Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0942-18
Intern Med 57: 2975-2980, 2018
http://internmed.jp

【 CASE REPORT 】

Legionella Pneumonia Complicated with Acquired Fanconi Syndrome

Ryo Koda[1], Ryo Itoh[2], Masafumi Tsuchida[1], Kazumasa Ohashi[2], Noriaki Iino[1], Toshinori Takada[2] and Ichiei Narita[3]

Abstract:

Legionella pneumonia is occasionally accompanied by renal complications; however, the cause of this remains unknown. We herein report a 70-year-old Japanese man with *Legionella* pneumonia who presented with hyponatremia, hypophosphatemia, and hypouricemia. The levels of urinary β2-microglobulin and N-acetyl-β-D-glucosaminidase were remarkably high, indicating severe renal tubular damage. The presence of glycosuria and aminoaciduria as well as increased fractional excretion of uric acid and decreased tubular reabsorption of phosphate indicated that the patient's condition was complicated with Fanconi syndrome. After antimicrobial therapy, the electrolyte abnormalities and renal tubular damage were completely resolved.

Key words: aminoaciduria, *Legionella* pneumonia, Fanconi syndrome, rhabdomyolysis

(Intern Med 57: 2975-2980, 2018)
(DOI: 10.2169/internalmedicine.0942-18)

Introduction

Legionella pneumophila infection is an important cause of severe community-acquired pneumonia. Various extrapulmonary symptoms can develop during the clinical course of *Legionella* pneumonia. In addition, rhabdomyolysis-associated acute renal failure (ARF) and acute tubulointerstitial nephritis (ATIN) have been reported to develop following infection (1-3). Furthermore, complications of electrolyte imbalances, such as hyponatremia and hypophosphatemia, are distinct clinical features of *Legionella* pneumonia (4). Recently, acquired Fanconi syndrome has been reported to be a rare complication of *Legionella* pneumonia (5) and is suggested to be causative of these electrolyte imbalances (6).

We herein report a case of *Legionella* pneumonia that included hyponatremia, hypouricemia, and hypophosphatemia. Increased fractional excretion of uric acid and decreased tubular reabsorption of phosphate suggested an impaired reabsorptive function of the renal proximal tubules. In addition, the presence of glycosuria and aminoaciduria were later confirmed, thereby indicating the patient's complication with Fanconi syndrome.

Case Report

A 70-year-old Japanese man was referred to our emergency department because of general fatigue, myalgia, and a non-productive cough over the past 3 days. He did not drink, but he had smoked 20 cigarettes per day for 35 years. His family and personal medical history was unremarkable. He did not take any regular medications. Three weeks prior to admission, he had visited a hot spring resort in another prefecture. Upon admission, he looked sick. His weight was 51.7 kg, and his height was 160 cm (body mass index 20.2 kg/m^2). His body temperature was 39.2℃, pulse rate 94/min, blood pressure 118/66 mmHg, and oxygen saturation 98% on room air. His consciousness was clear. Auscultation of the chest revealed coarse crackles in the left lower lung field. His heart sounds were normal without any audible murmur. His abdomen was soft without tenderness. The bilateral cost-vertebral angle was not tender. Skin rashes, edema formation, cyanosis, and joint swelling were absent, but he showed myalgia in his extremities. His skin turgor

[1]Department of Nephrology, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Japan, [2]Department of Respiratory Medicine, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Japan and [3]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Science, Japan
Received: February 1, 2018; Accepted: March 14, 2018; Advance Publication by J-STAGE: June 6, 2018
Correspondence to Dr. Ryo Koda, ryokouda@gmail.com

Table 1. Laboratory Data upon Admission.

Blood cell count	
WBC (/μL)	14,000 (3,300-8,600)
Hemoglobin (g/dL)	14.1 (13.7-16.8)
Platelet ($\times10^4$/μL)	19.2 (15.8-34.8)
Urinalysis	
pH	6.5
Glucose	(1+)*
Ketones	(-)
Blood	(3+)*
Protein	(2+)*
RBCs (/HPF)	10-19*
WBCs (/HPF)	1-4
β_2-microglobulin (μg/L)	83,326* (13-287)
NAG (U/L)	58.1* (<11.3)
Sodium (mEq/L)	30
Potassium (mEq/L)	54.8
Phosphate (mg/dL)	60.2
Calcium (mg/dL)	2.2
Osm (mOsm/kg/H_2O)	410
Creatinine (mg/dL)	107
Uric acid (mg/dL)	33.3
Protein (mg/dL)	85
Myoglobin (ng/mL)	>15,000*
Arterial blood gas	
pH	7.581* (7.35-7.45)
pCO_2 (torr)	24.4* (32-48)
pO_2 (torr)	56.2* (83-108)
HCO_3^- (mEq/L)	23 (24-26)
Others	
FENa (%)	0.23
FEK (%)	13.8 (10-20)
%TRP (%)	69* (81-90)
FEUA (%)	15.5* (5.5-11)

Biochemical data	
Creatinine kinase (IU/L)	8,611* (59-248)
Creatinine kinase MB (IU/L)	47* (0-25)
Blood urea nitrogen (mg/dL)	13 (8-18.4)
Creatinine (mg/dL)	1.05 (0.65-1.07)
Uric acid (mg/dL)	2.1* (3.7-7.8)
Sodium (mEq/L)	128* (138-145)
Potassium (mEq/L)	3.9 (3.6-4.8)
Chloride (mEq/L)	93* (101-108)
Calcium (mg/dL)	8.1* (8.8-10.1)
Inorganic phosphate (mg/dL)	1.9* (2.7-4.6)
TSH (μIU/mL)	0.66 (0.5-5)
Triiodothyronine (pg/mL)	1.82* (2.3-4)
Thyroxine (ng/dL)	1.29 (0.9-1.7)
ACTH (pg/mL)	6.2* (7.2-63.3)
Cortisol (μg/dL)	38.4* (4-18.3)
Renin (ng/mL/h)	0.8 (0.3-2.9)
Aldosterone (ng/dL)	10.4* (35.7-240)
Antidiuretic hormone (pg/mL)	2.4* (0.3-3.5)
BNP (pg/mL)	46.6* (<18.4)
1,25-$(OH)_2$ vitamin D (pg/mL)	108* (20-60)
intact-PTH (pg/mL)	48 (10-65)
FGF-23 (pg/mL)	<10
Blood sugar (mg/dL)	140* (70-109)
Hemoglobin A1c (%)	5.8 (4.6-6.2)
ESR (mm/h)	54* (0-9)
C-reactive protein (mg/dL)	15.75* (0-0.14)
Osm (mOsm/kg/H_2O)	261* (275-290)
Anti-nuclear antibody	<40
Anti-SS-A antibody	<0.5
Anti-SS-B antibody	<0.5
Rheumatoid factor (IU/mL)	3 (0-18)
Immunoglobulin G (mg/dL)	834* (861-1,747)
Immunoglobulin A (mg/dL)	447* (93-393)
Immunoglobulin M (mg/dL)	36 (33-183)
CH50 (U/mL)	43 (30-45)

Abnormal values are indicated by asterisks (*).

ACTH: adrenocorticotropic hormone, BNP: type B natriuretic peptide, CH50: homolytic complement activity, ESR: erythrocyte sedimentation rate, FEUA: fractional excretion of uric acid, FEK: fractional excretion of potassium, FENa: fractional excretion of sodium, NAG: N-acetyl-β-D-glucosaminidase, Osm: osmolality, TSH: thyroid-stimulating hormone, %TRP: tubular reabsorption of phosphate

was decreased, and his oral mucosa was dry, indicating that the patient was dehydrated. No apparent abnormalities were noted during a neurological examination.

Laboratory findings upon admission showed a white blood cell count of 14,000/μL, red blood cell count of 5.96×10^6/μL, hemoglobin of 14.1 g/dL, platelet count of 19.2×10^4/μL, erythrocyte sedimentation rate of 54 mm/h, blood glucose of 140 mg/dL, hemoglobin A1c of 5.8%, and C-reactive protein of 15.75 mg/dL. Elevated levels of liver enzymes and creatinine kinase and decreased levels of serum sodium, inorganic phosphate, and uric acid were also noted (major laboratory findings are summarized in Table 1). The urinary level of myoglobin exceeded the measurable value (>15,000 ng/mL). A routine electrocardiogram showed a normal sinus rhythm without significant ST segment changes. Chest X-ray showed consolidation in the left lower lung field (Fig. 1). Chest computed tomography (CT) and a bronchogram revealed alveolar consolidations in the left lower lung lobe. A Legionella urinary antigen test (Binax-NOW® Legionella; Alere Scarborough, Maine, USA) was positive, resulting in a diagnosis of *Legionella* pneumonia. A urinalysis showed glycosuria despite the patient's normal blood glucose level. In addition, an increased fractional excretion of uric acid (FEUA, 15.5%) and decreased tubular reabsorption of phosphate (%TRP, 69%) despite hypouricemia and hypophosphatemia suggested an impaired reabsorption of these substances in the renal tubules. We measured the urinary β_2-microglobulin (β_2-MG) and N-acetyl-β-D-

glucosaminidase (NAG) levels and found them to be remarkably high (83,326 μg/L and 58.1 U/L, respectively). Panaminoaciduria was confirmed by high-performance liquid chromatography.

These findings indicated that the present case was complicated with Fanconi syndrome. Hyponatremia (serum sodium level of 128 mEq/L) was also noted at the time of admission. The thyroid and adrenal function as well as the plasma renin and aldosterone levels were within the normal range. His serum antidiuretic hormone (ADH) level was not suppressed (2.4 pg/mL) despite his hyponatremia and low serum osmolality (261 mOsm/kg/H_2O). Based on his physical findings and decreased fractional excretion of sodium (0.23%), we suspected that he was experiencing a volume-depleted condition. A decreased HCO_3^- concentration (21.7 mEq/L) and hypokalemia (3.3 mEq/L) were noted the next day, which were consistent with the urinary loss of bicarbonate ion and potassium.

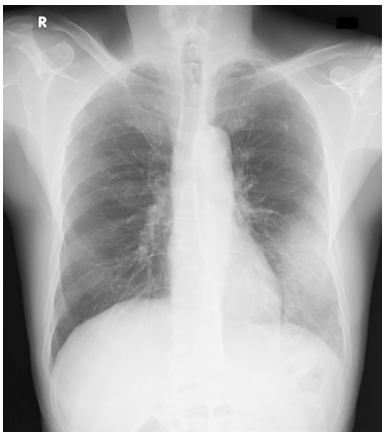

Figure 1. **Chest X-ray findings upon admission. Consolidation was noted in the left lower lung field.**

He was treated with 500 mg of intravenous azithromycin for 5 days followed by 500 mg of oral levofloxacin for 7 days. At the same time, fluid resuscitation therapy immediately and uneventfully corrected his hyponatremia. His rhabdomyolysis, hypophosphatemia, hypouricemia, and renal proximal tubular injury were all improved after *Legionella* pneumonia was successfully treated. The FEUA and %TRP returned to nearly within the normal range (Fig. 2).

Discussion

Fanconi syndrome is caused by the massive loss of filtered substances, such as electrolytes, uric acid, amino acids,

AZM: azithromycin 500mg/day*5days
LVFX: levofloxacin 500mg/day*7days

	AZM	LVFX		
day	1	6	20	48
CRP (mg/dL)	15.75	3.78	0.03	0.03
CPK (IU/L)	8611	798	158	NA
urine β2-MG (μg/L)	83326	2461	29.6	57.4

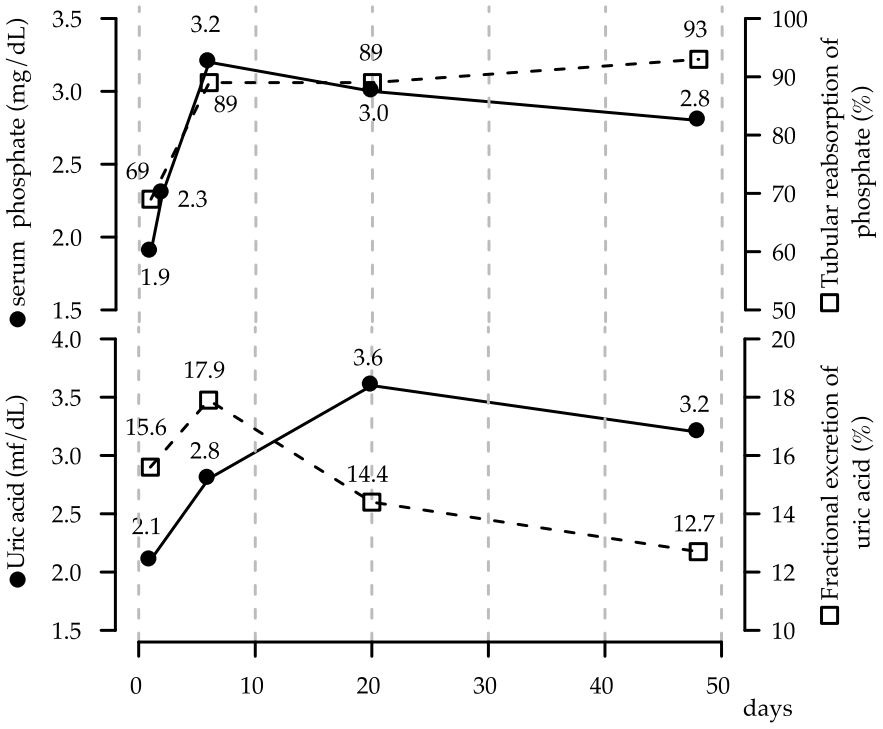

Figure 2. **Clinical course.**

glucose, and bicarbonate ions, due to the impaired re-absorptive function of the proximal tubules (7). The impaired mitochondrial function is proposed as a mechanism underlying the acquired form of Fanconi syndrome (8). Since the process of active reabsorption requires extensive energy production, epithelial cells in the renal proximal tubules are rich in mitochondria (9). Mitochondrial dysfunction therefore results in an insufficient proximal tubular function and eventually leads to Fanconi syndrome, as clinically demonstrated by the analysis of congenital mitochondrial disease (10).

Our case showed an increased fractional excretion of uric acid and decreased tubular reabsorption of phosphate despite hypouricemia and hypophosphatemia, glycosuria, and panaminoaciduria, all of which were consistent with the clinical feature of Fanconi syndrome. The levels of FGF-23, intact-PTH, and 1,25$(OH)_2$-vitamin D further indicated that hypophosphatemia was the consequence not of hormonal disorders but of the impaired re-absorption of the renal proximal tubules. Fanconi syndrome is usually accompanied by metabolic acidosis due to the massive loss of bicarbonate ions via the urine (7). An arterial blood gas analysis at admission revealed respiratory alkalosis with insufficient metabolic compensation in the present patient (pH 7.581, pCO_2 24.4 torr, and HCO_3^- 23 mEq/L). He was complicated with metabolic alkalosis, since the expected HCO_3^- concentration was 20.8 mEq/L (calculated using a formula for acute phase: $HCO_3^- = 24\text{-}0.2\times\Delta pCO_2$). The next day, after he received fluid replacement therapy, a reduced HCO_3^- concentration was noted (21.7 mEq/L). Contraction alkalosis due to volume depletion may have concealed the concomitant metabolic acidosis at the time of his initial presentation. Regarding the serum potassium value, the urinary potassium concentration was high (54.8 mEq/L), and the patient actually developed hypokalemia (3.3 mEq/L) the next day, indicating an impaired potassium re-absorption in the proximal tubules.

The etiology of acquired Fanconi syndrome includes medications, such as adefovir (11) or tenofovir (12), hematological diseases [paraprotein-related kidney disease (13) and direct tumor cell invasion (14)], and autoimmune disorders causing interstitial nephritis (15). Our patient was not taking any medications suspected to cause Fanconi syndrome. Blast cells were undetected in a peripheral blood smear, and a monoclonal protein band was absent on serum electrophoresis. Antinuclear antibodies, anti-SSA/SSB antibody, and anti-mitochondrial M2 antibody were negative. These laboratory findings and his clinical course, in which the renal proximal tubular injury and electrolyte imbalances fully recovered after the treatment of *Legionella* pneumonia, strongly suggest that this patient's Fanconi syndrome was mediated by a *Legionella* infection.

Fanconi syndrome associated with *Legionella* pneumonia is an extremely rare condition, and only two other cases have been reported to date (5, 6). We summarized the reported cases in Table 3. The exact pathophysiology of this condition remains unknown, but at least three mechanisms may be considered: 1) rhabdomyolysis and myoglobinuria-induced tubular injury, 2) direct *Legionella pneumophila* infection in the renal tubules, and 3) a complication of acute tubulointerstitial nephritis (ATIN). Our case showed extremely elevated levels of creatinine kinase (8,611 IU/L) and urinary myoglobin (>15,000 ng/mL) at the time of admission, indicating the presence of rhabdomyolysis as a complication of *Legionella* infection. Plotnikov et al. evaluated the effects of direct myoglobin toxicity in the kidney in an experimental study (16). They demonstrated that myoglobin induces oxidative stress and causes mitochondrial dysfunction in the renal tubules. Thus, it is conceivable that Fanconi syndrome in *Legionella* pneumonia is the result of the toxic effect of myoglobin to the mitochondrial function in proximal tubules.

The extremely elevated urinary β2-MG and NAG levels in our patient may have been caused by proximal tubular injury via exposure to a large amount of filtered myoglobin. As such, although the glomerular filtration itself was not impaired, the re-absorptive function in the proximal tubules may have been transiently impaired by myoglobinuria-induced mitochondrial dysfunction, thereby leading to the development of Fanconi syndrome. The urinary myoglobin level was not described in the two previous reports (5, 6) (Table 3); however, the serum CK level was elevated in all cases, suggesting the possibility of complication with rhabdomyolysis and myoglobinuria.

Kinoshita-Takahashi et al., who reported the previous two cases of Fanconi syndrome associated with *Legionella* pneumonia, speculated that a direct infection of *Legionella pneumophila* in the proximal tubules disrupted the mitochondrial function (5). This was supported by the findings of a human autopsy case report of a patient infected with *Legionella* pneumonia. In that report, using immunofluorescence, researchers observed that *Legionella* was present throughout the renal proximal tubules (17). Other experiments have shown that mitochondrial messenger RNA synthesis is impaired in the amoeba *Dictyostelium discoideum* following *Legionella* infection (18). *Legionella pneumophila* can cause bacteremia (19), thereby exposing the renal proximal tubules to direct infection via blood stream dissemination. However, as the authors discussed, they did not confirm their hypothesis in their case report by a kidney biopsy. The definitive cause of Fanconi syndrome in the present patient also remains unclear, since we did not perform a kidney biopsy to obtain histological evidence of the direct invasion of *Legionella* pneumophila into the renal proximal tubules, myoglobin-induced obstructive tubulopathy or mitochondrial injury, or concomitant tubulointerstital nephritis.

Acute tubulointerstitial nephritis (ATIN) can also develop during the clinical course of *Legionella* pneumonia, possibly via direct bacterial infection or by rhabdomyolysis-induced indirect action (3). Some cases require additional corticosteroid treatment for prolonged kidney injury (2, 20). Autoimmune disorders causing interstitial nephritis are known to be

Table 2. Reported Cases with Legionnaires' Disease-associated Fanconi Syndrome.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Gender	75/M	57/M	65/M	63/M	70/M
Treatment	PZFX, GRNX	PZFX, LVFX, GRNX	AZM	LVFX	AZM, LVFX
Blood test					
Urea nitrogen (mg/dL)	17	41	14	11	13
Creatinine (mg/dL)	0.88	2.23	0.85	0.75	1.05
Uric acid (mg/dL)	2.4	2.7	3.8	1.4	2.1
Sodium (mEq/L)	121	143	128	128	128
Potassium (mEq/L)	3.4	3.5	3.6	3.3	3.9
Chloride (mEq/L)	83	107	91	93	93
Phosphorus (mg/dL)	1.3	2	1.5	1.2	1.9
Creatine phosphokinase (IU/L)	670	2,330	2,999	12,675	8,611
Urinalysis					
Protein	2+	2+	2+	2+	2+
Glucose	3+	2+	2+	+	1+
Aminoaciduria	+	+	+	+	+
%TRP	54	51	47.9	81.1	69
FEUA	18.7	42.8	11.7	18.6	15.5
β_2-microglobulin (μg/L)	80,397	110,556	67,900	115,000	83,326
NAG (U/L)	18	19.7	51.2	22.9	58.1
Reference	(5)	(5)	(6)	(6)	Present case

AZM: azithromycin, FEUA: fractional excretion of uric acid, GRNX: garenoxacin, LVFX: levofloxacin, NAG: N-acetyl-β-D-glucosaminidase, PZFX: pazufloxacin, %TRP: tubular reabsorption of phosphate

associated with Fanconi syndrome (15). Thus, ATIN may be another etiology for Fanconi syndrome in *Legionella* pneumonia. In our case, however, ATIN was unlikely, as typical findings (e.g., skin rash, arthralgia, eosinophilia, or leukocyturia) suggesting the development of ATIN were not conspicuous.

Conclusion

We experienced an extremely rare case of Fanconi syndrome associated with *Legionella* pneumonia with rhabdomyolysis and myoglobinuria with multifactorial causes. Further case reports will be useful for clarifying the exact mechanism underlying Fanconi syndrome associated with *Legionnaires'* disease. This will help determine the appropriate management of electrolyte imbalances, which are major clinical complications associated with this potentially fatal infection.

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

Acknowledgement

We thank S. Oono and H. Sasaoka for assisting with the biochemical analyses, including those of the urinary amino acids.

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