Fanconi Syndrome Associated with Hyponatremia in Two Patients with *Legionella* Pneumonia

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Abstract

*Legionella pneumophila* is a cause of community-acquired pneumonia that is reported to induce electrolyte disorders, including hyponatremia, hypokalemia, and hypophosphatemia. We herein report two Japanese men with *Legionella* pneumonia and hyponatremia and hypophosphatemia. These findings were associated with an elevation of urinary low-molecular-weight tubular protein, including urinary β2-microglobulin, N-acetyl-β-D-glucosaminidase, the fractional excretion of phosphate and uric acid, and the presence of glycosuria and panaminoaciduria, suggesting that their electrolyte disorders had been caused by Fanconi syndrome. In these two cases, hyponatremia was probably due to salt wasting. Electrolyte disorders caused by *Legionella* pneumonia are corrected by treatment of the primary disease and fluid administration.

Key words: *Legionella* pneumonia, hyponatremia, hypophosphatemia, Fanconi syndrome

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Introduction

*Legionella pneumophila* is a cause of community-acquired pneumonia that also induces electrolyte disorders, such as hyponatremia, hypokalemia, and hypophosphatemia. However, the mechanisms of these electrolyte disorders have not yet been clarified. We herein report two cases of *Legionella* pneumonia who presented with hyponatremia and hypophosphatemia, which may have been caused by Fanconi syndrome and renal salt wasting due to proximal tubular dysfunction.

Case Reports

Case 1

A 65-year-old Japanese man was admitted to our hospital for fever and headache over the past 2 days. He had no relevant medical history, no history of infectious diseases or renal diseases, and he was not on any medication. On admission, physical examination indicated a blood pressure of 153/100 mmHg, pulse rate of 128 beats/min, and body temperature of 39.1°C. The patient was conscious and non-edematous, although his skin turgor had decreased. His laboratory findings on Day 2 (Table 1) were as follows: white blood cell count (WBC) 12,890/μL (Neutro: 91.7%, Eosino: 0.0%, Baso: 0.1%, Mono: 2.5%, Lymph: 5.7%), red blood cell count (RBC) 439×10⁴/μL, hemoglobin (Hb) 13.5 g/dL, hematocrit (Ht) 38.5%, platelet count (Plt) 16.6×10⁴/μL, aspartate aminotransferase (AST) 108 U/L, alanine aminotransferase (ALT) 52 U/L, blood urea nitrogen (BUN) 14 mg/dL, creatinine 0.85 mg/dL, creatine kinase (CK) 2,999 IU/L, C-reactive protein (CRP) 27.08 mg/dL, B-type natriuretic peptide (BNP) 23.9 pg/mL, proteinuria (++), glycosuria (++), and urine WBC (-). Antidiuretic hormone (ADH), plasma renin activity (PRA), and aldosterone were not measured. A computed tomography (CT) scan of the
Table 1. Laboratory Findings in the Two Cases.

| Laboratory investigation                  | Result of Case 1 (Day 2) | Result of Case 2 (On admission) | Reference range                  |
|-------------------------------------------|--------------------------|---------------------------------|----------------------------------|
| **Blood cell count**                      |                          |                                 |                                  |
| White blood cell count                    | 12.8×10^3/μL             | 5.96×10^3/μL                    | 3.59-9.64×10^3/μL               |
| Neutro                                    | 91.7%                    | 88.0%                           | 41.2-74.7%                       |
| Eosino                                    | 0.0%                     | 0.0%                            | 0.2-8.4%                         |
| Baso                                      | 0.1%                     | 0.0%                            | 0.2-1.8%                         |
| Mono                                      | 2.5%                     | 4.4%                            | 3.1-8.0%                         |
| Lymph                                     | 5.7%                     | 7.6%                            | 21.2-51.0%                       |
| Red blood cell count                      | 439×10^4/μL              | 517×10^4/μL                     | 400-552×10^4/μL                 |
| Hemoglobin                                | 13.5 g/dL                | 14.4 g/dL                       | 13.2-17.2 g/dL                  |
| Hematocrit                                | 38.5%                    | 41.4%                           | 40.4-51.1%                       |
| Platelet count                            | 16.6×10^4/μL             | 15.4n10^4/μL                    | 14.8-33.9×10^4/μL               |
| **Blood biochemistry**                    |                          |                                 |                                  |
| Serum sodium                              | 128 mEq/L                | 128 mEq/L                       | 138-146 mEq/L                    |
| Serum potassium                           | 3.6 mEq/L                | 3.3 mEq/L                       | 3.6-4.9 mEq/L                    |
| Serum chloride                            | 91 mEq/L                 | 93 mEq/L                        | 99-109 mEq/L                     |
| Corrected serum calcium                   | N.D.                     | 8.9 mg/dL                       | 8.7-10.3 mg/dL                   |
| Serum phosphorus                          | 1.5 mg/dl                | 1.2 mg/dl                       | 2.5-4.7 mg/dl                    |
| Urea nitrogen                             | 14 mg/dl                 | 11 mg/dl                        | 8-22 mg/dl                       |
| Creatinine                                | 0.85 mg/dl               | 0.75 mg/dl                      | 0.6-1.1 mg/dl                    |
| Estimated GFR                             | 70 mL/min/1.73 m^2       | 81 mL/min/1.73 m^2              | 90-120 mL/min/1.73 m^2           |
| Uric acid                                 | 3.8 mg/dL                | 1.4 mg/dL                       | 3.6-7.0 mg/dL                    |
| Total protein                             | 6.1 g/dl                 | 5.9 mg/dl                       | 6.7-8.3 g/dl                     |
| Albumin                                   | 2.8 g/dl                 | 2.8 mg/dl                       | 3.9-4.9 g/dl                     |
| Aspartate transaminase                    | 108 U/L                  | 201 U/L                         | 13-33 U/L                        |
| Alanine transaminase                      | 52 U/L                   | 84 U/L                          | 6-30 U/L                         |
| Alkaline phosphatase                      | 152 U/L                  | 124 U/L                         | 115-359 U/L                      |
| γ-glutamyltransfer                       | 24 U/L                   | 28 U/L                          | 10-47 U/L                        |
| Creatinine kinase                         | 2,999 IU/L               | 12,675 IU/L                     | 62-287 IU/L                      |
| Lactate Dehydrogenase                    | 398 U/L                  | 673 U/L                         | 119-229 U/L                      |
| C-reactive protein                        | 27.08 mg/dL              | 19.86 mg/dL                     | 0-0.3 mg/dL                      |
| **Arterial blood gas**                    |                          |                                 |                                  |
| pH                                       | 7.494                    | 7.540                           |                                  |
| PaO_2                                     | 64.5 mmHg                | 62.4 mmHg                       | 80-100 mmHg                      |
| PaCO_2                                    | 23.4 mmHg                | 21.7 mmHg                       | 35-45 mmHg                       |
| HCO_3^-                                   | 17.9 mmol/L              | 18.5 mmol/L                     | 22-26 mmol/L                     |
| **Urine**                                 |                          |                                 |                                  |
| Urine protein                             | 2+                       | 2+                              | Negative                         |
| Urine occult blood reaction               | +                        | 3+                              | Negative                         |
| Urine glucose                             | 2+                       | +                               | Negative                         |
| Urine WBC                                  | +                        | ±                               | Negative                         |
| Urine sodium                              | 64.6 mmol/L              | 43.8 mmol/L                     |                                  |
| Urine potassium                           | 42.8 mmol/L              | 31.2 mmol/L                     |                                  |
| Urine chloride                            | 54.5 mmol/L              | 49.0 mmol/L                     |                                  |
| Urine creatinine                          | 120.59 mg/dL             | 109.61 mg/dL                    |                                  |
| Urine urea nitrogen                       | 742.8 mg/dL              | 982.1 mg/dL                     |                                  |
| Urinary osmolality                        | 570 mOsm/kg H_2O         | 628 mOsm/kg H_2O                |                                  |
| **Fraction Excretion**                    |                          |                                 |                                  |
| Sodium                                    | 0.36%                    | 0.2%                            |                                  |
| Urine acid                                | 11.7%                    | 18.6% (Day 2)                   |                                  |
| Phosphate                                 | 52.1%                    | 18.9%                           |                                  |
| **Endocrinological data**                 |                          |                                 |                                  |
| BNP (type B natriuretic peptide)          | 23.9 pg/mL               | 60.9 pg/mL                      | <18.4 pg/mL                      |

N.D. not determined.

chest showed a ground-glass appearance in the left middle and lower lung lobes, and the urinary antigen test for *Legionella pneumophila* (Immunocatch<sup>®</sup>, Eiken Kagaku, Co., Ltd., Tokyo, Japan) was positive. We diagnosed his pneumonia as *Legionella* pneumonia based on these findings.

As shown in Table 1, hyponatremia, hypophosphatemia, and hypouricemia existed at the time of his admission. Hypophosphatemia and hypouricemia were associated with an elevation of the fractional excretion of phosphate (FEP, 52.1%) and uric acid (FEUA, 11.7%). Furthermore, elevated levels of urine low-molecular-weight tubular proteins, including urinary β2-microglobulin (β2MG) and N-acetyl-β-D-glucosaminidase (NAG), and the presence of glycosuria and panaminoaciduria as assessed via high-performance liquid chromatography (L-8500, Hitachi, Tokyo, Japan) were detected (Table 2). These findings suggested that his hypo-
phosphatemia and hypouricemia were secondary to Fanconi syndrome. With regard to hyponatremia, the presence of hypouricemia and the elevation of both FEUA and FEP suggested that the cause of hyponatremia was renal salt wasting (1). In addition, his physical findings suggested he was volume-depleted, which was consistent with renal salt wasting. For these reasons, we commenced the intravenous administration of azithromycin with normal saline and Ringer’s solution without fluid restriction, a regimen which gradually improved his electrolyte imbalance (Figure). Once fluid administration was commenced, his urinary osmolality decreased, which is consistent with renal salt wasting (Figure). Two weeks of this treatment improved his general condition and electrolyte imbalance.

**Case 2**

A 63-year-old Japanese man was admitted to our hospital for fever, cough, and diarrhea. He had a medical history of cerebral infarction, gastric ulcer, and polycythemia vera, and was being treated with clopidogrel, nizatidine, and camostat mesilate. Physical examination on admission indicated a blood pressure of 159/89 mmHg, pulse rate of 102 beats/min, and body temperature of 39.7°C. He was conscious and non-edematous, and he complained of dryness of the mouth. His laboratory findings (Table 1) at admission were as follows: WBC 5,960/μL (Neutro: 88.0%, Eosino: 0.0%, Baso: 0.0%, Mono: 4.4%, Lymph: 7.6%), RBC 517×10^12/μL, Hb 14.4 g/dL, Ht 41.4%, Plt 15.4×10^11/μL, AST 201 U/L.

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**Table 2. Urinary Amino Acid Levels in the Two Cases.**

| Amino Acid                          | Normal range (μmol/day)* | Case 1    | Case 2    |
|-------------------------------------|--------------------------|-----------|-----------|
| Taurine                             | 322.2–5214.5             | 2,147.9   | 2,680.1   |
| Phosphoethanolamine                 | 31.0–110.0               | 105.7     | X         |
| Urea                                | 130.3–493.2              | 182.7     | 228.1     |
| Aspartic acid                       | < 12.7                   | 8.6       | 5.8       |
| Hydroxyproline                      | N.D.                     | N.D.      | N.D.      |
| Threonine                           | 79.9–528.3               | 603.8     | 205.8     |
| Serine                              | 208.8–1,020.0            | 1,132.2   | 570.9     |
| Asparagine                          | 60.7–372.3               | 597.1     | 372.5     |
| Glutamic acid                       | 11.3–42.7                | 34.6      | 31.9      |
| Glutamine                           | 207.0–1,357.3            | 579.3     | 530.1     |
| Sarcosine                           | < 99.0                   | 40.0      | 31.6      |
| α-Aminoacidic acid                  | 16.7–118.6               | 55.4      | 41.2      |
| Proline                             | N.D.                     | N.D.      | N.D.      |
| Phosphoethanolamine                 | 652.1–3,670.6            | 658.1     | 462.7     |
| Alanine                             | 141.2–833.9              | 812.6     | 710.0     |
| Citrulline                          | 13.5–55.6                | 87.2      | 26.1      |
| Valine                              | < 27.1                   | 79.3      | 35.4      |
| Cysteine                            | 24.8–82.2                | 96.6      | 87.5      |
| Cystathionine                       | 23.7–170.9               | 252.0     | 94.2      |
| Methionine                          | < 44.7                   | 28.0      | 28.1      |
| Isoleucine                          | < 20.2                   | 11.3      | 8.2       |
| Leucine                             | 7.5–23.5                 | 16.2      | 13.7      |
| Tyrosine                            | 24.6–89.3                | 82.0      | 55.8      |
| Tyrosine                            | 50.6–308.4               | 345.3     | 195.2     |
| Phenylalanine                       | 27.2–110.2               | 457.9     | 378.7     |
| γ-Amino-β-hydroxybutyric acid       | N.D.                     | N.D.      | N.D.      |
| β-Alanine                           | < 153.0                  | 8.2       | N.D.      |
| β-Amino-iso-butryric acid           | < 1,623.9                | 333.0     | 1,395.1   |
| γ-Aminobutyric acid                | N.D.                     | X         | X         |
| Monoethanolamine                    | 195.3–606.2              | 296.2     | 258.5     |
| Homocystine                         | N.D.                     | N.D.      | N.D.      |
| Histidine                           | 436.4–2,786.5            | 1,357.0   | 1,021.9   |
| 3-Methylhistidine                   | 113.4–480.9              | 272.5     | 267.3     |
| 1-Methylhistidine                   | 59.3–2,816.2             | N.D.      | T.R.      |
| Carnosine                           | < 87.6                   | 19.0      | 19.9      |
| Anserine                            | < 231.4                  | N.D.      | N.D.      |
| Tryptophan                          | 20.7–150.7               | 263.3     | X         |
| Hydroxylysine                       | < 22.9                   | 2.8       | N.D.      |
| Ornithine                           | 6.9–43.9                 | 67.1      | 36.3      |
| Lysine                              | 51.6–1,639.6             | 290.3     | 74.3      |
| Arginine                            | 11.6–54.8                | 16.8      | 16.9      |

Underlining indicates an abnormal value.

N.D. means not detected.

X means not measured.

*Urea: mmol/day.
**Figure.** Clinical course of cases 1 and 2. AZM: Azithromycin, LVFX: Levofloxacin, FGF-23: fibroblast growth factor 23, U-β2 MG: urinary β2-microglobulin, U-NAG: urinary N-acetyl-beta-D-glucoasaminidase, CRP: C-reactive protein, UA: Uric acid, FE: fractional excretion, Osm: Osmolality
ALT 84 U/L, BUN 11 mg/dL, creatinine 0.75 mg/dL, CK 12,675 IU/L, CRP 19.86 mg/dL, BNP 60.9 pg/mL, proteinuria (++), glycosuria (+), and urine WBC (±). ADH, PRA, and aldosterone were not measured. A chest CT scan showed a ground-glass appearance in the right lower lung lobe, and the urinary antigen test for *Legionella pneumophila* was positive. These findings suggested a diagnosis of *Legionella* pneumonia.

As shown in Table 1, hyponatremia, hypophosphatemia, and hypouricemia existed at the time of his admission. Despite the hypophosphatemia and hypouricemia, both FEP and FEUA were elevated. Furthermore, elevated levels of low-molecular-weight tubular protein, including urinary β₂ MG and NAG, and the presence of glycosuria and panaminoaciduria were detected (Table 2). These findings suggested that his hypophosphatemia and hypouricemia had been caused by Fanconi syndrome. As in the previous case, the presence of hypouricemia and elevated FEUA (18.6%) and FEP (18.9%) suggested that the cause of hypouricemia was renal salt wasting (1). In addition, his physical findings suggested he was volume-depleted, which was also consistent with renal salt wasting. For these reasons, we commenced the intravenous administration of levofloxacin with normal saline and Ringer’s solution without fluid restriction, a regimen which gradually improved his electrolyte imbalance. The administration of Ringer’s solution caused his urinary osmolality to decrease, which is consistent with renal salt wasting (Figure). Two weeks of this treatment improved his general condition and electrolyte imbalance.

**Discussion**

The two cases described herein shared two important clinical features: Hypophosphatemia and hypouricemia were caused by Fanconi syndrome, and hyponatremia seemed to not be caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH), but by renal salt wasting due to proximal tubular dysfunction.

In these two cases, hypophosphatemia and hypouricemia associated with *Legionella pneumophila* pneumonia had been caused by Fanconi syndrome. The renal manifestations of *Legionella pneu-

omia* reportedly include microscopic hematuria, acute kidney injury due to rhabdomyolysis (2-4), acute tubular necrosis (5), and acute tubulointerstitial nephritis (5, 6). One previous article from Japan reported that two patients with *Legionella* pneumonia showed Fanconi syndrome (7), which is characterized by a dysfunction of the proximal tubule leading to elevated urinary excretion of amino acids, glucose, phosphate, and uric acid (8). The authors concluded that *Legionella pneumophila* might infect the proximal tubular cells, induce mitochondrial dysfunction, and cause Fanconi syndrome (7). In our two cases, the laboratory findings, which included elevated FEUA, FEP, urinary β₂ MG, and urinary NAG, and the presence of glycosuria and panaminoaciduria, were consistent with Fanconi syndrome. Interestingly, in both cases, fibroblast growth factor (FGF)-23 at admission, determined by an enzyme-linked immunosorbent assay (ELISA) kit (Kainos Laboratories, Tokyo, Japan), was not elevated despite the increase in FEP, which is also consistent with Fanconi syndrome. Of further note, our cases lacked any other etiology for Fanconi syndrome, such as drug therapy (with cisplatin, ifosfamide, tenofovir, cidofovir, adefovir, didanosine, gentamicin, azathioprine, etc.) or heavy metal poisoning, and their abnormal laboratory data rapidly normalized with treatment of the *Legionella* pneumonia. As described in a previous case report (7), we speculated that Fanconi syndrome in these patients had been caused by *Legionella* pneumonia. In both the previous cases (7) and our cases, Fanconi syndrome was successfully treated by treating the primary disease.

In our patients, the clinical course of hyponatremia suggested that its etiology was more likely to be renal salt wasting than SIADH. Hyponatremia often occurs in *Legionella* pneumonia patients (9-14). Although it is crucial for physicians to understand the various etiologies of hyponatremia, as their treatments differ, the mechanism of hyponatremia in *Legionella* pneumonia has not yet been clarified. The main cause of hyponatremia due to *Legionella* pneumonia is reportedly SIADH (15, 16). However, Schuetz et al. reported that, although the serum sodium levels in patients with *Legionella* pneumonia are much lower than those due to other causes of community-acquired pneumonia, the level of Copeptin (CT-ProVasopressin), which is a precursor of ADH, is not significantly elevated (17). They concluded that salt loss might be a cause of hyponatremia and recommended hydration and salt repletion for treatment (17). In our cases, we postulated that hyponatremia due to *Legionella* pneumonia had been caused by renal salt wasting due to proximal tubular dysfunction. Recently, several important diagnostic markers have been proposed to distinguish SIADH from renal salt wasting. Bitew et al. reported that patients with *Legionella* pneumonia showed elevated FEP due to proximal tubular dysfunction (18). Maesaka et al. reported that saline infusion reduced ADH secretion caused by volume depletion, thereby resulting in excretion of dilute urine and correction of hyponatremia in renal salt wasting patients (19). Maesaka et al. further reported that FEUA exceeding 11% is consistent with both SIADH and renal salt wasting (20). In our cases, both FEUA and FEP were elevated, and urinary osmolality decreased by administration of saline and Ringer’s solution (Figure), suggesting that the condition was due to renal salt wasting. Furthermore, a previous article reported that hyponatremia caused by SIADH either does not improve or is aggravated by isotonic saline administration (21, 22). This phenomenon is most likely to occur when the patient’s urinary osmolality is above 530 mOsm/kg (23). In spite of the high urinary osmolality in our cases, their hyponatremia rapidly responded to the administration of saline and Ringer’s solution, which is contrary to what occurs with SIADH.

However, the findings in our patients had some discrepancies with renal salt wasting. First, while fractional excretion
of sodium (FENa) is usually increased in salt wasting, it was not elevated in both of our cases. However, urinary Na exceeded 40 mmol/L in both cases. The previous cases of renal salt wasting described by Maesaka et al. also presented decreased urinary Na and FENa (18, 19), and the authors concluded that these parameters might have been low due to reduced sodium ingestion (1). Second, in patients with renal salt wasting, FEUA is reported to remain above 11% after correction of hyponatremia, but it normalizes after treatment of SIADH (1, 20). In our case 2, the elevated FEUA resolved after improvement of hyponatremia. The precise reason for this is not clear, but we speculate that rapid improvement of proximal tubular dysfunction may have affected improvement of FEUA (Figure).

As a limitation associated with our report, we did not measure the hormone levels, including thyroid hormone, cortisol, ADH, plasma renin activity, and aldosterone. However, in both our cases, hyponatremia improved by fluid administration, and normonatremia was maintained after treatment. This suggests that their diagnosis was neither hypothyroidism nor adrenal insufficiency. Reportedly, an elevated plasma renin activity and increased plasma aldosterone levels support the diagnosis of renal salt wasting (1). However, a recent review stated that it is difficult to evaluate these data in hyponatremic patients because their levels are affected by saline infusion, and hence, FEUA should be used to diagnose this condition (20).

We herein reported two cases of Legionella pneumonia that were associated with Fanconi syndrome and hyponatremia. In such patients, the electrolyte imbalance should be corrected by treatment of the primary disease, with additional consideration of fluid administration. FEUA and monitoring the urinary osmolality during the administration of saline may be useful in diagnosing salt wasting. Further studies are needed to clarify the mechanisms of hyponatremia in Legionella pneumonia.

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

Authorship: All authors had full access to the data and played a role in writing this manuscript.

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