

# Acute-onset paralysis in a patient of rheumatoid arthritis

Ankur Nandan Varshney, Pratibha Prasad, Nilesh Kumar, Nand Kumar Singh

From the Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Correspondence: Ankur Nandan Varshney · Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India 221005 · T: 9411491192 · drankurnvarshney@gmail.com

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Renal tubular acidosis (RTA) is a disorder of renal acidification characterized by inability to acidify urine to pH <5.5 despite the presence of severe systemic metabolic acidosis and hypokalemia. Hypokalemia leads to acute-onset paralysis and may be a presenting manifestation of RTA. Its association with various autoimmune disease has been reported previously in published reports, but has not been much emphasized. We, hereby, report a case of RTA that presented during the flare of rheumatoid arthritis (RA). A 42-year-old female, a known case of RA for 5 years, presented with persistent joint pain for 1 week and acute-onset quadriparesis for 3 days. Primary investigations revealed hypokalemia with metabolic acidosis. She was managed conservatively with potassium supplements and bicarbonate supplements along with steroids and disease-modifying anti-rheumatic drugs. Such a presentation of renal tubular acidosis in a patient during the flare of rheumatoid arthritis is distinctly rare and previously unreported in published studies.

Rheumatoid arthritis (RA) is known to have wide extra-articular manifestations. Among these, renal involvement is well documented. Renal tubular acidosis (RTA) is a non-anion-gap (hyperchloremic) metabolic acidosis, which results either from proximal tubular bicarbonate wasting or impaired distal acid secretion. The hallmark of this entity is an inability to acidify the urine maximally (<pH 5.5) in the face of metabolic acidosis accompanied by hypokalemia, hypercalciuria and/or, nephrolithiasis. The association of RTA with various autoimmune diseases (SLE, Sjogren syndrome, hypothyroidism), though rare, have been reported previously.

The association of RTA with RA is distinctly rare, and the diagnosis of RTA during a flare of RA in a patient already on disease-modifying anti-rheumatic drugs is previously unreported. The presented case also highlights the role of autoimmunity in the pathogenesis of RTA.

## CASE

A 42-year-old female, a known case of RA for 1 year, presented with joint pain along with morning stiffness for 7 days, myalgia for 4 days, and weakness of all 4 limbs for 3 days. It was followed by an acute-onset weakness

of bilateral lower limbs (proximal > distal) followed by the weakness of upper limb and associated tachypnea (single breath count 12). There was no history suggestive of fever, impairment of higher neurological functions, cranial nerves/bladder/bowel involvement, raised intracranial tension, or history of high carbohydrate food intake. On a detailed enquiry, the patient gave the history of RA for 4 years, and she was on oral methotrexate (15 mg weekly) and folic acid (5 mg weekly) on a regular basis. The family history and personal history were insignificant. On examination, the patient was lean and thin with stable vital signs. Her general examination was normal except for mild pallor. There was swelling and tenderness present over multiple peripheral joints (bilateral metacarpophalangeal joint, wrist, and ankle). Her distal interphalangeal joints were slightly flexed, suggestive of swan neck deformity but not fully developed (**Figure 1**). The examination of cardiovascular, respiratory, and abdominal symptoms was unremarkable. Neurological examination revealed a power of 3/5 in the bilateral upper limb and 2/5 in the bilateral lower limb at all joints. All deep tendon reflexes were diminished, and the Babinski sign was negative. Sensory examination was completely normal.

On primary investigation in the emergency ward,



**Figure 1.** Clinical photograph of bilateral hands of the patient showing swan-neck deformity.

arterial blood gas analysis revealed pH 7.26 (acidosis), partial pressure of oxygen ( $PO_2$ ) 114.6 mm Hg, partial pressure of carbon dioxide ( $PCO_2$ ) 26.9 mm Hg, serum bicarbonate 12.9, anion gap 11, sodium 137 meq/L, and potassium 1.8 meq/L. The picture is suggestive of metabolic acidosis with compensatory respiratory alkalosis. Hemoglobin was 9.6 gm/dL with normal white blood and platelet counts. Liver function tests were normal. Fasting blood sugar was 82 mg/dL, blood urea nitrogen was 69 mg/dL, and serum creatinine was 1.84 mg/dL. Serum calcium and chloride levels were within normal limits; however, the serum magnesium level was slightly low (1.5 mg/dL). Urine analysis showed pH 6.8, urine osmolality 690 mOsmol/L, urine potassium level 154 meq/L, and trans-tubular potassium gradient 33.85, suggesting a renal loss of potassium. Urinary anion gap was positive favoring a diagnosis of distal or type I RTA. Urine calcium/creatinine ratio of a fasting urine sample was 0.62 ( $<0.4$ ). All inflammatory markers were increased (erythrocyte sedimentation rate=45 mm, C-reactive protein=37). Rheumatoid factor was 1054 IU/mL anti-citrullinated cyclic protein antibodies were 125 IU/mL, and the patient was negative for antinuclear antibodies and anti-double-stranded DNA antibodies. Thyroid profile was normal. Anti-TTG and cortisol levels were normal. Human immunodeficiency virus, hepatitis B surface antigen, and anti-hepatitis C virus were non-reactive. The ultrasonography of abdomen revealed that kidneys were normal in size with no evidence of calcification.

Treatment was initiated with intravenous and oral potassium and magnesium supplement. Metabolic acidosis was corrected with bicarbonate supplements. For RA, methotrexate was continued, and the patient was

shifted from hydroxychloroquine to leflunomide (20 mg daily). She was also given oral steroids to provide symptomatic relief. Hypokalemia got corrected over a period of 3 days, gradually improving the limb weakness. The patient was discharged on tablet sodium bicarbonate and syrup potassium chloride. Steroid was tapered after 15 days and was completely withdrawn after 1 month. The patient was in our follow-up for 3 months attending the rheumatology clinic regularly and was symptom free later. Her potassium levels, measured on 2 subsequent visits, were within normal limits.

## DISCUSSION

RA is a systemic autoimmune disorder with widely known extra-articular manifestations. These are more common in sero-positive patients especially those with high titers of rheumatoid factors.<sup>1</sup> Renal involvement is less common and could be a result of underlying disease activity or therapy related due to disease-modifying anti-rheumatic drugs. The usual renal manifestations are glomerulonephritis (usually mesangial), secondary amyloidosis, interstitial nephritis, and drug-induced side effects.<sup>2</sup> The clinical picture is of either persistent proteinuria, persistently elevated serum creatinine signifying the drug-related damage during the early course of disease, or isolated hematuria associated with the continued disease activity.<sup>3</sup>

Distal (classic or type 1) RTA is a familial or acquired disorder of the distal nephron characterized by failure to lower urinary pH resulting in a hyperchloremic metabolic acidosis. The underlying mechanism is not well understood, but the suggested mechanisms may include either a defective proton pump (secretory defect) or an unfavorable electrical gradient for  $H^+$  secretion (voltage defect) or back diffusion of  $H^+$  or bicarbonate (gradient or permeability defect).<sup>4</sup> An inability to maintain a pH gradient across the distal tubule could be attributed to a defect in the basolateral  $HCO_3^-/Cl^-$  exchanger or subunits of the  $H^+$ -ATPase. Distal RTA can also lead to nephrolithiasis secondary to hypercalciuria, hyperphosphaturia, hypocitraturia, and low urine.<sup>5</sup> A urine pH  $>5.5$  in the presence of non-anion gap systemic metabolic acidosis is diagnostic for distal RTA. The hypokalemia can be a presenting manifestation, and a patient of distal RTA can present as hypokalemic periodic paralysis.<sup>6</sup>

The cause of RTA may be primary (sporadic or inherited) or secondary. Sporadic and inherited cases can be the result of genetic defects in AE1 (anion exchanger 1; encoded by the SLC4A1 gene) or  $H^+$ -ATPase.<sup>6</sup> There is a case report of a child with profound hypokalemia that was assumed to have a defect in  $H^+$ ,  $K^+$ -ATPase

function.<sup>7</sup> There is a distinct form of endemic distal RTA that occurs in Thailand, especially in the summer. Possible causes include dietary potassium deprivation coupled with a high insensible loss of potassium from sweat or as a result of environmental vanadate intoxication.<sup>6</sup> Secondary causes include drugs (amphotericin, toluene, lithium carbonate).

Various autoimmune diseases have been found to be associated with RTA. These include Sjogren syndrome, systemic lupus erythematosus, primary biliary cirrhosis, cutaneous vasculitis, hench-scholein purpura, and hypothyroidism.<sup>8</sup> Out of these, the association with the Sjogren syndrome is most frequent, and a strong emphasis has been on this association including pathogenesis. A set of autoantibodies have been described against carbonic anhydrase II in patients of the Sjogren syndrome.<sup>9</sup> This association has been confirmed by inducing such antibodies in laboratories in animal models.<sup>10</sup> Li et al reported a series of 6 cases of patients of systemic lupus erythematosus with distal RTA, but a pathogenic association was not determined.<sup>11</sup> However, such detailed studies are lacking with regard to other autoimmune diseases particularly RA.

A study of immune-related distal RTA<sup>8</sup> that includes 34 patients with various autoimmune diseases (none of them had RA) finds that immune-related

distal RTA had similarities to immune-related potassium losing interstitial nephritis. Wrong et al reported in this study that both these aforementioned diseases share common characteristics of being common in post-pubertal females, hypokalemia, and having pronounced features of auto-immune diseases.<sup>8</sup> The only difference is the presence of metabolic acidosis in the RTA group.

Musculoskeletal complaints per se are not uncommon in distal RTA in the absence of rheumatologic disorders and can be a presenting manifestation too. Negi et al<sup>12</sup> reported a case of distal RTA who initially presented with musculoskeletal complaints, and later these complaints resolved after correcting hypokalemia. Harrington et al<sup>13</sup> reported a series of 48 patients out of which 25 had musculoskeletal complaints. These were attributed to hypokalemia and underlying bone disease.

Although the association of distal RTA with auto-immune disease is widely known, its presentation along with the flare of RA is distinctly rare and previously unreported. The exact mechanism is unclear, but it could be asserted that autoimmune diseases, such as RA, are associated with a multiple set of auto-antibodies, and any of these may cross-react with H<sup>+</sup> or K<sup>+</sup>-ATPase pump giving rise to RTA. However it is a matter of debate and invites more research in this area.

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