

[ CASE REPORT ]

## Acquired Fanconi Syndrome in a Patient with Nontyphoidal *Salmonella* Bacteremia

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### Abstract:

Nontyphoidal *Salmonella* is a common cause of bacterial gastroenteritis, occasionally causing bacteremia. We herein report the case of an 80-year-old man who presented with bacteremia and pre-renal acute kidney injury (AKI) secondary to diarrhea caused by nontyphoidal *Salmonella*. Despite AKI improvement on fluid administration, some serological abnormalities, such as hypokalemia, hypophosphatemia, and hypouricemia, and abnormal urinary findings emerged, including renal glycosuria and aminoaciduria. Fractional excretion of phosphate and uric acid was increased, suggesting that the serological and urinary abnormalities may have arisen from Fanconi syndrome. Physicians should consider acquired Fanconi syndrome when patients with nontyphoidal *Salmonella* bacteremia present with electrolyte disorders.

**Key words:** *salmonella* bacteremia, hypokalemia, hypophosphatemia, Fanconi syndrome

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### Introduction

Nontyphoidal *Salmonella* (NTS) species are a common cause of bacterial gastroenteritis, and up to 8% of those cases develop bacteremia (1). Few papers have reported associations of salmonella infection with renal manifestations, including electrolyte disorders (2). Two reports described the intravenous administration of attenuated NTS (*Salmonella enterica* spp. *enterica* serovar *typhimurium*) to patients with metastatic melanoma causing hypophosphatemia as an adverse event (3, 4). Furthermore, guinea pigs infected with *Salmonella* organisms became hypophosphatemic before death (5). However, the underlying mechanisms have yet to be fully elucidated.

We herein report the case of a patient with NTS bacteremia who presented with Fanconi syndrome.

### Case Report

An 80-year-old Japanese man with a history of hypertension, prostate cancer, pemphigoid, and arterial fibrillation on

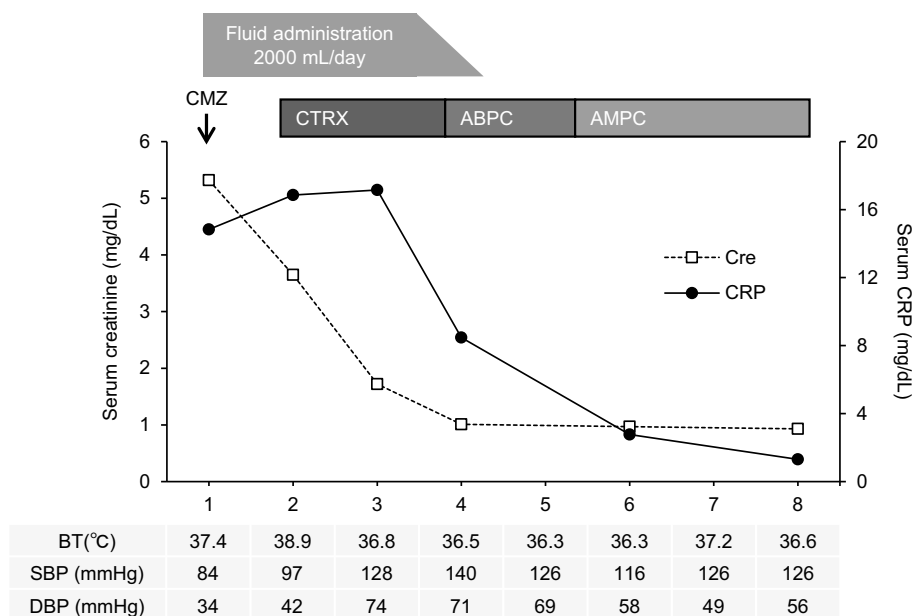
a pacemaker was admitted to our hospital because of pre-renal acute kidney injury (AKI) caused by diarrhea and a loss of appetite over the course of 3 days.

On admission, a physical examination showed a blood pressure of 84/34 mmHg, heart rate of 51 beats/min, and body temperature of 37.6°C. The patient was conscious, and the abdomen was soft and flat. Laboratory findings were as follows: white blood cell (WBC) 10,200/ $\mu$ L; red blood cell (RBC) 2.95 $\times$ 10<sup>4</sup>/ $\mu$ L; hemoglobin (Hb) 9.6 g/dL; hematocrit (Ht) 26.7%; platelet (Plt) 23.2 $\times$ 10<sup>4</sup>/ $\mu$ L; aspartate transaminase (AST) 31 U/L; alanine transaminase (ALT) 24 U/L; blood urea nitrogen, 55.6 mg/dL; creatinine, 5.32 mg/dL; creatinine kinase (CK), 413 (U/L); C-reactive protein (CRP), 14.83 mg/dL; urinary N-acetyl- $\beta$ -D-glucosaminidase (NAG), 21.7 U/L; and urinary  $\beta$ 2 microglobulin (MG), 1,851  $\mu$ g/L. Venous blood gas findings were as follows: pH 7.307; pCO<sub>2</sub> 30.6 mmHg; HCO<sub>3</sub><sup>-</sup> 14.8 mmol/L. Urinalysis findings were as follows: pH 5.0; Protein (2+); Glucose (-); Ketone (-); Blood (2+); WBC (-). The fractional excretion of sodium (FENa) and fractional excretion of urea nitrogen (FEUN) were 0.37% and 24.9%, respectively. Computed tomography showed that the kidneys were not enlarged. We diagnosed

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**Figure 1.** Clinical course of *Salmonella* bacteremia in this case. CMZ: cefmetazole, CTRX: ceftriaxone, ABPC: ampicillin, AMPC: amoxicillin, BT: body temperature, SBP: systolic blood pressure, DBP: diastolic blood pressure

him with pre-renal AKI secondary to decreased extracellular fluid volume due to diarrhea caused by infectious gastroenteritis.

We started antibiotics and fluid administration for infectious gastroenteritis and pre-renal AKI. On day 2 of hospitalization, *S. enterica* with O8 antigen was detected in blood cultures, so we switched antibiotics from cefmetazole to ceftriaxone. After the susceptibility of *Salmonella enterica* was determined, we further switched antibiotics as shown in Fig. 1. With these treatments, serum creatinine and CRP gradually improved (Fig. 1).

However, hypokalemia with elevated urinary excretion of potassium (day 2), hypouricemia with elevated urinary excretion of urate (day 4), hypophosphatemia with elevated urinary excretion of phosphate (day 4), and glycosuria under conditions of normoglycemia developed (Fig. 2). Urinary methionine (high-performance liquid chromatography; SRL, Tokyo, Japan) was also observed, and the level of FGF23, which causes phosphaturia, was 35.9 pg/mL (normal range: 19.9-52.9 pg/mL). Six months before admission, the serum uric acid, potassium, and phosphorus levels had been 3.7 mg/dL, 4.9 mEq/L, and 3.7 mg/dL, respectively. Based on these findings, we considered these electrolyte abnormalities to be due to acquired Fanconi syndrome.

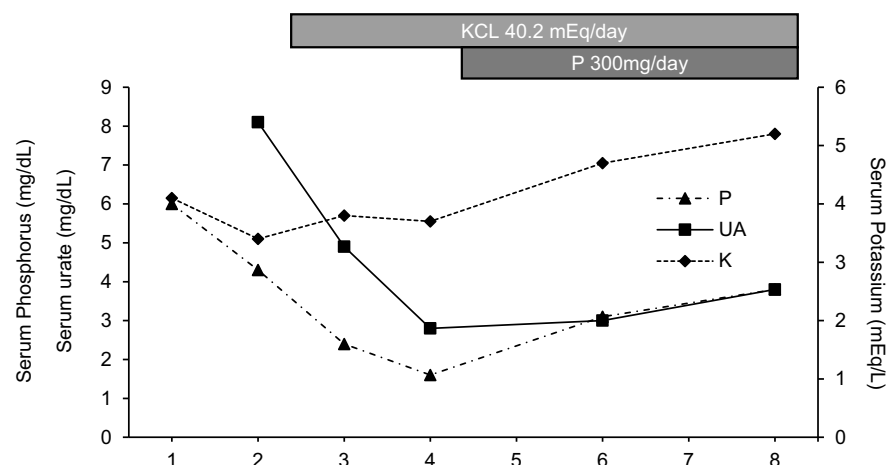
We started oral potassium chloride and monobasic sodium phosphate monohydrate, dibasic sodium phosphate anhydrous as potassium and phosphate supplementation, and the serum potassium and phosphate levels improved (Fig. 2). Hypouricemia and renal glycosuria also gradually improved without intervention. The general condition of the patient improved, and he was discharged on Day 11.

## Discussion

The present case was diagnosed as NTS bacteremia. During the treatment of bacteremia, the patient developed Fanconi syndrome. To our knowledge, this is the first case report of acquired Fanconi syndrome secondary to *Salmonella* bacteremia.

Fanconi syndrome is a syndrome of inadequate reabsorption in the renal proximal tubules. Inherited Fanconi syndrome is often related to underlying genetic diseases, such as cystinuria, Lowe syndrome, and Wilson's disease (6). This syndrome can also be caused by secondary elements, such as drug side effects, vitamin D deficiency, and metal toxicity. The intravenous administration of attenuated *S. typhimurium* to patients with metastatic melanoma was previously reported to cause hypophosphatemia as an adverse event (3, 4), and guinea pigs infected with *Salmonella* organisms also became hypophosphatemic before death (5). However, the mechanisms underlying this hypophosphatemia have yet to be fully elucidated.

The present patient developed hypokalemia and hypophosphatemia during the treatment of *Salmonella* bacteremia. These abnormalities occurred alongside an increased urinary excretion of potassium and phosphate. Furthermore, glycosuria and aminoaciduria were also present, and we attributed these abnormalities to Fanconi syndrome. This patient did not have any relevant diseases (i.e., multiple myeloma, Sjögren syndrome, amyloidosis, or nephrotic syndrome) and was not taking any medications (i.e., cisplatin, ifosfamide, tenofovir, cidofovir, adefovir, didanosine, gentamicin, or azathioprine) known to cause acquired Fanconi syndrome. We could not exclude the possibility that the pa-



**Figure 2. Clinical course of electrolyte disorders in this case. UA: uric acid**

tient had acute tubular necrosis (ATN), which often causes acquired Fanconi syndrome in the recovery period. However, the FENa and FEUN decreased despite a reduced glomerular filtration rate (GFR), and the elevation of urinary tubular protein levels ( $\beta$ 2-MG and NAG) was also small. These findings suggested that the abnormalities were not caused by ATN.

Cefmetazole and ceftriaxone can also cause Fanconi syndrome. Despite the frequent use of these drugs, there have been no reports of drug-induced acquired Fanconi syndrome. Furthermore, this case showed elevated potassium excretion despite the presence of AKI and hypokalemia from the early phase of hospitalization. For these reasons, we concluded that the abnormalities were not due to drug-induced acquired Fanconi syndrome.

Although we diagnosed this case with acquired Fanconi syndrome secondary to NTS bacteremia, we could not clarify the underlying mechanisms. We previously reported that *Legionella pneumoniae* causes acquired Fanconi syndrome (7-10). Some researchers have stated that mitochondrial dysfunction causes an impaired proximal tubular function in Fanconi syndrome (11), and we speculated that *L. pneumoniae* might infect the proximal tubular cells and interfere with the mitochondria, leading to Fanconi syndrome (8). One of the possible underlying mechanisms inducing acquired Fanconi syndrome is mitochondrial dysfunction. Mitochondrial fatty acid oxidation is the primary energy source in proximal tubules, and its dysfunction leads to the suppression of proximal tubular solute transport (12).

*Legionella* and *Salmonella* are both intracellular pathogens. *Salmonella* has also been reported to affect mitochondria and induce cell death (7, 8), and we speculate that mitochondrial dysfunction might lead to acquired Fanconi syndrome.

Several limitations associated with the present study warrant mention. First, our hypothesis that the kidney injury had been caused mainly by pre-renal AKI was confirmed by laboratory data, not histologically. Second, we did not perform a kidney biopsy and could not prove that the morphological changes in proximal tubular dysfunction were due to NTS bacteremia.

## Conclusion

In conclusion, electrolyte disorders in the present patient, including hypokalemia and hypophosphatemia, due to *Salmonella* bacteremia were caused by acquired Fanconi syndrome. Physicians should consider the presence of secondary Fanconi syndrome when patients with *Salmonella* bacteremia present with electrolyte disorders.

**The authors state that they have no Conflict of Interest (COI).**

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