Concise Report

Symptomatic renal tubular acidosis (RTA) in patients with systemic lupus erythematosus: an analysis of six cases with new association of type 4 RTA

S. L. Li, L. B. Liou, J. T. Fang and W. P. Tsai

Objectives. We have analysed the association between different parameters of renal tubular acidosis (RTA) with clinical and laboratory parameters in patients with systemic lupus erythematosus (SLE).

Methods. Review of hospital database records between 1978 and 2003 revealed six SLE patients with RTA. Correlations and comparisons were done by Spearman rank correlation coefficient and the $\chi^2$ test.

Results. Four patients had hypokalaemia (type 1 RTA) and two patients had hyperkalaemia (type 4 RTA). Three patients with type 1, but no patients with type 4 RTA, had medullary nephrocalcinosis. The majority of SLE patients with distal RTA (type 1 and type 4) had nephritis with proteinuria. No seronegative SLE was noted, and all patients were negative for anticardiolipin antibodies. There was a noticeable trend of higher serum potassium levels with increased SLE Disease Activity Index (SLEDAI; $P<0.1$) and nephritic manifestation (haematuria, $P<0.1$). The mean SLEDAI scores were 11.75 and 27.5 for type 1 and type 4 RTA patients, respectively.

Conclusions. When present in patients with SLE, classic distal RTA (type 1) is the most common. In particular, we report here for the first time two cases of type 4 RTA in SLE patients with higher SLEDAI scores than patients with type 1 RTA. Medullary nephrocalcinosis or renal urolithiasis has not been found in our patients with type 4 RTA. Higher serum potassium levels seem to be associated with higher SLEDAI scores and more severe nephritic manifestations in patients with distal RTA.

KEY WORDS: Renal tubular acidosis, Systemic lupus erythematosus, Nephrocalcinosis.

Renal tubular acidosis (RTA) is a rare complication of SLE and can cause diagnostic difficulty [1]. Unfortunately, a delay in diagnosis may result in renal insufficiency [2]. Jessop et al. [3] observed impaired tubular reabsorption of phosphate and decreased urine acidification in two and seven of 12 such patients, respectively. It is therefore of vital importance to accurately diagnose RTA in a timely fashion for optimal management. Though single case reports on RTA in SLE patients have been presented in the distant past [4–8], a series has not been published since 1974. Therefore, we present six cases of RTA in SLE patients admitted to Chang Gung Memorial Hospital over a 25-yr period.

Methods and patients

We searched our hospital database for patients admitted between 1978 and 2003 who satisfied clinical- and chemical-diagnostic criteria for RTA and SLE. Six patients were identified. The patients had a normal anion gap metabolic acidosis, and all patients fulfilled the 1982 American College of Rheumatology criteria for SLE. The diagnosis of RTA and its subtypes were established based on arterial blood gas analysis, the calculated plasma and urine anion gaps, and the serum potassium level.

Demographic and clinical data were recorded for each patient, including age and sex, arterial blood gases, plasma and urine anion gap determinations, serum potassium levels, renal function tests, 24-h urine total protein excretion, renal ultrasonogram interpretation, anti-nuclear antibodies (ANA) and anticardiolipin antibody titres, urinalysis, SLE criteria, and concomitant diseases. The medical literature between 1960 and 2003 was searched with Medline using the keywords ‘RTA’ and ‘SLE’.

For statistical analysis, we used SPSS software (SPSS for Windows, version 10.0; SPSS, Chicago, IL, USA). Correlations were determined with the Spearman rank correlation coefficient, and comparisons were made using the $\chi^2$ test. A $P$-value <0.05 was considered statistically significant. Moreover, $P<0.1$ was interpreted as a noticeable trend or an apparent association, considering the rarity of this complication of RTA in SLE, for which it was difficult to collect a large number of cases.

Results

Demographic data

The mean age of the one male and five female patients was 26.5±4.5 yr (range 22–31 yr), and the mean duration of SLE prior to onset of RTA was 3 yr (range 0.1–8 yr; Table 1).
Renal tubular acidosis in SLE

Table 1. Clinical and laboratory data of six patients with RTA in SLE

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Duration of lupus (yr)</th>
<th>pH</th>
<th>HCO₃⁻</th>
<th>CO₂</th>
<th>Anion gap</th>
<th>Serum K</th>
<th>BUN Cr</th>
<th>24 h urine protein</th>
<th>Renal stone history</th>
<th>MN</th>
<th>UTI</th>
<th>Urine analysis</th>
<th>SLEDAI</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>7.0</td>
<td>7.045</td>
<td>17.3</td>
<td>23.8</td>
<td>8.0</td>
<td>3.0</td>
<td>15.9</td>
<td>3.20</td>
<td>Type 1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>36.2</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>8.0</td>
<td>7.324</td>
<td>21.0</td>
<td>36.3</td>
<td>5.0</td>
<td>2.9</td>
<td>ND</td>
<td>Type 1</td>
<td>Type 1</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>55.9</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>0.1</td>
<td>7.396</td>
<td>14.8</td>
<td>24.2</td>
<td>11.2</td>
<td>3.3</td>
<td>16.1</td>
<td>Type 1</td>
<td>Type 1</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>154.0</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>0.1</td>
<td>7.276</td>
<td>17.2</td>
<td>38.2</td>
<td>12.0</td>
<td>2.6</td>
<td>21.1</td>
<td>Type 1</td>
<td>Type 1</td>
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<td>Yes</td>
<td>Yes</td>
<td>82.0</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>3.0</td>
<td>7.340</td>
<td>13.0</td>
<td>24.2</td>
<td>9.0</td>
<td>6.5</td>
<td>89.3</td>
<td>Type 4</td>
<td>Type 4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>71.5</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>0.1</td>
<td>7.340</td>
<td>20.8</td>
<td>32.0</td>
<td>5.2</td>
<td>5.1</td>
<td>13.0</td>
<td>Type 4</td>
<td>Type 4</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>18.4</td>
</tr>
</tbody>
</table>

Normal ranges: HCO₃⁻, 22–26 mmol/l; serum K, 3.5–4.8 mmol/l; BUN, 6–21 mg/dl; Cr, 0.4–1.4 mg/dl; 24-h urine protein, <0.15 g/day; C3, 73–134 mg/dl; urine RBC, 0–5/high-power field.

Concomitant diseases

Several co-existent medical conditions were identified, including iatrogenic Cushing’s syndrome, overlapping syndrome (SLE and polymyositis), ankylosing spondylitis, diabetes mellitus and hypertension. This diabetes had been well controlled. No patient suffered from dry eye or dry mouth. Of four patients with a history of urinary tract infection, two had urolithiasis before diagnosis of RTA.

Clinical features and laboratory data at the time of RTA diagnosis

All six patients with SLE had normal anion gap metabolic acidosis. The pH value range of arterial blood gases was 7.045–7.396 (mean 7.291) and the anion gap range was 5–12 (mean 8.4) (Table 1). Four patients had hypokalaemia and the remaining two had hyperkalaemia. Five patients had proteinuria with a mean urine total protein excretion of 3.464 g/day (range 1.27–5.60 g/day). Five patients had normal renal function at the time of diagnosis of RTA and one was diagnosed with renal insufficiency on presentation with RTA (Table 1). Three of the patients had microhaematuria and three patients had asymptomatic pyuria. Three type 1 RTA patients had medullary nephrocalcinosis by renal ultrasonography, and two of these three patients had urolithiasis before the diagnosis of RTA. The mean SLEDAI score was 11.75 for type 1 patients and 27.5 for type 4 patients. Low complement 3 levels were found in three patients at the time of RTA diagnosis (Table 1).

ANA was the most common diagnostic criterion of SLE (six patients), followed by lupus nephritis (five patients), immunological disorders including elevated anti-double-stranded DNA levels (four patients), malar rash (four patients), arthritis (four patients), haematochemical disorders (four patients), oral ulcers (two patients), discoid rash (two patients), photosensitivity (one patient) and serositis (one patient; data not shown). Four patients had both speckled and homogeneous ANA patterns, and two had a speckled pattern only. No neurological involvement or anticardiolipin antibodies were noted in the six patients.

Types of renal tubular acidosis

Type 1 RTA with hypokalaemia was diagnosed in four of the six patients, and was therefore the most common subtype (Table 1). The other two patients had type 4 RTA with hyperkalaemia, without evidence of medullary nephrocalcinosis or renal urolithiasis.

Laboratory correlation between RTA and SLE

In the six RTA patients there was no significant correlation between the serum bicarbonate level, as determined by arterial blood sampling and other laboratory measures (Table 2). While not statistically significant, there was a noticeable trend of higher potassium levels with increased SLE disease activity (SLEDAI, P < 0.01) and nephritic manifestation of greater severity (haematuria, P < 0.1). Interestingly, among type 1 RTA patients, a higher serum bicarbonate level was significantly associated with lower levels of complement component 3 (P < 0.005), and a higher serum potassium level was significantly correlated with more severe haematuria (P < 0.005).

Medical treatment and outcome

After the diagnosis of RTA had been confirmed, oral or parenteral corticosteroids were administered to all six patients. Initially, four patients received oral prednisolone at a dose of 20 mg/day and one patient received oral prednisolone at a dose of 60 mg/day. One type 4 RTA patient (case 5) received parenteral hydrocortisone at a dose of 300 mg twice daily due to her critical condition. Hydroxychloroquine was also administered to one patient (200 mg/day). Three of four type 1 RTA patients received combination treatment with corticosteroids, sodium bicarbonate and potassium chloride due to acidaemia and hypokalaemia, and the serum potassium levels of these three patients were well within the normal range during outpatient follow-up (case 2 in Table 3). Case 2 received an increased dose of oral prednisolone and hydroxychloroquine at the time of the 15- and 24-month follow-up due to lupus peritonitis. One type 4 RTA patient (case 6) received corticosteroid treatment only and was then followed as an out-patient (Table 3). Unfortunately, another type 4 RTA patient (case 5) with chronic renal insufficiency needed haemodialysis at the time of admission because of urosepsis and acute renal failure. Septic shock and multiple organ failure then developed and the patient subsequently died.

Discussion

Renal tubular acidosis was first described by Lightwood [9] and Butler et al. [10] in children and by Baines et al. in adults [11]. Two
main subtypes of RTA were initially described, types 1 and 2, though at least three types, including type 4, have now been recognized [12].

Type 1 RTA, also known as classic distal RTA [13, 14], is due to inability of the distal tubule to establish an adequate pH gradient between the blood and the distal tubular fluid. Patients with type 1 RTA often have hypokalaemia (as in our cases 1, 2, 3 and 4 in Table 1) as a result of the excessive urinary excretion of potassium.

### Table 3. Serum K and HCO₃ levels and medication control in out-patient department follow-up

<table>
<thead>
<tr>
<th>Time</th>
<th>Serum K (mEq/l)</th>
<th>HCO₃ (mEq/l)</th>
<th>Urine RBC</th>
<th>Complement 3</th>
<th>Prednisolone (mg/day)</th>
<th>Sodium bicarbonate (mg/day)</th>
<th>Potassium chloride (mg/day)</th>
<th>HCQ (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>2.9</td>
<td>21.0</td>
<td>2</td>
<td>35.9</td>
<td>40</td>
<td>1.8</td>
<td>2.25</td>
<td>0</td>
</tr>
<tr>
<td>1 month</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>1.2</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>2 months</td>
<td>3.3</td>
<td>10</td>
<td>68.4</td>
<td></td>
<td>20</td>
<td>2.4</td>
<td>1.5</td>
<td>200</td>
</tr>
<tr>
<td>3 months</td>
<td>3.3</td>
<td></td>
<td>66.8</td>
<td></td>
<td>20</td>
<td>2.4</td>
<td>1.5</td>
<td>200</td>
</tr>
<tr>
<td>4 months</td>
<td>3.6</td>
<td>27.7</td>
<td>6</td>
<td>68.5</td>
<td>20</td>
<td>2.4</td>
<td>1.5</td>
<td>300</td>
</tr>
<tr>
<td>8 months</td>
<td>3.4</td>
<td>26.0</td>
<td>13</td>
<td>58.4</td>
<td>25</td>
<td>1.2</td>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>10 months</td>
<td>3.7</td>
<td>27.5</td>
<td>0</td>
<td>68.0</td>
<td>10</td>
<td>1.2</td>
<td>3</td>
<td>300</td>
</tr>
<tr>
<td>15 months</td>
<td>3.8</td>
<td>30.7</td>
<td>7</td>
<td>68.3</td>
<td>15</td>
<td>0.6</td>
<td>1.5</td>
<td>300</td>
</tr>
<tr>
<td>24 months</td>
<td>3.9</td>
<td>29.2</td>
<td>3</td>
<td>73.5</td>
<td>17.5</td>
<td>0.6</td>
<td>1</td>
<td>400</td>
</tr>
</tbody>
</table>

**Type 4 distal RTA (case 6)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Serum K (mEq/l)</th>
<th>HCO₃ (mEq/l)</th>
<th>Prednisolone (mg/day)</th>
<th>Azathioprine (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>5.1</td>
<td>20.8</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>2 months</td>
<td></td>
<td></td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td>25</td>
<td>25</td>
</tr>
<tr>
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<td>13 months</td>
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<td>15</td>
<td>25</td>
</tr>
<tr>
<td>16 months</td>
<td>3.9</td>
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<td>15</td>
<td>25</td>
</tr>
<tr>
<td>26 months</td>
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<td>10</td>
<td>50</td>
</tr>
<tr>
<td>29 months</td>
<td>4.2</td>
<td></td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>30 months</td>
<td>3.6</td>
<td></td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>31 months</td>
<td></td>
<td></td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>42 months</td>
<td></td>
<td></td>
<td>15</td>
<td>50</td>
</tr>
</tbody>
</table>

Normal range for serum: K, 3.5–4.8 mEq/l; HCO₃, 22–26 mEq/l; C₃, 73–134 mg/dl; urine RBC, 0–5/high power field.

HCQ, hydroxychloroquine.
Renal tubular acidosis in SLE

as in our cases 2, 3 and 4 (Table 1) [15]. In contrast, in type 4 RTA, also referred to as hyperkalaemic distal RTA, distal tubule secretion of both potassium and hydrogen ions is abnormal, resulting in hyperchloremic acidosis with hyperkalaemia (as in our cases 5 and 6). Type 4 RTA is an acquired disorder that is frequently accompanied by a moderate degree of renal insufficiency, as in our case 5.

Many different conditions have been associated with distal RTA. The major causes of this disorder include primary idiopathic disease, hereditary diseases such as Wilson’s disease, disorders of calcium metabolism and nephrocalcinosis, drugs such as amphotericin B and lithium carbonate [16], toxins, obstructive uropathy, sickle cell anaemia [17], diabetic nephropathy, tubulointerstitial nephropathies, and autoimmune disorders. With the exception of tubulointerstitial nephropathies and autoimmune disorders, our patients were not affected with these conditions. The most common identifiable autoimmune causes of RTA in adults are SLE [18, 19], Sjögren’s syndrome and rheumatoid arthritis. However, no evidence suggests Sjögren’s syndrome or rheumatoid arthritis in the patients reported here.

SLE can be associated with a variety of tubular defects. Though distal RTA (including hyperkalaemic type) had been presented previously [4], ours is the first report of an association between type 4 RTA and SLE disease activities (cases 5 and 6 in Table 1). In type 4 RTA, the degree of hyperkalaemia is correlated with a high SLEDAI, as in our cases 5 and 6, and has a poor prognosis, as in our case 5. Generally, impaired tubular function in SLE exists in patients with acute nephritis or nephritic syndrome. Moreover, Tektonidou et al. observed that antiphospholipid syndrome nephropathy occurred almost exclusively in those with anti-phospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant) [20]. In our study, antiphospholipid syndrome nephropathy is excluded by serology negative for anticardiolipin antibodies and no signs or symptoms of arterial and venous thromboses. Though tubulointerstitial involvement with pyuria (as in our cases 2, 3 and 5) is well recognized in SLE, the tubular dysfunction is usually latent and presents after the diagnosis of SLE has been established [21]. In our study, three patients had distal RTA at the time of the initial diagnosis of SLE, whereas the other three patients exhibited a latent presentation, occurring a mean of 6 yr later. Furthermore, there is no significant correlation between SLE disease duration before the onset of RTA and the SLEDAI score.

Tubular atrophy, interstitial infiltration and fibrosis have been reported in 50–70% of patients with SLE. Occasional reports have suggested the possibility of interstitial nephritis in the absence of glomerular changes in SLE [16]. However, in our study, five of six patients had lupus glomerulonephritis with significant proteinuria. Jessop et al. [3] attended 12 SLE patients with RTA, six of whom (50%) were known to have renal impairment. In contrast, five of our six SLE patients presented with normal renal function and proteinuria (only 16.7% abnormal). Indeed, previous renal dysfunction may not be a major risk factor for distal RTA.

The involvement of the complement system in human glomerulonephritis has been suspected since Gunn’s observation in 1914 of low serum complement levels in postscarlatina glomerulonephritis [22]. Depressed levels of serum complement have also been found in lupus glomerulonephritis [23]. However, the degree of complement does not appear to correlate with renal tubular acidosis [24]. Though a higher serum bicarbonate level was significantly associated with lower levels of complement component 3 in our type 1 RTA patients (Table 2), it needs a larger study to confirm our observations of association between RTA severity and complement levels. Besides, there has been no report of association between serum potassium and haematuria in RTA or SLE. Among our type 1 RTA patients, a higher serum potassium level is significantly correlated with more severe haematuria (Table 2). Because tubulointerstitial nephritic manifestation with pyuria is characteristic of RTA, we believe that haematuria may be associated with the severity of lupus glomerulonephritis. Further study is needed.

Urolithiasis with medullary nephrocalcinosis and recurrent urinary tract infection are frequently found in type 1 RTA. However, in our study, because of the small number of cases, the χ2 test statistic did not demonstrate a statistical significant association between type 1 RTA and medullary nephrocalcinosis or recurrent urinary tract infection.

Renal biopsies of patients with distal RTA and SLE generally show interstitial nephritis, although a correlation between tubular dysfunction and the degree of histological interstitial lesions is usually absent [25]. The persistent pyuria and proteinuria without glomerular casts in our patients (cases 2, 3 and 5) without renal biopsy are consistent with the diagnosis of interstitial nephritis. Nevertheless, histological proof was lacking, and nephrocalcinosis can also be associated with proteinuria [26].

Adequate treatment of distal RTA is not always possible and the interstitium may become irreversibly damaged due to long-standing nephrocalcinosis. Therefore, symptomatic correction of the chronic acidemia is the mainstay of treatment in such cases. Reversing the acidemia with sodium bicarbonate and potassium chloride is known to prevent nephrocalcinosis and urolithiasis. Hypokalaemia in type 1 RTA is also corrected by reversing the acidemia, as evidenced with cases 2 (Table 3), 3 and 4 herein (case 1 was lost to follow-up). Sometimes, though, potassium supplementation without correction of acidosis can lead to recurrent hypokalaemia as a result of ongoing urinary potassium wasting [27]. In contrast, treatment of type 4 RTA is directed at reducing serum potassium, as acidosis will usually improve spontaneously once the hyperkalaemic block of ammonium production is eliminated (as in our case 6).

In patients with SLE or Sjögren’s syndrome, treatment of the interstitial nephritis with corticosteroids can reverse RTA [8, 28]. In some of our patients, treatment with corticosteroids had some effect on the acidosis, with serum bicarbonate levels returning to normal (Table 3). Sometimes, the serum bicarbonate level remains low, probably due to the resistance of distal RTA to treatment with corticosteroids, resulting from diffuse and irreversible destruction of the tubular interstitium [29]. Nevertheless, and most importantly, the resistance of distal RTA to corticosteroids can be remedied by symptomatic treatment with alkali therapy to prevent complications of distal RTA.

In conclusion, this is the first series on RTA in SLE that includes more than only case reports to be published since 1974. This study highlights the previously under-recognized problem of RTA in SLE. Diagnosis of these two diseases rests, of course, on a high index of suspicion. Though distal RTA can be the first manifestation of SLE, preceding other symptoms of SLE by years, all our patients had these two conditions at the same time or suffered SLE before the occurrence of RTA. RTA is a prominent feature of lupus nephritis and is intimately associated with nephritic manifestations. Type 1 RTA leads to recurrent symptomatic acidemia, hypokalaemia, nephrocalcinosis and frequent urolithiasis. Though no patients with type 4 RTA had nephrocalcinosis, patients with type 4 RTA and hyperkalaemia (cases 5 and 6) have higher SLEDAI scores and carry a poorer prognosis than type 1 RTA patients. Distal RTA can be resolved after corticosteroid therapy is initiated, and chronic acidemiacan be well controlled by alkali therapy. Further study of additional patients will be needed to support our observation.

The authors have declared no conflicts of interest.

References