Nail Changes in COVID-19: A Cross Sectional Study From India

Abstract

Background: Various nail manifestations have been reported with COVID-19; mostly in the form of isolated reports. Objective: This cross-sectional study was carried out to assess nail changes in hospitalized patients with moderate to severe COVID-19. Methods: Nail findings in 43 adults being treated for COVID-19, were evaluated after obtaining informed written consent. Nail changes involving fingernails and toenails were documented as new-onset or pre-existing changes. Disease status, hematological and biochemical tests, inflammatory markers, treatment administered and outcomes were also recorded. The frequency of changes in fingernails and toenails were statistically compared. Results: The red half-moon sign (32.5%) and nail bed erythema (34.8%) were the commonest changes seen in fingernails; while apparent leukonychia (46.5%) and distal brown discoloration (51.1%) were commonest changes in toenails. The difference in frequency of changes seen between fingernails and toenails was statistically significant (p < 0.05). Nail changes correlated with systemic involvement in these patients. Limitations: Single-center evaluation in a limited number of patients, without using augmented examination techniques like onychoscopy, nail fold capillaroscopy, or fluorescense. Those with less severe disease or with rapid fatality could not be studied. Conclusion: Nail changes in COVID-19 are common and reflect the systemic nature of illness, being a harbinger of underlying complications.

Keywords: Apparent leukonychia, COVID-19, Delta variant, India, nail, nail bed erythema, red half-moon, SARS-CoV2

Introduction

The nail unit is a ‘window to systemic disease’, thus serving as an alarm for physicians regarding various illnesses.\(^1\) Expectedly, nail manifestations have been reported with COVID-19 (Coronavirus Disease) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) virus, the pandemic illness ravaging our world from March 2020.\(^2\)\(^-\)\(^7\) However, these are mostly in the form of isolated reports of individual findings, in one or few patients, belonging to different age groups, severity of disease and geographical areas.\(^8\)\(^-\)\(^13\) To the best of our knowledge, no comprehensive study has been carried out evaluating the spectrum of nail changes associated with COVID-19 or their incidence.

We in India, were hit by a deadly second wave of resurging COVID-19 infection in the first half of 2021, propelled by SARS-CoV2 variants B.1.617.1 and B.1.617.2 (Kappa and Delta variants).\(^14\) We analyzed the nail changes in patients with moderate to severe COVID-19 admitted under our care during this resurgence of cases during April- May 2021.

Methodology

COVID-19 patients admitted under our care in COVID High Dependency Unit (HDU) were evaluated after stabilizing their condition. Post their admission, patients were initiated on treatment as per institutional protocol and disease stage. Those not improving or not able to maintain oxygen saturation were transferred to Intensive Care Units for invasive ventilation, when needed. Among patients stabilized in our HDU and continued on therapy, details of mucocutaneous changes including nail changes were recorded. The study was carried out in accordance with Code of Ethics of World Medical Association (Declaration of Helsinki) for experiments involving humans. Data was recorded and analyzed in an anonymized fashion.

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After obtaining an informed written consent, nail findings were recorded for fingernails and toenails, as new onset changes and pre-existing changes, based on the clinical appearance and/or patient history. Data regarding onset and progression of COVID-19, days of illness, treatment administered, clinical status, hematological, biochemical, serological investigations and final outcome were also recorded. The day of clinical symptom onset was taken as the reference point.

Nail examination included meticulous examination of nail unit and periungual area along with clinical photography, done in good light after completely removing any traces of nail paint, and cleaning the surface. Persistent exogenous pigment (residual henna, hair color remnants etc.) were separately recorded. Augmented examination with dermoscopy, Wood’s lamp or capillaroscopy, or other investigations like direct microscopy or nail biopsy, could not be done due to non-availability of the equipment bedside, the need to minimize duration of exposure to health care workers, and the emergent nature of the condition in many patients.

Recorded data was statistically analyzed using Microsoft Excel® v2016. Frequency of morphological changes in fingernails and toenails was calculated. These were compared using Student’s t-test to verify the hypothesis of independence of variables at a 5% significance level. A $P$ value $\leq 0.05$ was considered as significant.

**Results**

A total of 55 patients (32 males and 23 females) were admitted with COVID-19 during April-May, 2021, in dermatology ward of a tertiary care teaching hospital, converted to COVID HDU. Their mean age was 55.4 ± 14.5 years (range 26-92 yrs). Of these, 46 had severe COVID-19 while 9 had moderate disease. Diagnosis was confirmed by RT-PCR test (46 patients), Rapid antigen test (5), or chest CT scan with corroborative findings (4). Their comorbidities included pre-existing diabetes (16), hypertension (18), hypothyroidism (3), asthma, obstructive airway disease, previous cerebrovascular accident, coronary artery disease (2 patients each), and neurodegenerative disease (1).

Patients were initiated on COVID-19 treatment as per institutional protocol including oxygen (mode determined by oxygen saturation (SpO2) at presentation and during the course of stay), anticoagulation (low-molecular weight heparin), and antibiotics (including doxycycline, azithromycin, ceftriaxone, piperacillin-tazobactam, teicoplanin, chosen based on patient’s condition or co-morbidities). Corticosteroid administration was based on disease stage, extent of desaturation, patient weight, serum levels of inflammatory markers and presence of comorbidities. Dexamethasone, methylprednisolone and prednisolone were used, with 21 patients receiving pulse methylprednisolone (125 mg twice a day for 3 days). Remdesivir (22 patients) or Favipiravir (2) were administered to patients in early phase after determining renal and liver function. Known diabetics or those with deranged blood sugars during treatment received insulin therapy (25 patients).

Of the 55 patients, 10 were transferred for intensive care while 2 expired early. Rest 43 patients, stabilized in our HDU, were examined in detail as per protocol. By this time, their mean Spo2 was 86.3 ± 10.7% (range 40-97%) on room air, while 21 were still on supplemental oxygen (10-15 L/min). Nail examination was done on an average of 17.8 ± 6.7 day of their illness (range 8-38th day), with the date of symptom onset being taken as day 0. Mean age of examined 43 patients was 53.04 ± 14 years (25 males, 18 females). Recent onset changes were found in 32/43 (74.4%) patient’s fingernails and 36/43 (83.7%) patient’s toenails. Pattern and frequency of these changes with differences in toenails and fingernails are outlined in [Table 1].

The commonest finding in fingernails was nail bed erythema [NBE] (15, 34.8% patients) in varying patterns, including central, distal, transverse or longitudinal [Figure 1a, b, c]. The ‘red half-moon sign’ was seen in 14 (32.5%) patients, mostly located on either or both thumbnails but also viewed on other fingernails [Figure 2a, b]. Apparent leukonychia was also common, seen in 11 (25.5%) patients in varying patterns, including half-and-half nails (5) and Muehrcke’s transverse white bands (3) [Figure 3]. A distinctive distal brown discoloration representing a prominent onychodermal band was seen in 6 (13.9%) patients [Figure 4]. Splinter hemorrhages could be visualized in fingernails of 4 (9.3%) patients [Figure 5].

| Table 1: Comparative frequency of nail and periungual manifestations in fingernails and toenails in patients with COVID-19 (n=43) |
|-----------------|-----------------|-----------------|------------------|
| Nail changes | Fingernails (n/%) | Toenails (n/%) | $P$ |
| No changes | 11 (25.5%) | 7 (16.2%) | 0.37 |
| Nail bed erythema (NBE) | 15 (34.8%) | 4 (9.3%) | $<0.005^*$ |
| Red half-moon sign | 14 (32.5%) | 1 (2.3%) | $<0.005^*$ |
| Apparent leukonychia | 11 (25.5%) | 20 (46.5%) | 0.027* |
| Half and half nails | 5 (11.6%) | 5 (11.6%) | 1 |
| Muehrcke’s bands | 3 (6.9%) | 7 (16.2%) | 0.15 |
| Distal brown discoloration | 6 (13.9%) | 22 (51.1%) | $<0.005^*$ |
| Splinter hemorrhages | 4 (9.3%) | 2 (4.6%) | 0.42 |
| Vasculitic/periarticular lesions | 0 (0) | 2 (4.6%) | 0.15 |
| True leukonychia | 0 (0) | 2 (4.6%) | 0.15 |
| Bluish discoloration | 1 (2.3%) | 0 (0) | 0.32 |
| Dotted lunula | 1 (2.3%) | 0 (0) | 0.32 |
| Recent onset melanonychia | 1 (2.3%) | 0 (0) | 0.32 |
| Subungual hematoma | 0 (0) | 1 (2.3%) | 0.32 |

$^*$|$P<0.05$ was taken to be significant

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*Grover, et al.: Nail changes in COVID-19*
Toenails showed distal brown discoloration as the most common finding (22, 51.1%) [Figure 6]. Apparent leukonychia was common (20, 46.5%), including patterns like half-and-half nails (5, 11.6%) and Muehrcke’s bands (7, 16.2%) [Figure 7]. NBE was much less frequent (3, 6.9%) than fingernails. Recent onset proximal nail fold (PNF) hyperpigmentation as well as vasculitic lesions suggestive of COVID toes were seen in 2 patients each (4.6%). True leukonychia, and splinter hemorrhages were seen with same frequency (4.6%). Red half-moon sign, and subungual hematoma (1 each) were seen. Overall, NBE and red half-moon sign were significantly more common in fingernails (p < 0.05) while apparent leukonychia and distal brown discoloration were significantly more common in toenails (p < 0.05).

Nail findings possibly unrelated to COVID included longitudinal melanonychia (12/27.9%), onychorrhexis (10/23.2%), punctate leukonychia, mega-lunula, Beau’s lines, exogenous discoloration (4/9.3% each), PNF hyperpigmentation (3/6.9%), pitting, onychomycosis, clubbing, and pterygium (1 case each) in fingernails. COVID unrelated findings in toenails included onychomycosis (17/39.5%), onychorrhexis (10/23.2%), Beau’s lines (8/18.6%), onychoschizia (5/11.6%), median canaliform dystrophy, onychomadesis, and ragged cuticle with hyperkeratotic nail folds (1 patient each).

Routine hematological investigations were largely within normal limits, with most patients presenting with initial low leukocyte counts and platelet counts, tending to recover over a week. Biochemical abnormalities were frequent in liver and renal function. Mean serum bilirubin was 0.76 mg/dL (normal 0.3-1.3 mg/dL); mean SGOT/AST (Serum glutamic oxaloacetic transaminase) was 100 U/L (normal 12-38 U/L); mean SGPT/ALT (Serum glutamic pyruvic transaminase) was 99.6 U/L (normal 7-41 U/L); mean ALP (Alkaline phosphatase) was 137.8 IU/L (normal 33-96 IU/L); and mean serum protein was 6.96 (normal 6.7-8.6 g/dL). Similar derangements in renal function included higher mean blood urea of 55.1 mg/dL (normal 15-43 mg/dL) and mean serum creatinine of 1.18 mg/dL (normal 0.5-1.2 mg/dL). Among the inflammatory markers, the mean values for IL-6 (interleukin-6) was 79.7 pg/Ml (normal <1.8 pg/ml), mean CRP (C-reactive protein) was 82.6 mg/dL (normal <10 mg/dL), mean serum ferritin was 1113.7 mcg/L (normal 10-248 mcg/L), and mean D-dimer levels were 391 ng/mL (normal 220-740 ng/mL).

Death was the outcome in 6/43 patients (mean 16.1 days; range 6-36 days), while 37 patients (67.2%) were discharged after a mean period of 24.8 ± 8.6 d (range 10-40 days).
Discussion

Since the pandemic has set in, nail and periungual changes with COVID-19 are being sporadically described in literature [Table 2]. However, these are mostly isolated reports describing individual signs. Variables like the effect of drugs, duration of disease, fingernails versus toenails, organ systems involved etc., have been incompletely documented in most. There are no previous reports from the Indian subcontinent. Hence, we conducted this cross-sectional study to capture comprehensive data regarding nail manifestations during an unprecedented COVID crisis affecting the nation’s capital.

The nail as a unit can provide valuable information regarding COVID-19 systemic involvement.[19] This was borne out in our study where changes like nail bed erythema and apparent leukonychia formed the predominant manifestations. In fact, nail changes help us draw parallels in COVID with previously known multisystem illnesses like the Kawasaki disease,[15] helping understand the disease course. Though the pathogenesis of most of the nail changes reported in COVID-19 is not conclusively known, they might be closely related to the known key components of this disease viz. inflammation and predisposition towards intravascular coagulation. The nail unit, especially the nail bed, being a very vascular structure, is likely to be affected and demonstrate changes signifying both these anomalies. In addition, nail changes associated with hepatic or renal derangement, deranged blood sugars, altered serum proteins etc., are also reflected. An earlier study documented microcirculatory disorders arising from thrombosis, to be the most important factor determining the pathogenesis.
Table 2: Nail changes in COVID-19 described in literature

| Year   | Author                      | Nail Changes described                  | Number of patients | Patient details                          | Treatment received                                           |
|--------|-----------------------------|----------------------------------------|--------------------|------------------------------------------|-------------------------------------------------------------|
| 2020   | Kolivras et al.[2]          | COVID-19 chilblains                    | 1                  | 23 yr/M; Low grade fever; cough          | -                                                           |
| 2020   | Alobaida and Lam[3]         | Beau’s lines                           | 1                  | 45 yr/M; Mild COVID-19 disease           | Hydroxychloroquine, Lopinavir-ritonavir, ceftriaxone, heparin |
| 2020   | Neri et al.[4]              | Red half-moon nail sign                | 1                  | 60 yr/F; Moderate disease                | Hydroxychloroquine, Azithromycin, Oseltamivir, ceftriaxone   |
| 2020   | Senturk and Ozdemin[5]       | Onychomadesis                          | 1                  | 47 yr/F; Moderate disease                | Hydroxychloroquine, Azithromycin, Oseltamivir, ceftriaxone   |
| 2020   | Méndez -Flores et al.[6]    | Red half-moon nail sign                | 1                  | 37 yr/F; Mild COVID 19                  | Domiciliary management                                      |
| 2020   | Ide et al.[7]               | Beau’s lines, leukonychia              | 1                  | 68 yr/M; Moderate-severe                | Hydroxychloroquine, 6-MP                                     |
| 2021   | Guider and Ozunal[8]        | Nail fluorescence (blue)               | 6                  | 22-44 yr; 3 M; 3 F                     | Favipravir                                                  |
| 2021   | Kayiran MA et al.[9]        | Nail fluorescence (green)              | 4                  | 19-33 yr; 1 M; 4 F                     | Favipravir                                                  |
| 2021   | Tammaro et al.[10]          | Orange discoloration                   | 1                  | 89 yr; F                                | -                                                           |
| 2021   | Fernandez-Nieto et al.[11]  | Transverse leukonychia                 | 1                  | 47 yr/M; Mild disease                   | Lopinavir-ritonavir combination                              |
| 2021   | Ladozhskaya-Gapeenko EE et al.[12] | Capillary micro-aggregates (100%), irregular blood flow, pendulum like movements, stasis, avascular zones. | 11 | ICU admissions with acute respiratory failure | Nail bed capillaroscopy done |
| 2021   | Gülseren- and Yalcin-Armagan[13] | Nail fluorescence (yellow-white)       | 4                  | 26-46 yr                                | Favipravir                                                  |
| 2021   | Present study               | Distal brown discoloration, Apparent leukonychia, nail bed erythema, nail bed erythema, red half-moon sign, splinter hemorrhages etc. | 43 | 26-92 yrs; 25 M; 18 F Moderate to severe COVID-19 infection | Oxygen, corticosteroids, low molecular weight heparin, remdesivir, favipravir, azithromycin, doxycycline, ceftriaxone, etc., |

of organ damage in severe COVID-19.[12] This may also hold true for nail. Much of this microvascular damage could be complement mediated,[16] and the nail unit could be an important window reflecting the occurrence of such changes. Similar mechanisms could explain the presence of splinter hemorrhages in our patients.

The first report of a novel nail manifestation of COVID-19 appeared in Nov 2020[4] in the form of “red half-moon sign”, reported in a 60 year old lady, 2 weeks after onset of COVID symptoms. It was seen as a distally convex, erythematous band, involving all fingernails and bordering the lunula, persisting for more than a month and growing wider. The next report by Mendes-Flores et al.[6] reported its onset after 2 days and persistence for a week only. As previously reported by Lindsley, Kawasaki disease is also characterized by transverse bands of erythronychia, but located more distally.[17] In our series, we saw the red half-moon sign in fingernails of 32.5% patients involving the thumbs mostly, but also in the great toenail in a patient. Importantly, in a similar proportion, nail bed erythema (diffuse, patchy, transverse or longitudinal) was a prominent finding. Red half-moon sign could in fact be analogous to transverse erythronychia, bordering the lunula. It has also been proposed to be a gross manifestation of disorder of microcirculation in patients with COVID-19.[12] The nail bed having more vascularity than the nail matrix, reflects vascular changes more prominently, explaining the marked erythema just next to the lunula which is an abrupt border of transition between these two epithelia. Varying times of onset have been attributed probably because of a spectrum of changes possible due to variable effect on nail bed microcirculation.

Chilblain-like lesions or COVID toes were described as acute onset, infiltrated and painful papules to plaques involving toes in pauci-symptomatic young patients.[2] Our patients had more severe disease with none reporting such acute-onset symptomatic papules. However, few resolving lesions were identified in two patients at the time of examination. Chilblain-like lesions reflect COVID induced microangiopathic changes, and signify a better prognosis. Periungual desquamation has been described as a manifestation of MIS-C (Multi-system Inflammatory Syndrome in Children) which could be a COVID-19 manifestation.[18] Another case in an adult has been described as well.[19] None of our patients were children, and none had this manifestation. Beau’s lines, also known as ‘COVID nails’, are seen 1-3 months after the onset of symptoms.[13] Though Beau’s lines were present in many of our patients [Table 1], their depth, width, and distance from the proximal nail fold suggested origin preceding COVID-19 illness.

Nail fold and nail bed capillaroscopy can offer more insights towards the microcirculatory changes
accompanying COVID-19,[12-20] as the horizontally lying capillaries in these locations, permit detailed evaluation of their morphology and flow. However, we could not perform this study. Another manifestation reported is nail and hair fluorescence correlated with the intake of Favipiravir, though it is not clear whether the drug or its active metabolite is responsible.[8,9,13] Though Favipiravir was administered to a few of our patients, we could not elicit the nail or hair fluorescence in our patients.

Another notable finding reported in literature is transverse orange chromonychia, involving the distal nail bed, seen up to 16 weeks after the episode of COVID.[10] It appears 5-8 days after illness onset, involves distal half of nail bed and migrates distally. Authors proposed it to be a result of closely spaced splinter hemorrhages, which may or may not be associated with onycholysis. Similar features have been described in Kawasaki disease.[10] Though none of our patients were followed up longitudinally, we could see yellowish brown discoloration involving toenails in a 35 year old male with severe COVID-19, in the third week of illness. Though the correlation with COVID cannot be confirmed, there was no other apparent cause. Other than this, clearly visualized splinter hemorrhages were seen involving fingernails more commonly than toenails.

Apparent leukonychia is a marker of systemic diseases, known to reflect changes in nail bed vascularity, and can present in various patterns.[11] This was seen in a substantial number of our patients. Terry’s nails were initially described in cirrhosis as a distal, thin, pink to brown, transverse band (0.5–3.0 mm wide which doesn’t get obscured), with white or light pink proximal nail, with or without the lunula.[21] They have since been described in many other disorders including chronic congestive heart failure, adult-onset diabetes, and even as an isolated nail finding. In our patients, the prominence of the distal pink/brown band (termed the onychodermal band by Terry[22]) was seen predominantly on the toenails. Half-and-half (Lindsay’s) nails was another pattern commonly seen in our series. Described in chronic renal disease, this pattern has a 20–60% wider distal red-brown band as compared to Terry’s nails.[1] Muehrcke’s lines accompany severely low serum albumin,[23] probably resulting from vascular compression within the nail bed because of local edema. They have also been associated with multiple etiologies including nephrotic syndrome, liver cirrhosis, severe malnutrition, anticancer therapy,[24] severe cachexia in AIDS,[25] Cushing’s syndrome,[26] and even in patients with transient hypoalbuminemia,[27] or normoalbuminemia.[28] They were seen in many of our patients, both with normal and reduced serum proteins.

Nail matrix, even though less vascular, is known to be affected with COVID-19. True leukonychia akin to Mee’s lines was reported earlier on, signifying defective nail matrix keratinization.[17] Ide et al.[7] reported a patient with simultaneous Beau’s lines and true leukonychia clarifying that both changes are but different manifestations of the same matrix insult, the difference only being because of different parts of the matrix being affected to varying degrees. Onychomadesis is the outcome of a similar pathogenesis, albeit more severe. A longitudinal follow-up may have found an increase in the frequency of nail matrix manifestations like Beau’s lines, true leukonychia or onychomadesis.

Periungual nail changes include the desquamative changes reported with KawaCOVID like manifestation or chilblain-like lesions in younger patients.[29] Based on our data, we propose to classify nail changes associated with COVID-19, on the basis of the exact part of the nail unit affected [Table 3].

**Limitations**

This study was a single center, hospital based study involving a limited number of patients. The difference between pre-existing and new onset changes was difficult to establish conclusively. Relatively more severely affected cases were included, though the findings in a majority of less affected patients may be different. Very sick patients with rapid fatality or need for invasive ventilation could not be studied. The role played by drugs is also hard to determine. We could not perform augmented examination with dermatoscope or Wood’s lamp, or investigations like direct microscopy or biopsy, due to non-availability of routine facilities under COVID pressure.

**Conclusion**

Nail changes are a common occurrence in patients with COVID-19 and most of them reflect the systemic nature of the illness. The seemingly protean manifestations can mostly be explained by the vascular nature of the nail unit, showing early signs of ischemia and erythema. Some of the later changes could result from suppression of the nail matrix, disrupting nail growth. The red half-moon sign is seen in a large number of patients and involves fingernails (thumb nails) more commonly. Apparent leukonychia in various forms is a common finding, more often seen on toenails. These changes can be a harbinger of systemic involvement and subsequent complications.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
Table 3: Classification of nail and periungual changes reported with COVID-19

| Nail matrix changes                      | Nail bed changes                        | Nail fold changes                      |
|------------------------------------------|-----------------------------------------|----------------------------------------|
| Beau’s lines                              | Nail bed erythema (NBE)                 | Chilblain like lesions (COVID toes)    |
| True leukonychia (Mee’s lines)           | Red half-moon sign                      | Periungual desquamation (Kawa-COVID)   |
| Onychomadesis                            | Apparent leukonychia                    | Nail Fold capillaroscopic abnormalities|
| Bluish discoloration                      | Half and half nails                     | Vasculitic lesions                     |
| Dotted lunula                            | Muehrcke’s bands                        | Proximal nail fold hyperpigmentation   |
| Melanonychia (longitudinal bands)        | Distal brown discoloration              |                                        |
| Green/Blue/Yellowish white fluorescence  | Splinter hemorrhages                    |                                        |
| (favipiravir induced)                     | Subungual hematoma                      |                                        |
|                                          | Distal melanonychia                     |                                        |

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Nil.

Conflicts of interest

There are no conflicts of interest.

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