Concurrent septic arthritis and urinary tract infection in a patient with nephrocalcinosis and vesicoureteral reflux

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An eight-month-old boy who presented with a 15-day history of vomiting was revealed to be suffering from urinary tract infection and nephrocalcinosis caused by vitamin D intoxication. During the treatment of vitamin D intoxication (alendronate, 5 mg/day), he developed urinary tract infection and septic arthritis of the left hip joint. Escherchia coli was isolated from his blood, urine, and joint fluid culture. He was operated, joint drainage was performed and appropriate intravenous antibiotic treatment was given for four weeks. After discharge, a voiding cystoureterogram revealed grade 4 vesicoureteral reflux in the right ureter. Combination of complex urinary anomalies associated with stagnation of urine flow and altered urinary dynamics, and metabolic urinary anomalies, such as hypercalciuria/nephrocalcinosis, may facilitate the occurrence of rare systemic complications of urinary tract infection.

Key words: nephrocalcinosis, urinary tract infection, septic arthritis, vitamin D intoxication, infant.

Vesicoureteral reflux (VUR) is common in children under two years of age with a febrile urinary tract infection (UTI)¹. Infants with VUR carry the risk of ascending UTI and systemic complications. To date, four cases of UTI with subsequent septic arthritis have been reported in the literature in which all patients had urinary tract anomalies²-⁵. We present an eight-month-old male infant with vitamin D intoxication-induced nephrocalcinosis and VUR, accompanied by UTI and septic arthritis.

Case Report

An eight-month-old previously healthy boy was presented to the state hospital with the complaint of vomiting, and was diagnosed as urinary tract infection based on urinalysis (no urine culture was obtained). He was hospitalized, and intravenous (IV) fluids and antibiotics (for 2 weeks) were administered. Vomiting had ceased while he was receiving IV fluids and started again on discontinuation of IV fluids. During his hospitalization, his serum calcium level was found to be 14.2 mg/dl, which was thought to be a laboratory error. Because of prolonged and unremitting vomiting, the patient was referred to our center. He had been diagnosed as rickets and given 600,000 IU oral vitamin D one week before the vomiting started. On admission, physical examination revealed mild dehydration and no fever. Blood chemistry was normal other than calcium (15.0 mg/dl). Patient’s urinary calcium (mg/dl)/creatinine (mg/dl) ratio was high at admission (Table I). Urinalysis was normal. Vitamin D intoxication was suspected. Renal ultrasonography showed a slight dilation in the right pelvis and bilateral medullary nephrocalcinosis.

Cessation of vitamin D, low calcium intake, IV hydration, furosemide, and alendronate (5 mg/day) were instituted. Catheterized urine culture was sterile, and antibiotics were stopped. Patient’s serum calcium level returned to normal limits, and vomiting stopped within five days of admission to our hospital. Intravenous hydration and diuretic were stopped at this stage and alendronate treatment was continued. During the fifth day of admission his body temperature was
39.0°C, white blood cell (WBC) count 14,300 with 30% PMNL, 59% lymphocytes and 11% monocytes, sedimentation rate 56 mm/hour, and C-reactive protein (CRP) level 56.8 mg/dl.

On physical examination, there was no source for fever except bilateral tonsillar exudates. His catheterized urine and blood cultures were taken and ceftriaxone (50 mg/kg/day) was instituted. Fever lasted for two days without deterioration in patient’s condition. Extended spectrum beta-lactamase (ESBL)-producing Escherichia coli (10⁵ cfu/ml) was isolated from urine and blood cultures. Imipenem (60 mg/kg day) and amikacin (15 mg/kg/day) were started according to the susceptibility pattern.

The following day, it was noticed that the motion of the left leg and hip was painful. An ultrasonography of the hip joint showed an increase in the left joint space compared to the right. Gram-negative bacilli were seen in joint aspiration fluid, and E. coli was also isolated with a similar antibiotic resistance pattern to that of urine and blood. He was operated and antibiotic therapy continued.

Antibiotics were administered for one month and then the patient was discharged with urinary antibiotic (trimethoprim-sulfamethoxazole 2 mg/kg/day) prophylaxis. Other causes of hypercalciuria/nephrocalcinosis were eliminated by laboratory tests. Vitamin D level, which could not be measured at the time of admission, was 180 ng/ml (10-40 ng/ml) at the time of discharge. One month after the discharge, a voiding cystoureterogram revealed right grade 4 VUR and DMSA scan showed no scar tissue. Follow-up ultrasonography after 5 and 16 months of discharge showed the persistence of nephrocalcinosis in both kidneys. The patient is doing well with antibiotic prophylaxis and has had no urinary infection for 15 months, with normal serum calcium, urine calcium/creatinine ratio, and normal serum urea and creatinine levels. He is now walking without any limitation of hip movements. Growth of the patient is also normal.

**Discussion**

Septic arthritis is most commonly seen in young children. Half of the cases occur by two years of age⁶. The majority of infections are hematogenously acquired. In a 20-year retrospective analysis of 90 patients, Bonhoeffer et al.⁷ found the predominant causative microorganisms for septic arthritis were Staphylococcus aureus, Streptococcus spp. and Haemophilus influenzae in the 0-4 year-old patient group. Gram-negative septic arthritis is rarely reported in infants. An extra-articular source of infection must be sought in each case of Gram-negative septic arthritis, and the most likely candidate is the urinary tract. In infants, UTI is important both for its short- and long-term consequences. In the short term, it may cause pyelonephritis and suppurative complications. In the long term, renal damage, hypertension, and renal failure may ensue as a result of recurrent pyelonephritis.

### Table I. Serum and Urine Biochemistry of the Patient

<table>
<thead>
<tr>
<th>Age of patient (month)</th>
<th>Days after admission</th>
<th>Calcium (mg/dl)</th>
<th>Phosphorus (mg/dl)</th>
<th>ALP (mg/dl)</th>
<th>Sodium (mg/dl)</th>
<th>Potassium (mg/dl)</th>
<th>25 (OH) Vitamin D (10-40 ng/ml)</th>
<th>CBG: pH</th>
<th>HCO₃⁻</th>
<th>Urine calcium/creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to our hospital</td>
<td>8</td>
<td>15</td>
<td>4.4</td>
<td>98</td>
<td>138</td>
<td>3.9</td>
<td>Not obtained</td>
<td>CBG: pH</td>
<td>7.47</td>
<td>21.3</td>
</tr>
<tr>
<td>5th day</td>
<td>9</td>
<td>9.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st month</td>
<td>9</td>
<td></td>
<td>130</td>
<td></td>
<td></td>
<td>180 (10-40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st month</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>4th month</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th month</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALP: Alkaline phosphatase. CBG: Capillary blood gases.
Association of septic arthritis and UTI has been rarely reported\textsuperscript{2-5}. In all previously published cases, there were underlying anatomical abnormalities such as VUR with single ectopic ureter, VUR with antenatal hydronephrosis, and two cases of posterior urethral valves. The common feature of all these patients was hydroureteronephrosis and obstructed urinary flow. Hydronephrosis may have facilitated the systemic complication in these patients by resulting in urinary stagnation, therefore causing more bacteria to enter the bloodstream and increasing the chance of urosepsis. In addition to VUR, our patient had hypercalciuria/nephrocalcinosis.

Nephrocalcinosis is a complication of various metabolic disorders or drugs. Idiopathic hypercalciuria, renal tubular disorders and stoss vitamin D therapy may be associated with nephrocalcinosis\textsuperscript{8}. There is one reported case of concurrent nephrocalcinosis and VUR, in which authors claimed that nephrocalcinosis may have developed as a result of the precipitation of calcium in dilated collecting tubules secondary to VUR\textsuperscript{9}. However, shortness of the time interval between vitamin D administration and onset of symptoms and the subsequent clinical course provided strong evidence that hypercalciuria and nephrocalcinosis were due to vitamin D stoss therapy in our case. Although the association of nephrocalcinosis with UTI is controversial, some authors have suggested that hypercalciuria, which is the precursor of nephrocalcinosis, may increase the risk of UTI\textsuperscript{10-12}. They suggested that calcium oxalate microcrystals may damage uroepithelial cells and predispose patients to UTI, or that these crystals aggregate and provide a nidus for bacteria sequestration\textsuperscript{11,12}. In our patient, hypercalciuria may have contributed to the development of nephrocalcinosis and subsequent UTI. Although there was no urinary flow obstruction, hypercalciuria and nephrocalcinosis may have assisted the bacteria to overcome host defenses and enter the systemic circulation.

Although corticosteroids were considered to be the first-line therapy for prolonged hypercalcemia, there is an increasing trend toward the use of bisphosphonates in the treatment of childhood hypercalcemia from various causes\textsuperscript{13-15}. Bisphosphonate use in the treatment of vitamin D intoxication-induced hypercalcemia was previously reported\textsuperscript{14}. As seen in our case, normalization of vitamin D and calcium levels may take a long time due to the storage of vitamin D in adipose tissue. Moreover, prolonged use of corticosteroids may itself cause some adverse effects. Fifteen months after the therapy, no side effects were seen due to the alendronate treatment\textsuperscript{14}.

In one previously reported case, septic arthritis seemed to develop during the course of antibiotic treatment like in our patient\textsuperscript{2}. This situation raises the question of whether more virulent strains of Gram-negative bacteria might be associated with systemic complications. Johnson et al.\textsuperscript{16} showed that, in adult patients, extraintestinal pathogenic E. coli strains associated with UTI may also cause invasive non-urinary infections, i.e. septic arthritis, pneumonia, and meningitis, and these infections may develop even during the course of antibiotic treatment. Actually, in our case, symptoms of septic arthritis were seen one day after the specific antibiotics were started. Thus, it is reasonable to state that at the time specific antibiotics were started, septic arthritis had already begun.

In summary, in addition to the anatomic abnormalities, i.e. obstructed urinary tract, metabolic abnormalities such as hypercalcemia/hypercalciuria/nephrocalcinosis may also contribute to the development of rare systemic complications of UTI.

REFERENCES


