enteropathica
	Disorders with premature aging	Progeria

painful paronychia may be associated. Nail trimming becomes impossible because of thickening and fine grip functions of the fingers are jeopardized.

Focal, intensely painful palmoplantar keratoderma develops during early childhood when the child starts walking and other activities. Foamy white mucosal plaque simulating oral candidiasis is mostly present in type 1 PC. Affected children may have hoarseness of voice and rarely laryngeal stridor.[2] Natal teeth and multiple steatocystomas are indicative of the diagnosis of type 2 PC. Rarely, lusture-less kinky scalp hair (pili torti) and straightly stood-out eyebrow hairs are the features of this type.[3]

Nail changes and palmoplantar keratoderma in PC may be subtle[4] and variable among family members. This should not bar the clinician to make a clinical diagnosis of PC. Even the nail dystrophy may appear late (childhood or adulthood) in type 3 PC (PC tarda).

Nail patella syndrome

It is worth to examine the nails of a patient with nephrotic syndrome and early onset knee joint osteoarthritis resulting in pain and gait abnormality. Anonychia or nonprogressive micronychia (mostly involving thumb and index fingers) present since birth, and triangular lunula with distal apex in the midline are highly predictive of nail patella syndrome.[5] Nail hypoplasia is more marked on the ulnar sides of the involved fingers.

Although less highlighted, absence of skin creases on the dorsal aspects of distal interphalangeal joint is a more specific sign of this disorder; this finding may be present in these patients even in absence of nail changes.[5] Associated features are hypoplastic or aplastic patella (resulting in subluxation), hypoplasia of proximal radius and ulna (limitation of elbow movement), posterior iliac horns and webbing of the digits.[3]

Yellow nail syndrome

Upper and lower respiratory tract illnesses (sinusitis/bronchitis/recurrent bilateral pleural effusion/bronchiectasis) and primary lymphedema (80%)[6] in combination with thickened, yellow nails are the clues for clinical diagnosis of yellow nail syndrome. All the 20 nails are involved. Only nail changes (30%) or only lymphedema (30%) may be the presenting feature.[6] The color of the nail plate is variable from pale yellow to orange and often it is altered due to colonization by *Pseudomonas aeruginosa* (greenish black) or *Candida sp*.[1,7] History of very slow growth of the nails (<0.25 mm/week), longitudinal over-curvature (hump-like), obscured lunula and absence of cuticles are more specific findings in such cases.[1,7] There may be history of nonimmune fetal hydrops in other siblings.[8]

Porphyrias

Photo-onycholysis and marked koilonychia are the

characteristic features of various hereditary porphyrias like congenital erythropoietic porphyria (CEP), erythropoietic protoporphyria (EPP) and porphyria cutanea tarda (PCT).[2]

Other associated features of this group of disorders are erythrodontia (red fluorescence on Wood's lamp examination) and mutilating scars (CEP); skin pain on sun exposure, bullae on photo-exposed parts, shallow, elliptical scars on face (EPP); and bullae, scarring and hirsutism (PCT).[2]

Neuro-cutaneous syndromes

Garlic-clove fibromas (Koenen tumor) are multiple, elongated, pink or flesh-colored tumors with hyperkeratotic tips, arising from beneath the proximal and lateral nail folds (periungual) producing longitudinal midline depression on nail plate [Figure 1]. Such lesions appearing at puberty, along with facial angiofibromas and hypopigmented ash-leaf macules are characteristic of tuberous sclerosis complex (TSC). Frequency of these lesions in TSC varies from 15% to 52%, occurring more commonly on toes.[9] Although periungual lesions are common, subungual fibromas may also occur. Occasionally longitudinal midline groove on the nail plate may be the only finding in these patients and may result from cryptic subungual fibroma, impacting the nail matrix.[9]

Aldrich *et al*.,[9] have reported occurrence of red comets in 25% of adult patients with TSC in their series and considered this as a characteristic finding. These are partially blanchable linear red streaks with bulging at the distal end and surrounding pallor. Red comets are located at the middle of the nail plate and extend upto distal one-third without involving the free margin.[9] The lesions are persistent, nonprogressive and asymptomatic. These signify presence of telangiectasia with extravasated blood.[9] Other features recorded by these authors were splinter hemorrhage (50%) and longitudinal leukonychia (relatively uncommon).[9]

Telangiectasia of nail bed, visible as blanchable, punctate red dots should prompt the clinician to screen the patient for Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia).[10] These may bleed to give rise to splinter hemorrhage. History of recurrent epistaxis starting as early as during infancy, presence of numerous cutaneous and mucosal telangiectasia and repeated hemorrhagic episodes from multiple sites among several family members are the other clues to the diagnosis.[11] Expanded fungiform papillae of tongue due to presence of single, much dilated blood vessel in each of these (visible by capillary microscopy) is a diagnostic feature of this disorder.[11]

Disorder of keratinization

'V'-shaped notch on the free edge of the nail plate [Figure 2] along with alternate longitudinal red (erythronychia) and white (leukonychia) bands are the distinct features of Darier's disease. Splinter hemorrhages may be associated. Hyperkeratotic, greasy papules over seborrhoeic areas and cobblestone appearance of the hard palate are the main mucocutaneous features.

Vesiculo-bullous disorder

Longitudinal leukonychia is a diagnostic sign of Hailey-Hailey disease,[12] and may be helpful to differentiate this disorder from immunobullous disorders.

Some other genodermatoses may also share these nail changes and list of these has been presented in Table 2.

GENODERMATOSES WITH SIGNIFICANT NAIL INVOLVEMENT

Several genodermatoses have nail changes significant enough to attract clinician's attention during first visit, though not characteristic of these disorders.

Disorders of keratinization

Patients with trichothiodystrophy may have marked nail involvement. Brittle nails are a component of PIBIDS and IBIDS.[3] Other changes include ridging and splitting of nail plate, nail dystrophy, yellow discoloration, onychogryphosis and koilonychia. Diffuse alopecia, dental caries and ichthyosis are the main clinical features.

Psoriasiform nail changes (thickening and discoloration of nail plate, subungual hyperkeratosis, splinter hemorrhage) are seen in all types of palmoplantar keratoderma and Bazex's syndrome but are not diagnostic of these disorders. Marked nail changes are seen in trasgradient keratodermas like Mal de Meleda, scleroatrophy of Huriez, Olmsted syndrome etc. Huriez syndrome is characterized by marked scleroatrophy of the hands, diffuse palmoplantar keratoderma and hypoplastic nails. Prominent lunula, elongated cuticles and 'V'-shaped notch are the special features of this disorder.[13]

Table 2: List of some nail changes shared by various genodermatoses[10,19]

Nail manifestation	Characteristic feature of the genodermatosis	Other genodermatoses with same nail changes
Yellow discoloration of nail plate	Yellow nail syndrome	Cronkhite Canada syndrome, Hutchinson-Gilford syndrome, Incontinentia pigmenti, Trichothiodystrophy (toe nails)
Diminuted/ absent lunula	Yellow nail syndrome	Erythropoietic protoporphyria, Porphyria cutanea tarda, Iso-Kikuchi syndrome, Goltz's syndrome, Pachyonychia congenita
Koilonychia	Porphyrias	Incontinentia pigmenti, Dyskeratosis congenita, Nail-patella syndrome, Ellis-Van-Creveld syndrome, Acrogeria, Mal de Meleda PPK, Darier's disease, LEOPARD syndrome, Scleroatrophy of Huriez
Paronychia	Chronic mucocutaneous candidiasis	Rubinstein-Taybi syndrome, Acrodermatitis enteropathica, Junctional EB (hemorrhagic), Dyskeratosis congenita (suppurative), Pachyonychia congenita (recurrent, painful)
Longitudinal leukonychia	Hailey-Hailey disease	Tuberous sclerosis complex
Splinter hemorrhage	Osler-Weber-Rendu disease	Darier's disease, Tuberous sclerosis complex
Onycholysis	Yellow nail syndrome	Cronkhite-Canada syndrome, Epidermolysis bullosa (hemorrhagic), Witkop-Brearley-Gentry syndrome
Poor nail growth	Yellow nail syndrome	Lipoid proteinosis, Acrodermatitis enteropathica (chronic stage)
Periungual tumors	Tuberous sclerosis	Incontinentia pigmenti (warty lesions)
Splinter hemorrhage	Osler-Weber-Rendu syndrome	Tuberous sclerosis complex (red comets)
'V' shaped notch	Darier's disease	Scleroatrophy of Huriez.
Long cuticle	Kindler syndrome	Scleroatrophy of Huriez

Mechano-bullous disorders

Periungual or subungual bullae [Figure 3] producing hemorrhagic onycholysis should alert the clinician about the diagnosis of epidermolysis bullosa (EB).[14]

Nail changes are milder in EB simplex, like nail dystrophy and onychomadesis. Onychogryphosis of great toe nails may be a feature of EB simplex, Ogna variant.[14]

Severe nail changes like onychodystrophy and anonychia are seen in junctional and dystrophic EB (DEB).

Few clinical features are pointers to the diagnosis of junctional EB (JEB). Anonychia during neonatal period may be the presenting symptom. Drumstick appearance of the distal digits covered with granulation tissue is typical of Herlitz JEB.[14] Hemorrhagic paronychia in neonates is also a hallmark sign of this disorder.[14] Pseudosyndactyly (3-5%), hair loss and gross dental defects are seen in non-Herlitz JEB.

Toenails are dystrophic and frequently absent in DEB. Total anonychia is seen in recessive DEB [Figures 4 and 5]. Mitten deformity of hands and feet is the pointer to the diagnosis of the generalized recessive form of DEB (Hallopeau-Siemens variant).

Poikilodermatous disorders

Gross nail dystrophy and pseudosyndactyly may be observed in patients with Kindler syndrome. Long, thick cuticles covering up to almost half of the nail plate has been described in these patients [Figure 6].[15,16] These may be shiny and intact or fragile, with ruffled, lamellated appearance.

Nail dystrophy may be the initial presenting feature (evident by 5-13 years of age) of patients with dyskeratosis congenita. Subsequently nails may be attenuated to horny plugs or may be shed completely. There may be recurrent, suppurative paronychia. Reticulate pigmentation of neck and poikiloderma appear either simultaneously or thereafter.

Congenital immunodeficiency disorder

Markedly dystrophic nail plate and recurrent tender paronychia in a child with associated oral thrush warrants screening for chronic muco-cutaneous candidiasis (CMC).[3] Several family members may be affected. Crusted, granulomatous plaques on skin and dermatophyte infections are the other features.

Disorders of pigmentation

Periungual warty lesions with underlying osteolysis may appear in patients with incontinentia pigmenti during adolescence.[14]

GENODERMATOSES WITH NONSPECIFIC NAIL CHANGES

Many of the genodermatoses present with nonspecific nail changes. As such these changes are not indicators of any specific genetic disorder and may be seen even in many acquired conditions. In the following section, non-specific nail changes in various genodermatoses have been categorized.

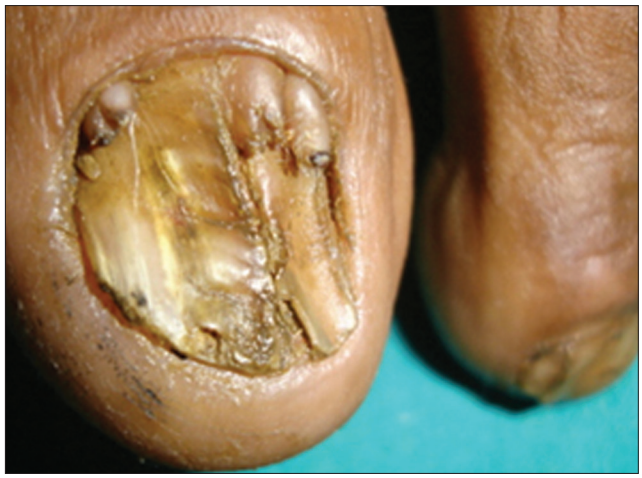

Figure 1: Multiple subungual fibromas producing midline depression on nail plate in tuberous sclerosis

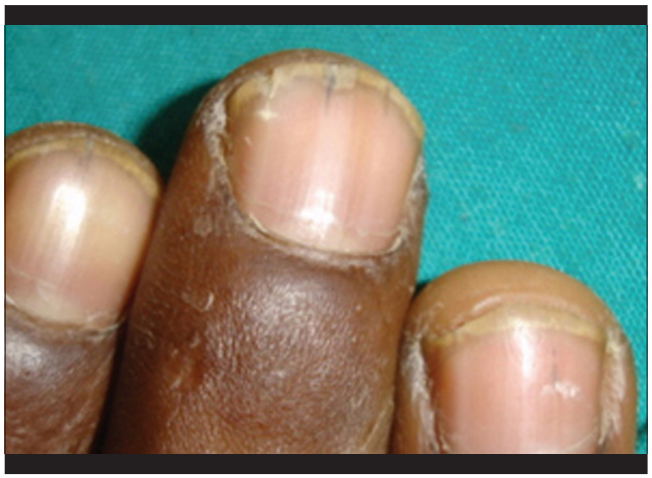

Figure 2: 'V'-shaped notch at the distal free edge of the nail plate, onycholysis and multiple splinter hemorrhages in Darier's disease

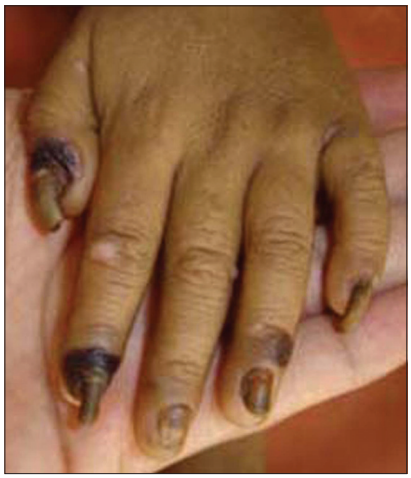

Figure 3: Periungual hemorrhagic bullae (dried up), discoloration, severe dystrophy and onychogryphosis of few nails in epidermolysis bullosa

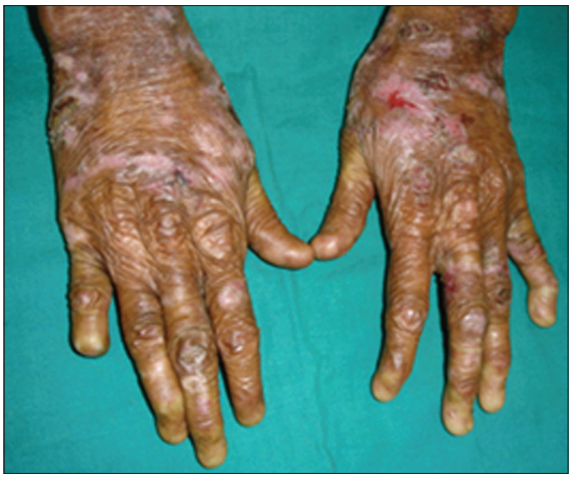

Figure 4: Anonychia of fingers in recessive dystrophic EB

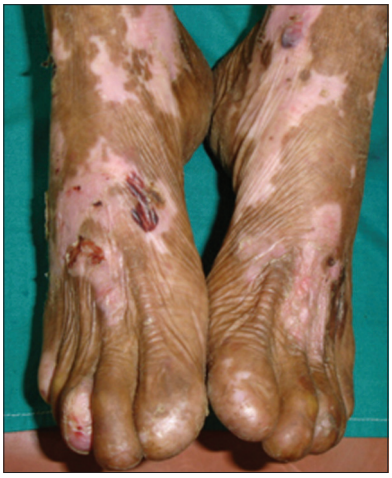

Figure 5: Complete anonychia of toes in recessive dystrophic EB

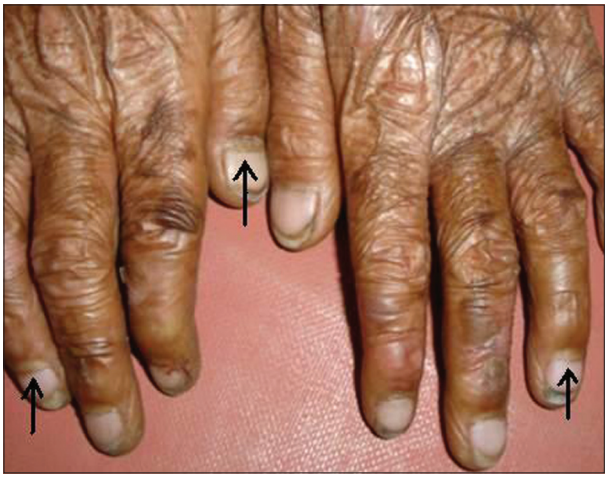

Figure 6: Long and thick cuticles (↑) on several finger nails with parchment-like skin on dorsa of the hands in a boy with Kindler syndrome

Alteration in nail texture

Various nail changes with variable combinations of hypotrichosis or alopecia, hypohidrosis, palmoplantar keratoderma and dental anomalies are seen in patients

with ectodermal dysplasia [Table 3].[17] Such changes include onycholysis, onychorrhexis or sometimes subtle changes like thin, brittle nails or short, thick nails. There is no distinct nail change characteristic of any of these disorders; however, in combination with other clinical features, nail changes may be helpful in diagnosis.

Onychorrhexis is a common feature in patients with ichthyosis and palmoplantar keratoderma.

Nail dystrophy

In Cronkhite-Canada syndrome, there is a characteristic nail dystrophy due to formation of ventral nail in absence of normal nail production by the nail matrix.[18] Other associated features are diffuse pigmentation of palms and macular pigmentation of dorsa of hands, gastrointestinal polyposis leading to protein-losing enteropathy and alopecia.

Nails in patients with Rothmund Thomson Syndrome may be small and dystrophic. The presenting features in these patients are photosensitivity, blistering, bird-like facies and early cataract in first few years of life; later they develop poikiloderma and parchment-like thin, atrophic skin over extremities.

Onychodystrophy may be a frequent feature of various types of ectodermal dysplasias, KID syndrome and all forms of progeria.

Table 3: Nail changes and other distinguishing clinical features in some ectodermal dysplasias[17]

Nail manifestation	Other distinguishing C/F	Genodermatoses
Onychodysplasia	Freckling, exfoliation of digits	ADULT syndrome
Nail dystrophy	Keratitis, ichthyosis, deafness	KID syndrome
	Wide-spaced conical teeth, deafness	Robinson's syndrome
Anonychia	Ankyloblepharon	Hay-Wells syndrome
	Decreased sweating, flexural pigmentation	Anonychia with bizarre flexural pigmentation
	Typical facies, mental retardation	Coffin-Siris syndrome
	Crumpled pinna, aplasia of fibula	Pfeiffer's syndrome
Thick and short nails	Severe dental caries, absent dermatoglyphics	BASAN's syndrome
Brittle nails	Curly hair, dolichocephaly	Tricho-Dento-Osseous syndrome
	Pear-shaped nose, high philtrum, tubercle below lower lip, maxillary prognathism, mandibular hypoplasia	Trichorhinophalangeal syndrome I
	Cystic eyelids, PPK	Schöpf-Schulz-Passarge syndrome
Spoon-shaped nails	Total alopecia, widely spaced small teeth	Odonto-onychodysplasia

Alteration in size of nail

Hypoplastic nails (micronychia/anonychia) are seen in various ectodermal dysplasia [Table 3], epidermolysis bullosa [Figure 7] and nail-patella syndrome. Whenever this feature is encountered, these conditions should be ruled out by looking for associated features. Iso-Kikuchi syndrome (congenital onychodysplasia of index finger), a rare condition presented with micronychia or anonychia[14] has also to be differentiated from nail-patella syndrome. Unlike nail patella syndrome, here the nail changes are more prominent on radial sides of the index fingers and there is no associated systemic feature. A convenient way to diagnose Iso-Kikuchi syndrome is X-ray of the affected fingers (lateral projection) which reveals 'Y'-shaped distal phalanx.[14]

Alteration in nail contour

Some of the genodermatoses are associated with change in shape of the nails. Among these, relatively distinct are 'long, narrow nails' of Marfan syndrome and 'turtle back configuration' of nails in patients with Fabry's disease.[14]

Onychogryphosis may be seen in patients with ectodermal dysplasias and fucosidosis.

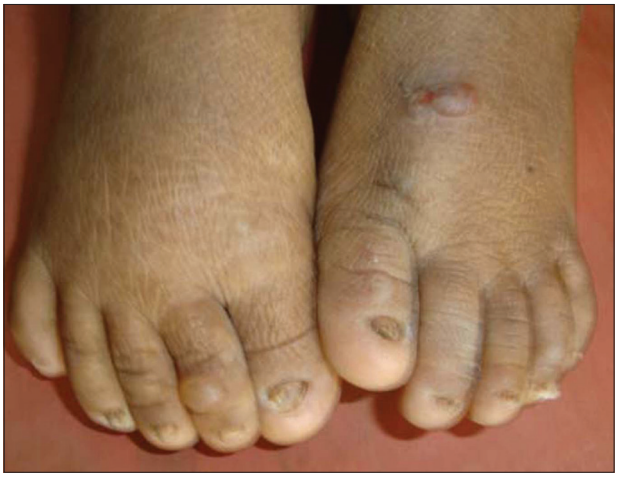

Figure 7: Hypoplastic toe nails with onychodystrophy in epidermolysis bullosa

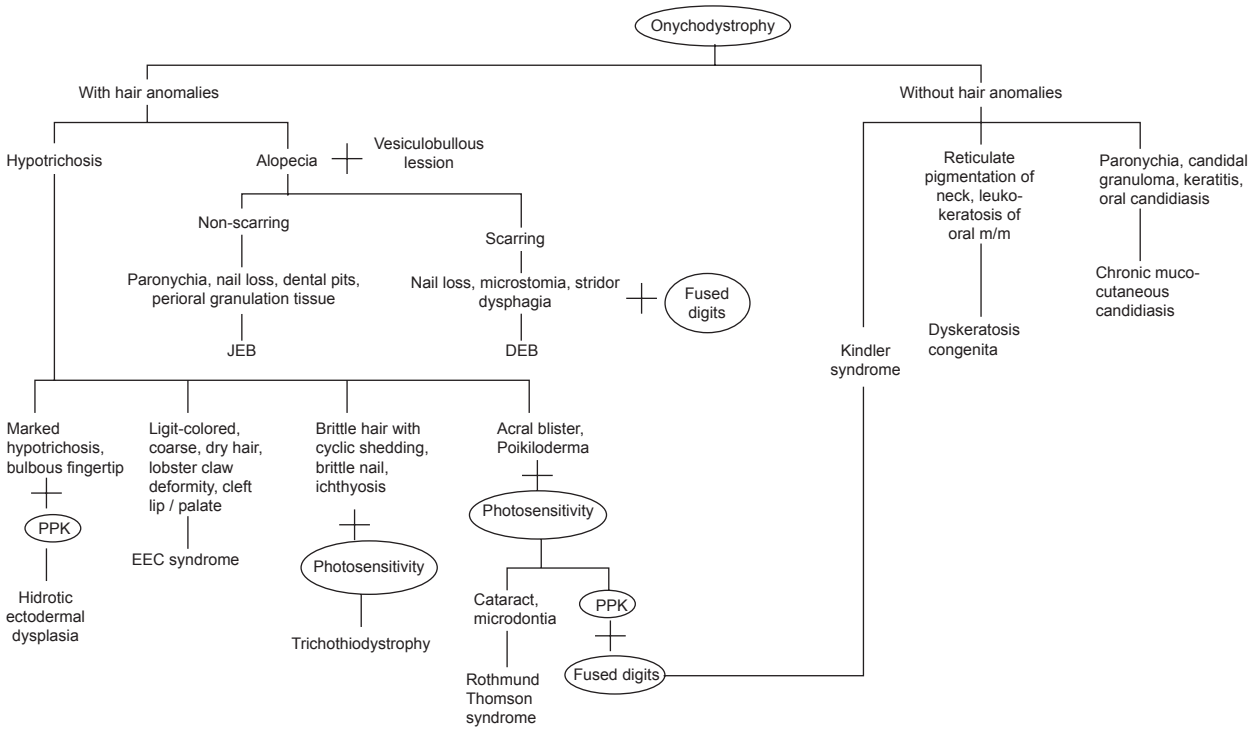

Figure 8: Diagnostic algorithm for genodermatoses presented with nail dystrophy

Koilonychia or hypercurvature of nail plate may be seen in various ectodermal dysplasias, ichthyoses and palmoplantar keratodermas. In patients with type 1 neurofibromatosis, 'pterygium inversus unguium' like changes may be seen.[14]

Alteration in nail color

Punctate brown spots or longitudinal pigmented bands on nails are seen in Peutz-Jeghers syndrome.[19] Periorificial, mucosal and acral lentigines and gastrointestinal polyposis are the presenting features.

Longitudinal brownish bands on nails with adult-onset macular pigmentation of lips and buccal mucosa are suggestive of Laugier-Hunziker syndrome.[19] Purple nail bands in a child with coarse facies, progressive psychomotor retardation and angiokeratoma on skin and tongue are suggestive of fucosidosis.[19]

Diffuse blue discoloration of nail plate is observed in hereditary acro-labial telangiectasia.[19] Diffuse gray discoloration of the nail plates may be seen in erythropoietic protoporphyria and ochronosis.

Yellowish brown nail plates or leukonychia are seen in ectodermal dysplasias and KID syndrome. Koiloleukonychia may be seen in patients with LEOPARD syndrome.[19]

Alteration in growth rate

Classically poor nail growth is a feature of yellow nail syndrome, but may also be seen in lipoid proteinosis and various types of ectodermal dysplasias.

In acrodermatitis enteropathica (chronic stage) there is complete arrest of nail growth, associated with sparse hair or total alopecia. Following repletion of zinc, nail plates show Beau's lines.

The list of genodermatoses with nail changes is endless. However, many of such disorders are practically rare. Moreover, very few disorders are associated with specific nail changes. So nail changes may guide a clinician to differentiate a genodermatosis from an array of similar-looking disorders but does not provide conclusive diagnosis. In all such cases a diagnostic algorithm may be figured out depending upon associated features like other cutaneous or systemic manifestations, hair and teeth involvement, facial morphology and skeletal anomalies. Figure 8 presents a diagnostic approach to patients presenting with onychodystrophy. Definitive diagnosis of any genodermatosis is possible only by genetic studies but examination of nails may be an important step in this process.

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