Nail changes associated with distal renal tubular acidosis (RTA) in pediatric patients

Miguel Ángel Cardona-Hernández[1]*, Leonel Fierro-Arias[2], Fermín Jurado Santa-Cruz[3],
Maribet González-González[4], Mónica Olivia Rivera-Martínez[5], Mónica Elizabeth De la Torre-García[6]
and Ana Luisa Cabrera-Pérez[7]

[1]Dermatologic oncology surgeon, Centro Dermatológico "Dr. Ladislao de la Pascua", México, D.F.; [2]Dermatologic oncology surgeon, Hospital General de Mexico "Dr. Eduardo Liceaga", Mexico, D.F.; [3]Director, Centro Dermatológico "Dr. Ladislao de la Pascua", México, D.F.; [4]Dermatopathologist, Centro Dermatológico "Dr. Ladislao de la Pascua"; [5]Dermatology fourth year resident; [6]Dermatology third year resident; [7]Dermatology second year resident

Abstract

Renal tubular acidosis is a disease prevalent in childhood, responsible for a decrease in growth due inadequate acid-base levels regulation. It is well known that systemic conditions can generate or accompany nail changes by different pathophysiologic mechanisms, however no one has ever found or reported any association of onychopathy with renal tubular acidosis so far. That is why we would like to share our experience on this topic. (Gac Med Mex. 2015;151:573-8)

Corresponding author: Miguel Ángel Cardona-Hernández, drmiguelcardona08@gmail.com

KEY WORDS: *Renal tubular acidosis. Nail disorders. Nails.*

Introduction

Renal tubular acidosis (RTA) encompasses a group of syndromes characterized by defects in renal tubular transport and in hydrogen ions secretion, but where normal glomerular function is maintained. It consists of hyperchloremic metabolic acidosis with anion gap at regular levels[1]. It is predominant in children and, although its incidence in our country is not known due to a lack of a registry of renal diseases, in 2006, García de la Puente reported a prevalence of 35 cases for every 10 thousand medical files in the National Institute of Pediatrics[2].

With regard to its pathogenesis, RTA can be primary or idiopathic (as well as transient or permanent) or secondary. It can be classified in 4 types, with the main being distal RTA (dRTA) or type I-RTA and proximal RTA (pRTA) or type II-RTA[3]. In the former, there is incapacity to reduce pH under 5.5[4], the secretion of hydrogen ions (H+) and ammonium is decreased in the collector tubule intertwined alpha cells[5], in addition to decreased regeneration of systemic bicarbonate, thus resulting in the development of chronic metabolic acidosis. There are two dRTA variants: one of them involves elevated urinary bicarbonate losses and is known as type III RTA; the other is associated with hyperkalemia and is referred to as hyperkalemic or type IV RTA[2]. In proximal or type II RTA, proximal alkali resorption is decreased, which causes bicarbonaturia and its ensuing serum reduction[2]. The degree of acidemia determines the development of calciuria,

Correspondence:

*Miguel Ángel Cardona-Hernández

Centro Dermatológico "Dr. Ladislao de la Pascua", SSDF

Dr, Vértiz, 464 Esq. Eje 3 Sur

Col. Buenos Aires, Del. Cuauhtémoc

C.P. 06780, México, D.F., México

E-mail: drmiguelcardona08@gmail.com

since the lower the blood bicarbonate, the higher the calcium urinary excretion[3].

The defect can involve only bicarbonate resorption or it can be part of a widespread proximal tubular dysfunction, which is known as Fanconi syndrome (glycosuria, hyperaminoaciduria and hyperphosphaturia)[4].

Within the clinical approach, the patient should be inquired on the use of aminoglycosides, carbonic anhydrase inhibitors, amphotericin B, lithium, potassium-sparing diuretics, non-steroid antiinflammatory drugs, angiotensin-converting enzyme inhibitors, cyclosporine and valproic acid, among other that can cause RTA[2].

Failure to thrive is the primary symptom of this condition and is detected by a decrease in weight and height gains. There can be vomiting, hyporexia, constipation, polyuria, polydipsia, predisposition to dehydration due to intercurrent gastrointestinal conditions, unexplained fever, which is resolved with water ingestion. Infants have developmental and dentition delay; these manifestations will depend on the biochemical abnormalities present. The development of urolithiasis and nephrocalcinosis is common in patients with dRTA[2].

Conversely, clinical manifestations and calciuria are not common in pRTA, and even less in the pediatric population[4]. Calcium urinary elimination is reported to be high in infants and to progressively decrease with age and, therefore, hypocitraturia is relevant in the development of nephrocalcinosis and urolithiasis, where mainly calcium phosphate salts are deposited[5].

On physical examination there are data that can suggest genetical disorders or renal malformations such as: deformity of the pinnas, lumbosacral spine and/or genitals abnormality. Also, masses occupying the kidneys, facial or body hemihypotrophy, triangular face and fifth finger clinodactyly[2].

To establish the diagnosis, performing a gasometry is very useful, where metabolic acidosis is found by a decrease of serum bicarbonate; partial CO_2 (PCO_2) pressure is reduced by respiratory compensation and pH is low or normal, with this dependong on the severity of acidosis. If the obtained sample is venous, consideration should be taken into the fact that pH is 0.02 U lower, PCO_2 is 4 mmHg higher and HCO_3 is 1 mEq higher. The general urine examination is with the first or second urine of the day without the patient having ingested fluids (for at least 8 hours in infants and 10 to 12 hours in older children); under these conditions, the pH is acidic (5.5) and urinary density exceeds 1.020 g/l[2].

Usual treatment of RTA consists of two stages, with the first aiming to correct metabolic acidosis immediately and to find the adequate maintainance dose with any alkalizer, such as sodium bicarbonate, potassium bicarbonate or citrate salts, to reach a HCO_3 serum concentration > 20 mEq/l in infants and > 22 mEq/l in schoolchildren[6]. Usual doses are 3 to 5 mEq/kg/day for dRTA and 10 to 15 mEq/kg/day for pRTA distributed in 4 doses per day. Mid-term objectives are weight and height gain according to the impact of the process on the patient[2]. If this treatment is not implemented, this condition produces failure to thrive and rickets in children and osteomalacia in adults with renal function deterioration over the years[5]. The most important complications are bone demineralization, hypotonia or muscle paralysis, nephrocalcinosis and further progression to chronic renal disease as a consequence of it or other original non-controlled entity[2].

Nail changes in systemic diseases

Nail alterations have been reported in many systemic conditions. Since the year of 1967, more than 40 clinical signs in the nails related to specific pathologies were already described[7]. An example of these are: koilonychia (marked nail concavity)[8], which is characteristic of ferropenic anemia and some syndromes such as Plummer-Vinson syndrome[9]. Watchglass nails have an increase in longitudinal and transverse curvature with fibrovascular hyperplasia of the tissue closest to the cuticle. The angle formed by the dorsal face of the distal phalanx and the nail (known as the Lovibond angle) may be increased and associated with pleuropulmonary neoplasms, such as bronchogenic neoplasm, bronchiectases, pneumonic abscesses, empyema, pulmonary cystic fibrosis, etc. It has also been used as a marker of arteriovenous malformations, celiac disease, cirrhosis, inflammatory bowel disease and AIDS[9].

Another example of nail signs are Muehrcke's lines, whitish, narrow and transverse, usually pairwise distributed; these are associated with hypoalbuminemia, malnutrition and nephrotic syndrome[10]. Mees' lines (broader than the latter) can be single or multiple, characteristically occurring in arsenic or thalium poisoning, are also associated with empyemas, cyclosporine use, generalized lupus erythematous and exposure to chemotherapy. Beau's lines (transverse depressions on the nail plate) are secondary to delay or temporary block of growth, and can be caused by leukemia,

Table 1. Summarized data of the cases

Patient	Age	Sex	Nephrological diagnosis	Onychopathy evolution time	Topography	Other data	Nail changes
Case 1	4 years	Male	Primary distal RTA	4 months	3th and 4th fingers of both hands	Height and weight below the percentiles	Whitish-yellowish proximal band. Proximal onychomalacia
Case 2	7 years	Female	Primary distal RTA	5 months	1st and 4th fingers of right hand	Perforating reactive collagenosis diagnosis	Whitish transverse proximal band. Red-brown distal discoloration. Onychomalacia.
Case 3	5 years	Female	Primary distal RTA	1 year	5th finger of left hand	Atopic dermatitis diagnosis	Whitish transverse proximal band. Onychomalacia. Longitudinal striae. Reddish distal discoloration.

chemotherapy, chronic hypoxia, treatment with steroids, recurrent trauma or by prolonged stays in intensive care units[9].

"Half-and-half" nails are characterized by a proximal whitish coloration that is abruptly interrupted at 20 or 60% of the distal portion, which is pink, red or brown in color, and can occur both in hand and toe nails[11,12]. In 1962, Bean and Clifton described a distal reddish discoloration in the nails of two patients with azoemia; one year later, Lindsay concluded that this pattern is characteristic of these changes, thereby receiving his name[7]. These changes have been associated with exposure to chemotherapy and are only an occasional finding, but specific to chronic renal disease, with an estimated prevalence of 15 to 50%[8].

Terry's nails (especially occurring in advanced liver disease) show compromise in less than 20% of total distal and longitudinal band of the plate[13]. This abnormality is also found in congestive heart disease, diabetes mellitus, thyrotoxicosis, malnutrition and, physiologically, in geriatric patients[14]. Its pathophysiogenic mechanism is unknown, but an increase in the capilary network, with telangiectases in the proximal and distal band, has been proposed as probable cause. Seriousness of nail changes has not been correlated with distal band color tone or width, with levels of hypoalbuminemia, anemia or with cirrhosis severity[15]. It is possible for changes to be due to cell immunity depletion, systemic immunosuppression, ferropenia or hypoalbuminemia-associated tissue edema, and a viral etiology has not been demonstrated[16]. The appearance of transverse leukonychia is attributed to a temporary growth (onycogenesis) dysfunction or rather to some systemic condition causing abnormal keratinization, especially in the inner border of the plate.

In the histopathological field, nucleated cells with keratohyalin granules are observed[17]. In most the above mentioned conditions, the exact pathophysiogenic mechanism by which nail changes are produced is not yet well known[18].

Nail changes and renal disease

"Half-and-half" or Lindsay nails are a frequent finding in subjects with renal conditions; they occur in patients with some degree of nitrogen compounds elevation, especially uremia, with no correlation with the severity of the process[18,19]. Cases have been also described in patients on chemotherapy treatment, with zinc deficiencies, hepatic cirrhosis, Kawasaki's disease and, recently, Crohn's disease[14]. Changes do not disappear with finger pressure or are modified with nail growth, which implies assuming that there is damage at the level of the nail bed rather than the matrix. Histologically, an increase in the number of capillaries and the thickness of their walls is observed in the zone corresponding to the bed. There are also melanin deposits in the distal portion of the nail, which suggests that renal failure would lead to an increase in melanocitic activity and to secondary melanonychia[18]. They have also a high incidence in patients on hemodialysis, in whom the time on dialysis has been shown not to be the cause of these changes, but chronic elevations of urea levels. Nail changes do not improve with the implementation of treatment with dialysis, but sometimes they do with renal transplantation[20]. Other hypotheses

Figure 1. *Transverse white-yellowish band with proximal onychomalacia zones and erythematous distal zone at 4th finger of right hand.*
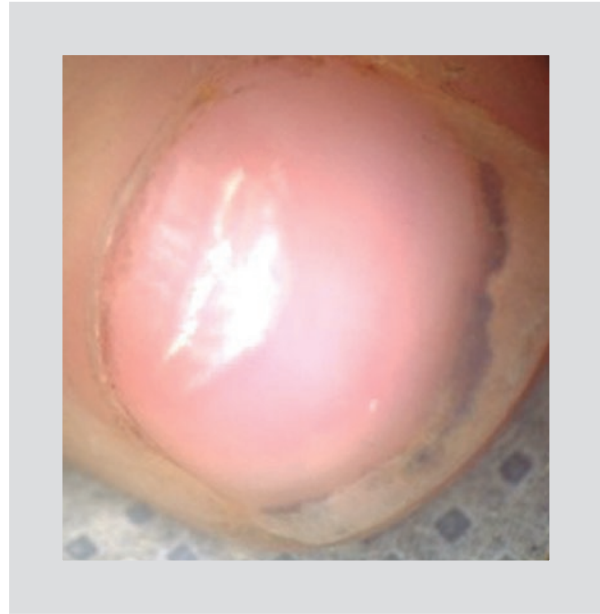

Figure 2. *Central transverse leukonychia band with distal reddish discoloration at 1st finger, right hand.*

mention that, due to poor filtration by dialysis, there is an elevated tissue concentration of beta-melanocyte-stimulating hormone. Lindsay proposed that manifestations were due to permanent venous constriction in the bed, which over time caused a particular dyschromia[18]. There is no reported correlation between the band thickness and duration or severity of renal disease, age, sex, proteinuria or other clinical or paraclinical parameters. The exact mechanism by which Lindsay's nails are produced remains uncertain[21].

Renal conditions have been mentioned as promoters of abnormal globulin deposits in the nails, conferring them the previously mentioned distinctive appearance; this is reported in 35% of the patients with chronic renal failure, in 20% of those with acute renal failure and only in 20% of people without concomitant uremia[22].

Description of cases

Case 1. Four-year-old preschool male patient, diagnosed with distal primary RTA on treatment with sodium citrate at 4 mEq/kg doses, with nitrogen compounds within normal levels and without complications associated with renal disease. He consulted because of the presence of nail changes developing over the previous 4 months. He had received topical treatment with miconazole and cyclopyroxolamine cream for 4 months without having experienced any improvement. On physical examination, changes were observed at the

proximal zone of the 3rd and 4th fingers in both hands, characterized by a proximal transverse white-yellowish band, which did not show any changes with finger pressure, with abrupt interruption when reaching 50% of the plate, with areas of onychomalacia and a red to brownish band found at the distal portion (Fig. 1). No other pathological signs were found on the rest of the skin and annexa. He had weight and height below the percentiles established for his age. Direct mycological testing was performed, which was negative, and treatment was started with hydroxypropyl-chitosan and methylsulphonylmethane (sulfur source) repairing lacquer applied at nights.

Case 2. Female patient, a seven-year-old school girl with a diagnostic history of primary distal RTA without current treatment. Nitrogen compounds levels were within normal parameters and without renal disease-associated complications. Present complaint was a suspected onychomycosis on the 1st and 4th fingers of the right hand, and she referred 5 months of evolution with no previous treatment indication. She denied ingesting other medications. Nail abnormalities were identified on the 1st finger, consisting of a transverse leukonychia band at the central proximal zone of the plate, without changes with finger pressure and with a marked reddish distal discoloration (Fig. 2) and at the level of the 4th finger, similar changes with greater width of the proximal whitish band and areas of onychomalacia (Fig. 3). In the rest of the skin and annexa, we found
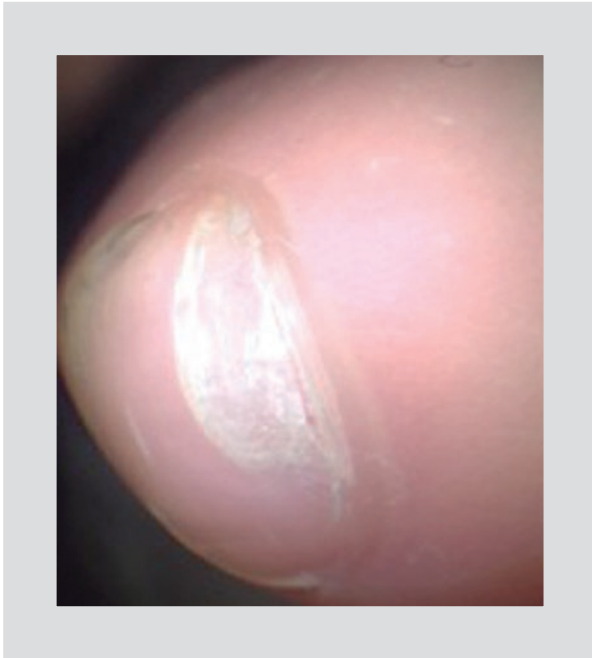
Figure 3. *Proximal transversal leukonychia band affecting 50% of the plate with abrupt demarcation, interrupted by intensely red distal zone.*
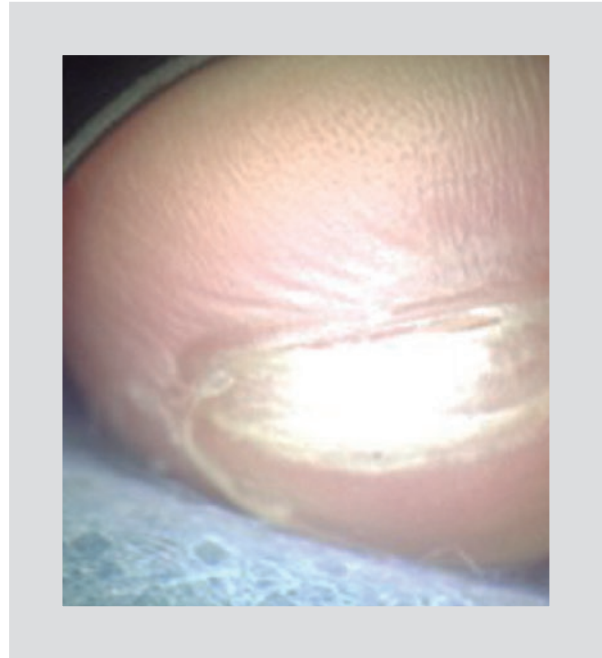

Figure 4. *Transverse leukonychia band, discrete striae with proximal onychomalacia and intensely red distal portion at 5th finger, left hand.*

crateriform lesions on upper and lower limbs consistent with reactive perforating collagenosis, which was corroborated by pathology; the patient was on treatment with topical retinoids, emollients and photoprotective agents. Weight and height were within established percentiles. Fungal infection was ruled out by means of direct testing and treatment was given with a topical panthenol, propyleneglycol and urea nail-repair preparation every 12 hours.

Case 3. Five-year-old female patient, a pre-school girl diagnosed with primary distal RTA on treatment with sodium citrate at 5 mEq/kg, with restored levels of nitrogen compounds and no renal disease-associated complications. She was referred to our specialty by her pediatrician to rule out onychomycosis of 1-year evolution. She had received treatment with terbinafine cream for 3 months with no improvement at all. She denied ingestion of any medication that could be associated with nail deterioration. On examination, abnormalities were found on the 5th finger of left hand, where a transverse leukonychia band affecting 50% of the proximal plate was observed, with areas of onychomalacia and abrupt interruption with marked redish distal zone (Fig. 4). In the rest of the skin and annexa, we found atopical dermatitis mild in severity on treatment with emollients, calcineurin inhibitors and sunscreen. Fungal infection was ruled out and treatment with lacque, similar to that of the first case, was indicated.

Comment and conclusions

The presented cases were referred by the Pediatrics Department already with the distal RTA diagnosis, which is the most common variety in the child population. No syndromic associations were found in the patients, but case number 1 had a history of a relative with short stature. The main complaint in the Pediatrics Department was failure to thrive, although no weight or height was identified outside the current percentile ranges for the Mexican population. None of the cases had clinical or paraclinical data of renal disease or renal failure, and there was no nitrogen compounds elevation that would compromise the function in this organ. No history of ingestion of any medication that might expose to any nail abnormality was identified in the history taking. Of note, in cases 2 and 3, concurrence was found of nail changes with the diagnoses of reactive perforating collagenosis (histologically confirmed) and atopical dermatitis, respectively.

Noteworthy, the described changes were not modified with finger pressure and did not show alterations with nail plate growth, which suggests a probable alteration at the level of the bed rather than the matrix.

Two of the three patients received previous topical antifungal therapy without any response. Mycological testing, performed in all patients for presumptive diagnosis, was negative, which ruled out fungal infection

etiology and only therapy with water-based nail repair agents was indicated, with sources of sulfir, silica, urea and collagen precursors.

It is important mentioning that the nail changes, identified by the patients' parents, occurred at least 4 years after the RTA diagnosis and after having implemented therapy with alkalizing agents and citrates in two of the cases. Nail abnormalities did not cause any symptoms at al, and the main reason for consultation with our specialty was their altered appearance.

In this work, we report on a small sample corresponding to a case series, and for this reason we cannot establish that distal RTA has direct correlation with or is the main reason to develop onychopathy. To our knowledge, and after a literature review, we did not find reports showing nail changes associated with this entity. To elucidate the cause or a strict association, further studies are required including a larger sample of the affected population. The relevance of this report lies in communicating the observed association, hoping that it serves in the future as a point of reference for subsequent works.

References

1. Batlle D, Haque SK. Genetic causes and mechanisms of distal renal tubular acidosis. Nephrol Dial Transplant. 2012;27(10):3691-704.
2. García de la Puente S. Acidosis tubular renal. Acta Pediatr Mex. 2006; 27(5):268-78.
3. Basu G, Sudhakar G, Mohapatra A. Renal tubular acidosis. Clinical queries: nephrology. 2013;2:166-78.
4. Peces R, Arrieta J, Batlle DC. Mecanismos y clasificación de la acidosis tubular renal. Nefrología. 1992;11(3):217-23.
5. Escobar L, Mejía N, Gil H, et al. La acidosis tubular renal distal: una enfermedad hereditaria en la que no se pueden eliminar los hidrogeniones. Nefrología 2013;33(3):289-96.
6. Gil-Peña H, Mejía N, Santos F. Renal Tubular Acidosis. J Pediatr. 2014; 164(4):691-98.
7. Lindsay PG. The half-and-half nail. Arch Intern Med. 1967;119(6):583-7.
8. Ocampo Chaparro JM, López GM. Coiloniquia asociada con ferropenia. Rev Med Risaralda. 2012;18(2):181-2.
9. Carrillo Esper R, Carrillo Córdova JR, Carrillo Córdova LD, et al. Alteraciones ungueales como marcador de enfermedad sistémica. Med Int Mex. 2010;26(3):243-9.
10. Short N, Shah C. Muehrcke's Lines. Am J Med. 2010;123(11):991-2.
11. Huang WT, Wu CC. Half-and-half nail. CMAJ. 2009;180(6):687.
12. Pérez Juárez B. El lenguaje de las uñas. Más Dermatol. 2011;15:4-12.
13. Pellegrino M, Taddeucci P, Mei S, et al. Half-and-half nail in a patient with Crohn´s disease. J Eur Acad Dermatol Venerol. 2010;24:1359-69.
14. Mendiratta V, Jain A. Nail dyschromias. Indian J Dermatol Venereol Leprol. 2011;77:652-8.
15. Li Z, Ji F. Terry's nails. Braz J Infect Dis. 2012;16(3):311-2.
16. Salem A, Gamil H, Hamed M, et al. Nail changes in patients with liver disease. J Eur Acad Dermatol Venerol. 2010;24:649-54.
17. Fujita Y, Sato-Matsumura K, Doi I, et al. Transverse leukonychia (Mees´ lines) associated with pleural empyema. Clin Exp Dermatol. 2006;32: 127-8.
18. Markova A, Lester J, Wang J, et al. Diagnosis of common dermopathies in dialysis patients: a review and update. Semin Dial. 2012;25(4):408-18.
19. Fernández Sánchez M, Orozco Topete R. Dermatosis en pacientes con insuficiencia renal crónica terminal. Dermatología Rev Mex. 2011;55(6): 352-8.
20. Dyachenko P, Monselise A, Shustak A, et al. Nail disorders in patients with chronic renal failure and undergoing haemodialysis treatment: a case-control study. J Eur Acad Dermatol Venerol. 2007;21:340-4.
21. Yu-Tzu T, Wei-Liang C, Shih-Hua L. The case. Do not forget nails. Kidney Int. 2008;74:395-6.
22. López Ibarra MM, Ledesma de la Torre CI. Frecuencia de las alteraciones ungueales en los pacientes internados en las áreas clínicas del Hospital de Especialidades del Centro Médico Nacional La Raza. Dermatología Rev Mex. 2003;47(2):71-6.