Clinicopathological characteristics and long-term prognosis of monoclonal immunoglobulin light chain associated Fanconi syndrome

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Abstract

Background and aims: Monoclonal immunoglobulin light chain associated Fanconi syndrome (LC-FS) is a rare disease that involves proximal tubules. As most of the reported cases came from western countries, we aimed to analyze the clinicopathological characteristics of Asian LC-FS and its treatment responses to chemotherapy.

Methods: A total of 26 LC-FS patients in a single-center were retrospectively studied.

Results: At diagnosis, the mean age of the 26 Asian LC-FS patients was 54.7 ± 14.7 years, with females accounting for 57.7%. They presented with different degrees of proximal tubular dysfunctions with normoglycemic glycosuria (88.0%), hyperphosphaturia (84.2%) and aminoaciduria (84.0%) as the most common features. The mean estimated glomerular filtration rate (eGFR) was (68.0 ± 26.4) ml/min per 1.73 m². After chemotherapy, renal response was achieved in 58.3% cases, which was accompanied by hematological response, and tubular response was acquired in 66.7% cases. During 3 years of follow-up, the eGFR levels significantly decreased in the monoclonal gammopathy of renal significance patients, few of whom (21.4%) had received chemotherapy.

Conclusion: Asian LC-FS patients had mild renal function disorder. The chemotherapy could improve both renal and tubular functions, which may be related to the hematological response.

Keywords: chemotherapy, Fanconi syndrome, monoclonal immunoglobulin light chain, renal function

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significance (MGRS) and multiple myeloma (MM). Waldenstrom macroglobulinemia (WM), a clonal B-cell lymphoproliferative disorder characterized by massive production of monoclonal immunoglobulin M (IgM) in serum, is increasingly recognized as another cause of LC-FS. To date less than 150 LC-FS cases have been reported, with different degrees of proximal tubular (PT) lesions and impaired renal function, as well as bone metabolism dysfunction. Most of the cases were reported by western countries. Although some of the literature focused on the treatment schemes and hematological response to certain agents, few have paid attention to the long-term outcomes and detailed renal and tubular response to chemotherapy in LC-FS patients.

In this study, we retrospectively studied a single-center cohort of 26 patients with LC-FS, trying to explore the clinicopathological characteristics and the appropriate therapy regimens to alleviate both renal and hematological dysfunction.

Methods

Patients and groups
Patients who were diagnosed with both renal FS and monoclonal gammopathy in Peking Union Medical College Hospital (PUMCH) from January 1998 to February 2019 were enrolled. The diagnoses of MGRS, MM, WM and primary plasma cell leukemia (PPCL) were based on the international criteria. According to renal FS definitions in the literature, the diagnosis of renal FS in this study was based on the five criteria, including (I) normoglycemic glycosuria, with positive urine glucose test in condition of normal blood glucose level; (II) aminoaciduria; (III) hypophosphatemia and hyperphosphaturia; (IV) hypouricemia, which should exclude other factors leading to it such as drugs, malnutrition, severe hepatic injury, Wilson’s disease, syndrome of inappropriate secretion of antidiuretic hormone, other malignant tumors, diabetes mellitus, pregnancy, and intractable diarrhea; and (V) proximal RTA. When patients met with items I, II, III, and IV, full blown FS was diagnosed. When patients had at least three of the above items or at least two of the above items as well as specific PT injuries confirmed by kidney biopsy, incomplete FS was diagnosed. The specific PT injuries in kidney biopsy include light chains deposition, crystalline formation or increased lysosomes in PT cells confirmed by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM). Exclusion criteria of this study were as follows: (I) the presence of other causes of renal FS, especially the use of any drugs known to induce PT dysfunction or autoimmune diseases; (II) inadequate data for the diagnosis of proximal tubulopathy.

A group of 25 primary Sjogren’s syndrome (pSS) associated FS (pSS-FS) was also enrolled as the control group. The diagnosis of pSS was made according to the revised version of the American-European Consensus Group.

Data collection
We retrospectively reviewed the demographic and clinicopathological features of the patients, including gender, age, clinical symptoms, physical and laboratory examination, renal biopsies, treatment regimens and follow-up data. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Renal tubular functions were measured through the following tests: serum phosphorus and uric acid; urine glucose and amino acid; 24-h urine excretion of phosphate, potassium, sodium and chloride; plasma creatinine and urine creatinine, and renal tubular reabsorption of phosphate (TmP/GFR).

This study was carried out in accordance with the Helsinki Declaration and received approval to exempt from full review by the local Ethic Committee of Peking Union Medical College Hospital (SK1153). Written informed consent of using the pathology data has been obtained from all patients before the renal biopsy.

Assessment of renal tubular functions

*Hyperphosphaturia.* Hyperphosphaturia was defined as one of the following standards: (I) increased urinary fractional excretion of phosphate [FEPO₄ = (urine phosphate × plasma creatinine)/(plasma phosphate × urine creatinine) × 100%, >20%] in the condition of hypophosphatemia; (II) increased 24-h phosphorus excretion (>100 mg/day) in the condition of hypophosphatemia; (III) decreased renal tubular reabsorption of phosphate (TmP/GFR < 0.77 mmol/L).
**Identification of RTA types.** Arterial blood gas analysis, urinalysis and urine electrolytes measurements were evaluated. Hyperchloremic metabolic acidosis was diagnosed when serum pH was <7.35 and serum bicarbonate levels were <24 mmol/l with normal anion gap. Urine anion gap was calculated by the formula (urine sodium + urine potassium – urine chloride). If patients had urine pH > 5.5, positive urine anion gap and hypokalemia at the same time, distal RTA was considered. The RTA type was further confirmed by sodium bicarbonate infusion test: sodium bicarbonate infusion was performed until the serum bicarbonate reached 24 mmol/L. Fractional excretion of bicarbonate (FEHCO3) was measured by the formula (urine bicarbonate × plasma creatinine)/(plasma bicarbonate × urine creatinine) × 100%. When FEHCO3 was >10–15%, proximal RTA was confirmed. When FEHCO3 was <5%, distal RTA was diagnosed.16,18,20,21

**Kidney biopsy**

Two-micrometer slides were cut from formalin-fixed and paraffin-embedded sections of kidney tissues, stained with hematoxylin and eosin, periodic acid–Schiff, periodic acid–silver methamine and Masson trichrome for light microscopy in the laboratory of Nephrology Department at PUMCH. At least eight sections were examined for each patient. All sections were examined by an experienced pathologist who was blinded to the patient’s characteristics. Immunofluorescent staining was performed using fluorescein isothiocyanate-conjugated polyclonal antibodies to IgG, IgM, IgA, C3, C4, C1q, fibrinogen, albumin, hepatitis B surface antigen, hepatitis B core antigen, κ-chain and λ-chain. Some of the kidney tissue samples were fixed in glutaraldehyde, and then ultrastructurally evaluated by EM.

**Treatment responses and follow-up**

We defined treatment responses as follows: renal response was defined by a ≥30% increase in eGFR remaining for at least 6 months or ≥50% decrease (>0.5 g/day) of 24-h proteinuria (urine protein must be >0.5 g/day pretreatment) with ≤25% decrease in eGFR.6,22 Tubular response was defined by a ≥50% improvement or back to the normal level of at least two of the above PT dysfunctions, with stable eGFR lasting for 6 months.6,9 Hematological response was defined based on the International Society of Amyloidosis criteria:23 complete response (CR), negative serum and urine immunofixation with normal FLC ratio; very good partial response (VGPR), serum dFLC (dFLC = pathogenic FLC – (minus) other FLC isotype) <40 mg/l (or dFLC reduction >90%); partial response (PR), serum dFLC decreases >50%; progressive disease (PD), serum dFLC increases at least 30%. The follow-up data were obtained at 1, 3, 6, 12, 24 and 36 months of follow up.

**Statistical analysis**

The continuous variables are expressed as mean value ± standard deviation if normally distributed or as median value (range). Categorical variables are expressed as number (percentage). The normally distributed continuous variables were compared using t-test between two groups; the non-normally distributed continuous variables were compared using the Mann–Whitney U-test between two groups; the categorical variables were compared using the χ² test or Fisher’s exact test. The survival analysis was conducted by Kaplan–Meier method and differences were assessed with the log-rank statistic. A statistical significance was set at two-sided p < 0.05. All of the statistical analyses were performed with SPSS version 23.0 software package (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8 (Version 8.01, Graphpad Software Inc., CA, USA).

**Results**

**Clinical features**

From January 1998 to February 2019, 28 LC-FS patients were identified in PUMCH. By excluding a suspected drug-associated FS and a patient with Sjögren’s syndrome simultaneously, 26 LC-FS patients were enrolled in this study. At diagnosis, their mean age was 54.7 ± 14.7 years with females accounting for 57.7%. The most common symptoms were fatigue (95.7%), ostealgia (88.5%) and nocturia (61.1%) (Table 2).

**Hematological features.** For the hematological index, our patients showed serum FLC ratio abnormal (100.0%), urine immunofixation electrophoresis (IFE) positive (90.0%), serum IFE positive (57.7%) and serum protein electrophoresis positive
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(54.2%) (Table 1). Most of our patients presented with positive \( \kappa \)-chains (84.6%), while only four patients had \( \lambda \)-chains, which were rare. The clinical and pathological characteristics of \( \lambda \)-positive LC-FS both in our cohort and in the literature are shown in Supplemental material Table S2 online. As to the heavy chain isotypes, 10 patients had heavy chains detected including IgG (26.9%), IgA (7.7%) and IgM (3.8%), respectively. In the other 16 (61.5%) cases only monoclonal light chains in their urine and/or serum could be detected. For the underlying malignancies, MGRS (53.8%) and MM (38.5%) accounted for most patients, while WM and PPCL occurred in only one case (3.8%) respectively (Table 1).

Renal characteristics. At diagnosis, the median serum creatinine level was 91 (range, 38–270) \( \mu \)mol/l, with mean eGFR (68.0 ± 26.4) ml/min per 1.73 m\(^2\). There were 11 (42.3%) patients who had eGFR less than 60 ml/min per 1.73 m\(^2\). Our patients showed different degrees of PT dysfunctions, including normoglycemic glycosuria (88.0%), hyperphosphaturia (84.2%), aminoaciduria (84.0%), hypouricemia (80.8%), hypophosphatemia (80.8%), RTA (69.6%) and hypokalemia (42.3%). Half of them had full-blown FS. Proteinuria (>0.5 g/day) was observed in 21 (87.5%) patients, with the median urine protein level of 2.34 (range, 0.08–13.76) g/day. Elevated urine \( \beta \)2-microglobulin, urine \( \alpha \)1-microglobulin and urine transferrin were found in all the patients (100.0%) who had these tests (Table 2). We further compared the clinical characteristics between two different causes of renal FS including LC-FS and pSS-FS. Compared with pSS-FS, the LC-FS group had an older age at diagnosis, higher prevalences of ostealgia and normoglycemic glycosuria, more severe proteinuria and a lower frequency of hypokalemia. (Table 2).

Renal pathology
Kidney pathology was reviewed in the 10 patients who received kidney biopsy, which showed various non-specific damages of PT epithelium (Table 3), including PT atrophy (80.0%) (Figure 1C), disappearance of the apical brush borders membrane (80.0%), tubular casts (60.0%) (Figure 1A), tubular basement membrane thickening (60%) and vacuolar degeneration (60%). Some specific features of LC-FS were observed in the proximal tubules, including \( \kappa \) deposition in PT cells found by IF (Figure 1D), crystalline and increased lysosomes in PT cells found by LM and EM (Figure 1B, E and F). Different degrees of interstitial fibrosis with infiltration of monocytes and lymphocytes were also detected in all of the 10 patients (Figure 1A and C).

| Table 1. Hematological characteristics of the light chain associated Fanconi syndrome patients. |
|---|
| **Hematological index** |
| Abnormal serum FLC \( \kappa/\lambda \) ratio | 10/10 (100.0%) |
| Urine IFE positive | 18/20 (90.0%) |
| Serum IFE positive | 15 (57.7%) |
| SPE positive | 13/24 (54.2%) |
| **Underlying malignancy** |
| MGRS | 14 (53.8%) |
| MM | 10 (38.5%) |
| WM | 1 (3.8%) |
| PPCL | 1 (3.8%) |
| **Light chain isotype** |
| Kappa | 22 (84.6%) |
| Lambda | 4 (15.4%) |
| **Heavy chain isotype** |
| IgG | 7 (26.9%) |
| IgA | 2 (7.7%) |
| IgM | 1 (3.8%) |
| Light chain only | 16 (61.5%) |

\( \kappa \), kappa; \( \lambda \), lambda; FLC, free light chain; IFE, immunofixation electrophoresis; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MGRS, monoclonal gammopathy of renal significance; MM, multiple myeloma; PPCL, primary plasma cell leukemia; SPE, serum protein electrophoresis; WM, Waldenstrom macroglobulinemia.
|                                | LC-FS n=26 | pSS-FS n=25 | p   |
|--------------------------------|------------|-------------|-----|
| **Demographic characteristics** |            |             |     |
| Gender, female                 | 15 (57.7%) | 23 (92.0%)  | 0.005 |
| Age at diagnosis, years        | 54.7 ± 14.7| 43.6 ± 11.3 | 0.004 |
| **Typical symptoms**           |            |             |     |
| Fatigue                        | 22/23 (95.7%) | 19 (76.0%)  | 0.129 |
| Ostealgia                      | 23 (88.5%) | 10 (40.0%)  | <0.001 |
| Nocturia                        | 11/18 (61.1%) | 12 (48.0%)  | 0.395 |
| Stress fracture                | 6 (23.1%)  | 9 (36.0%)   | 0.311 |
| **Renal function**             |            |             |     |
| Proteinuria, g/day             | 2.34 (24, 0.08–13.76) | 1.41 (22, 0.15–2.53) | 0.002 |
| Serum creatinine, μmol/l       | 91 (38–270) | 112 (34–224) | 0.169 |
| eGFR, ml/min per 1.73 m²       | 68.0 ± 26.4 | 60.9 ± 32.3 | 0.398 |
| eGFR <60 ml/min per 1.73 m²    | 11 (42.3%) | 12 (48.0%)  | 0.683 |
| **Tubular dysfunction**        |            |             |     |
| Full-blown FS                  | 13 (50.0%) | 9 (36.0%)   | 0.313 |
| Elevated urine β2-MG, mg/l     | 18/18 (100.0%) | 19/20 (95.0%) | 1.000 |
| Elevated urine α1-MG, mg/l     | 15/15 (100.0%) | 11/11 (100.0%) | 1.000 |
| Normoglycemic glycosuria       | 22/25 (88.0%) | 15 (60.0%)  | 0.024 |
| Hyperphosphaturia              | 16/19 (84.2%) | 17/20 (85.0%) | 1.000 |
| Urine phosphorus, mmol/day     | 18.40 ± 9.72 | 14.47 ± 8.02 | 0.219 |
| Decreased TmPO4/GFR            | 11/11 (100.0%) | 5/5 (100.0%) | 1.000 |
| Aminoaciduria                  | 21/25 (84.0%) | 20/24 (83.3%) | 1.000 |
| Hypouricemia                   | 21 (80.8%)  | 23/24 (95.8%) | 0.229 |
| Serum uric acid, μmol/l        | 96 (42–409) | 104 (24, 54–288) | 0.580 |
| Hypophosphatemia               | 21 (80.8%)  | 22 (88.0%)  | 0.745 |
| Serum phosphorus, mmol/l       | 0.62 (0.34–2.19) | 0.60 (0.31–1.16) | 0.925 |
| Renal tubular acidosis         | 16/23 (69.6%) | 21/23 (91.3%) | 0.137 |
| Plasma pH                      | 7.35 ± 0.04 | 7.33 ± 0.06 | 0.168 |
| Plasma HCO3–, mmol/l           | 19.1 ± 4.0  | 16.9 ± 3.4  | 0.052 |
| Hypokalemia                    | 11 (42.3%)  | 24 (96.0%)  | <0.001 |
| Serum potassium, mmol/l        | 3.6 (3.0–5.4) | 2.7 (1.3–3.6) | <0.001 |

Values for continuous variables are shown as mean ± standard deviation or median (n, range); values for categorical variables are shown as number or number/number analyzed (percentage). α1-MG, α1-microglobulin; β2-MG, β2-microglobulin; eGFR, estimated glomerular filtration rate; FS, Fanconi syndrome; LC-FS, light chain associated Fanconi syndrome; pSS-FS, primary Sjögren’s syndrome associated Fanconi syndrome; TmPO4/GFR, renal tubular reabsorption of phosphate.
including eight patients with MM, three with MGRS, one with WM and one with PPCL. The most common chemotherapy regimens were bortezomib-based ($n=6$) and melphalan-based regimens ($n=2$). Immunomodulatory drugs were also used in 10 patients, including thalidomide with dexamethasone ($n=8$) and lenalidomide with dexamethasone ($n=2$). Also, one patient received autologous stem cell transplantation. Among the eight MM patients with chemotherapy, the most common regimen was bortezomib-based therapy (62.5%). For MGRS, all three patients used thalidomide-based therapy (Supplemental Table S2). None of the patients altered or abandoned chemotherapy because of drug-associated side effects. At the same time, supplementary treatments (phosphorus, potassium and sodium bicarbonate) were also administered to correct their acid-basal or electrolyte disorders.

Renal and tubular responses. After a median 36 (range 0–133) months of follow-up, four patients died. None of the other 22 patients developed end-stage renal disease (ESRD) or required dialysis. The eGFR remained stable with decreased 24-h proteinuria (Figure 2A and B). Compared with the patients without chemotherapy, patients who received chemotherapy showed significant improvements in eGFR both at 6 months (80.6 ± 25.8 versus 61.8 ± 28.0 ml/min per 1.73 m$^2$, $p=0.029$) and at 36 months (81.1 ± 15.0 versus 54.6 ± 10.7 ml/min per 1.73 m$^2$, $p=0.032$) (Figure 3A). After 6 months of chemotherapy treatment, the chemotherapy group showed eGFR improvements (72.1 ± 23.9 versus 80.6 ± 25.8 ml/min per 1.73 m$^2$, $p=0.080$), which unfortunately did not have statistical significance (Figure 3A). But they did acquire a significant decline of proteinuria (4.14 ± 3.13 versus 1.34 ± 1.05 g/day, $p=0.002$) and remarkable elevations in serum phosphorus (0.59 ± 0.18 versus 0.91 ± 0.18 mmol/l, $p<0.001$) and uric acid (79 ± 22 versus 98 ± 36 μmol/l, $p=0.020$) (Figure 3C–E).

### Table 3. Renal pathological characteristics of the light chain associated Fanconi syndrome patients with kidney biopsy.

|                                | All cases N=10 |
|--------------------------------|----------------|
| **Light microscopy**          |               |
| Crystalline inclusions and protein droplets in PT cells, n [%] | 6 (60.0%)     |
| Tubular basement membrane thickening, n [%] | 6 (60.0%)     |
| Tubular atrophy, n [%]        | 8 (80.0%)     |
| Disappearance of apical brush borders membrane, n [%] | 8 (80.0%)     |
| Wall thickening and lumen stenosis of small vessels, n [%] | 8 (80.0%)     |
| Infiltration of monocytes and lymphocytes, n [%] | 10 (100.0%)   |
| **Immunofluorescence for light chains deposits** |           |
| Paraffin-embedded sections, n [%] | 2/4 (50%)   |
| Frozen sections, n [%]         | 1/8 (12.5%)  |
| **Electron microscopy**        |               |
| Crystalline inclusions with increased lysosomes in PT cells, n [%] | 2/4 (50.0%)  |
| Fibrils in mesangial region, n [%] | 1/4 (25.0%)  |

Values for categorical variables were shown as number or number/number analyzed (percentage).

PT, proximal tubular.
Renal and tubular responses were achieved in 58.3% and 66.7% of our cases, respectively.

Despite no significant differences in clinical characteristics between the LC-FS patients with MGRS and with other hematological etiologies (Supplemental Table S1), the MGRS group showed a significant reduction of eGFR compared with their baseline levels (Figure 2C), and only 21.4% of them had received chemotherapy.

**Hematological responses.** Our patients showed different degrees of hematological response, including CR (25.0%), VGPR (33.3%), PR (16.7%), stable disease (SD; 16.7%) and PD (8.3%). It is noteworthy that renal response occurred only in the patients with hematological response: 66.7% in CR patients and 83.3% in VGPR or PR patients. No renal response happened in hematological SD and PD patients (Figure 4).

**Discussion**
In this study, we reported the detailed clinico-pathological features, long-term renal prognosis and treatment responses of Asian LC-FS patients. The patients in our cohort had mild eGFR decline, and chemotherapy could improve both eGFR and tubular functions.

To date, most of the LC-FS case series have been reported from the United States, French cooperative group and our hospital (PUMCH). Most of the patients were from western countries, and PUMCH data previously focused on the hematological characteristics and did not describe the kidney pathological changes. In this study, we analyzed the renal pathology of 10 patients and observed some specific features, including protein droplets by LM, light chain deposits by IF and crystalline inclusions with increased lysosomes by EM. When compared with the patients from the largest cohort recently published by Vignon et al., the underlying malignancy distribution showed significant differences between two cohorts.
Also, our Asian patients had lower serum creatinine [91 (38–270) vs 171 (70–1278) mmol/l, p not available] and better eGFR levels (chronic kidney disease stage 1–2, 57.7% vs 6.1%, p < 0.001). This might result from racial differences, disease duration differences or potential bias from the limited sample size.

Our patients responded well to chemotherapy. Besides hematological and eGFR improvements, we also observed significant improvements in renal tubular functions, which lacked a detailed description in previously reported studies. Except for a few patients who died of primary disease progress or related complications, no patient developed ESRD or required dialysis in our study, which was much better than in other reports. Strikingly, three of our patients, who were with mild hematological symptoms and severe renal manifestations, also presented impressive improvements in renal and tubular functions after chemotherapy, which provided evidence for the benefit of active therapy in these patients.

Monoclonal FLCs may promote glomerular injury, but a more important feature is that the low molecular weight paraproteins can contribute to the tubular injury, which is the classic Bence Jones proteinuria. Although the detailed mechanism of renal FS complicated plasma cell dyscrasias was not clear, the impressive kidney pathological

Figure 2. Long-term prognosis of light chain associated Fanconi syndrome (LC-FS) patients. (A and B) The eGFR and 24-h proteinuria of the patients during 3 years’ follow-up. *Presents p < 0.05, **presents p < 0.001, compared with baseline 24-h proteinuria values (paired t test). (C) The eGFR changes of MGRS and other LC-FS patients. & & Presents p < 0.01, compared with baseline eGFR for other hematological diseases (paired t test); & presents p < 0.05, compared with baseline eGFR for MGRS (paired t test). (D) Kaplan–Meier survival plot for overall survival of MGRS patients and the other LC-FS patients. eGFR, estimated glomerular filtration rate; MGRS, monoclonal gammopathy of renal significance; MM, multiple myeloma; PPCL, primary plasma cell leukemia; WM, Waldenstrom macroglobulinemia.
feature is intracellular crystals deposition. One of the potential mechanisms is that FLCs can undergo homotypic polymerization in the endo-lysosomal system of the PT cells, which resulted in defective proteolysis, damaged hydrolase maturation, and impaired lysosomal acidification, thereby causing dedifferentiation and loss of reabsorptive capacity of PT cells, which was similar to those encountered in congenital lysosomal diseases. Of note, not all crystals were associated with LC-FS. Stokes et al. retrospectively reported that only 17 (37.0%) patients presented as FS in 40 patients with intratubular crystals. Recently, Luciani et al. disclosed the direct injury of PT cells by κ light chain in mice overexpressing renal Fanconi syndrome-associated κ light chain and primary cultures of PT cells exposed to κ light chain. The tubular dysfunction was related to loss of apical transporters and receptors (cubilin and megalin), which was also seen in other etiologies of renal FS, including pSS and tenofovir-related.

Monoclonal immunoglobulin light chain disease is one of the common etiologies of acquired renal FS. Also, some less common reasons for acquired renal FS include autoimmune diseases, such as pSS, systemic lupus erythematosus, vasculitis and idiopathic thrombotic thrombocytopenic purpura, usually with the diagnosis of γ heavy chain diseases. When compared with pSS-FS, LC-FS patients showed more severe proteinuria, which might result from excessive FLCs filtrated by the glomerular basement membrane and failing to be reabsorbed and degraded in the PT cells. For pSS-FS, we had reported decreased megalin and cubilin expression, which might contribute to the PT reabsorption defects, and was possibly caused by T helper 17 cells infiltration and formation of ectopic germinal centers. The different mechanisms might explain the differences in tubular dysfunctions, including less severe hypokalemia, more normoglycemic glycosuria and more ostealgia in the LC-FS patients, the latter of which was partly because of the osteolytic destruction of bones in MM.
Limitations
This study may have several limitations. First, as a retrospective study with limited cases, it is difficult to analyze the underlying affecting factors in chemotherapy responses. The number of patients with kidney biopsy was also limited. More cases and well-designed studies are needed for comparing different therapies and analysis of renal pathology further. Second, patients received chemotherapy and supplementary treatment simultaneously, which might interfere with the evaluations of treatment responses in terms of tubular functions. Third, patients with skeletal symptoms and hypophosphatemia did not receive further assessment of bone metabolism, which may provide more information on the relation between bone metabolism and renal FS.

Conclusion
In conclusion, Asian LC-FS patients had mild renal function disorder and different degrees of PT dysfunctions. Chemotherapy could improve both renal and tubular functions, which might be related to the hematological response.

Author contributions
Zhixin Chen: Methodology, Investigation, Writing – Original draft preparation. Jiaying Li: Methodology, Formal analysis, Writing – Original draft preparation. Xiaoxiao Shi: Formal analysis, Methodology, Writing – Reviewing & Editing. Ying Wang, Peng Xia, Wei Ye: Methodology, Data Curation. Wenling Ye, Yan Qin, Hang Li, Mingxi Li, and Xuemei Li: Resources, Writing – Reviewing & Editing, Supervision. Yubing Wen and Limeng Chen: Conceptualization, Resources, Data Curation, Writing – Reviewing & Editing, Project administration, Funding acquisition.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethical approval and consent to participate
This study was carried out in accordance with the Helsinki Declaration and received approval to exempt from full review by the local Ethic Committee of Peking Union Medical College Hospital (SK1153). Written informed consent of using the pathology data has been obtained from all patients before the renal biopsy.

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Supplemental material
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