Abstract:
Nephrotic syndrome can be caused by various diseases, from primary kidney diseases to systemic diseases. A kidney biopsy is useful for confirming the causes of nephrotic syndrome and in its management. We herein describe a case of nephrotic syndrome with thrombocytopenia, lymphadenopathy, systemic inflammation, splenomegaly, kidney enlargement, and progressive renal insufficiency. A kidney biopsy showed endothelial swelling with mild interstitial fibrosis and tubular atrophy. This case met the diagnostic criteria for TAFRO syndrome. Little is known about TAFRO syndrome, especially in relation to the associated kidney pathophysiology. The accumulation of a greater number of cases in which the kidney biopsy findings are investigated is needed to clarify the pathogenesis of kidney involvement in this condition.

Key words: nephrotic syndrome, renal dysfunction, small vessel lesions, TAFRO syndrome, idiopathic multicentric Castleman Disease

Introduction
Nephrotic syndrome can be caused by various diseases, from primary (idiopathic) kidney diseases to systemic diseases. TAFRO syndrome is a systemic inflammatory disease; the defining characteristics include thrombocytopenia (T), anasarca (A), fever (F), reticulin myelofibrosis (R), and organomegaly (O). This syndrome was first reported in 2010 (1). The diagnostic criteria were proposed in 2016 and 2017 (2, 3). While TAFRO syndrome can cause progressive kidney insufficiency or proteinuria (4, 5), little is known about the kidney involvement in TAFRO syndrome. We present a case of biopsy-proven nephrotic syndrome, which was later diagnosed as TAFRO syndrome.

Case Report
A 54-year-old woman was admitted to a nearby hospital for severe edema (12 kg weight gain over one month), pleural effusion, dyspnea, and fever. She had no relevant medical history, but she had smoked for approximately 35 years. Dyspnea forced her to quit smoking. Her father and brother suffered from colon cancer; her mother suffered from breast cancer. She had proteinuria (4.2 g/day), hematuria (Red Blood Cells [RBC] 50-90/high power field [HPF]), granular casts, hypoalbuminemia (2.2 g/dL), slight thrombocytopenia (platelet 9.2×10^4/μL), and systemic inflammation (C-reactive protein [CRP] 5.7 mg/dL), with a serum creatinine level of 0.6 mg/dL. Based on these findings, she was diagnosed with nephrotic syndrome. At two weeks after her admission to another hospital, she was referred to our hospital for further examination and treatment. Her initial vital signs at our facility included: body temperature, 38.4°C; blood pressure, 154/94 mmHg; heart rate, 103 bpm; and oxygen saturation, 98% at 2 L/minute of oxygen via nasal cannula. She complained of orthopnea. A physical examination revealed the absence of breath sounds over the bilateral lower lung fields, abdominal swelling due to ascites, and pitting edema in both legs. The laboratory results revealed thrombocytopenia...
Table. The Laboratory Tests on Admission.

| Test                          | Unit | Value       |
|-------------------------------|------|-------------|
| White Blood Cells             | IgG  | 116.60x10^3/μL | 1.022mg/dL  |
| Neu                           | IgA  | 79.3%       | 154mg/dL    |
| Ly                            | IgM  | 11.7%       | 52mg/dL     |
| Mon                           | IgG4 | 7.6%        | 10.0mg/dL   |
| Eo                            | Cryoglobulins | 1.1%    | -           |
| Ba                            | C3   | 0.3%        | 128mg/dL    |
| Red Blood Cells               | C4   | 356x10^3/μL | 20mg/dL     |
| Hb                            | ANA  | 9.7g/dL     | <40         |
| Ht                            | ds-DNA | 29.1% | <100IU/mL  |
| Platelet                      | SmAb | 6.9x10^3/μL | ≤7.0IU/mL   |
| PT-INR                        | MMP-3| 1.3         | 25.1ng/mL   |
| APTT                          | CCP Ab | 43.5 s | 1.2IU/mL    |
| Fibrinogen                    | RNP Ab | 529.0mg/dL | ≤7.0IU/mL   |
| D-dimer                       | SS-A Ab | 11.2μg/mL  | ≤7.0IU/mL   |
| Pleural fluid                 | SS-B Ab | Scl-70 Ab | 13.2IU/mL   |
| LDH                           | s-IL2 R | 102IU/L | 1.580U/mL   |
| TP                            | IL-6 | 4.1g/dL     | 8.2pg/mL    |
| Alb                           | PA-IgG | 2.4g/dL | 152ng/10^2cells |
| ADA                           | Antiplatelet Ab | 8.6IU/L | -           |
| Culture                       | MPO-ANCA | - | <100IU/mL   |
| Cytology                      | PR3-ANCA | Class II | <100U/mL    |
| TP                            | HBs Ag | 4.9 g/dL | 0.01 IU/mL  |
| Alb                           | HCV-Ab | 2.5g/dL | -           |
| BUN                           | EB VCA IgG | 29.1 mg/dL | +          |
| Cr                            | EB VCA IgM | 1.11 mg/dL | -          |
| eGFR                          | EB EBNA IgG | 40.7mL/min/1.73m^2 | +         |
| UA                            | Anti-Cytomegalovirus pp65 Ab | 5.9 mg/dL | -          |
| AST                           | HIV-Ab | 14 IU/L | -           |
| ALT                           | Beta D glucan | 8 IU/L | ≤5.0pg/mL  |
| ALP                           | Blood culture | 598 IU/L | -          |
| T-Bil                         | Utrasound | 0.8mg/dL | -          |
| γGTP                          | Utrasound | 102 IU/L | -          |
| LDH                           | Protein | 285 IU/L | 3.2g/gCr   |
| TG                            | Sugar | 148mg/dL | -           |
| LDL-C                         | Red Blood Cells | 80mg/dL | 12 /HPF    |
| Na                            | White Blood Cells | 135mEq/L | 11.7/HPF   |
| K                             | Granular casts | 5.0mEq/L | +          |
| CL                            | Epithelial cell casts | 100mEq/L | +          |
| Ca                            | Fatty casts | 7.2mg/dL | +          |
| P                             | NAG | 5.3mg/dL | 35.8 U/L   |
| CRP                           | β2MG | 7.0mg/dL | 3.83μg/L   |
| Hba1C (NGSP)                  | Bence Jones protein | 5.8% | -         |

Ab: antibody, ADA: adenosine deaminase activity, Ag: antigen, Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, Ba: basophils, B2MG: beta-2 microglobulin, BUN: blood urea nitrogen, C: Complement Component, CCP: anti-citrullinated protein, Cr: creatinine, CRP: C-reactive protein, ds: double stranded, EBNA: Epstein-Barr nuclear antigen, EBV: Epstein-Barr Virus, Eo: eosinophils, γGTP: gamma-glutamyl transpeptidase, Hb: hemoglobin, HBs: hepatitis B surface, HCV: hepatitis C virus, HIV: human immunodeficiency virus, Ht: hematocrit, Ig: Immunoglobulin, LDH: lactate dehydrogenase, LDL-C: low-density lipoprotein cholesterol, Ly: lymphocytes, MMP: matrix metalloproteinase-3, Mon: monocytes, MPO: myeloperoxidase, NAG: N-acetyl-beta-D-glucosaminidase, Neu: neutrophils, NGSP: National Glycohemoglobin Standardization Program, PA-IgG: platelet-associated immunoglobulin, PT-INR: prothrombin time-international normalized ratio, RBC: red blood cells, RNP: anti-ribonucleoprotein, Scl-70: anti-centromere, s-IL2R: soluble-interleukin 2 receptor, TG: triglycerides, T-Bil: total-bilirubin, TP: total protein, UA: uric acid, VCA: viral-capsid antigen, WBC white blood cells.
(platelet count 6.9×10⁴/μL), normocytic anemia (hemoglobin 9.7 g/dL), hypoalbuminemia (albumin 2.5 g/dL), systemic inflammation (CRP 7.0 mg/dL), slightly alkaline phosphatase elevation (598 IU/L), slight renal dysfunction (serum creatinine 1.1 mg/dL; estimated glomerular filtration rate [eGFR] 40.7 mL/min/1.73 m²), proteinuria (3.2 g/g creatinine [Cr]), hematuria (dysmorphic RBC 12/HPF), tubular dysfunction (urine N-acetyl-beta-D-glucosaminidase [NAG] 35.8 U/L and beta-2 microglobulin [B2MG] 3,831 μg/L), with granular casts, epithelial cell casts, and fatty casts (Table). Her immunoglobulin (Ig) levels were within the normal range, and her IgG4 level was 10.0 mg/dL. Neither M-protein nor cryoglobulins were detected. The patient was negative for antinuclear antibody (ANA), anti-double stranded DNA antibody, anti-Sm antibody, myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA), and proteinase-3 ANCA, matrix metalloproteinase-3, anti-citrullinated protein antibody, anti-ribonucleoprotein antibody, anti-SS-A antibody, anti-SS-B antibody, and anti-topoisomerase antibody. Her soluble-interleukin (IL) 2 receptor level was 1,580 U/mL, and her IL-6 level was 8.2 pg/mL (normal range 0-4 pg/mL). Her pleural fluid had exudative characteristics, and was sterile without malignant cells (Table). A chest X-ray film showed bilateral pleural effusion (a). Computed tomography showed cardiac effusion, pleura effusion (b), ascites, splenomegaly (c), and kidney enlargement (d).

**Figure 1.** Chest X-ray and computed tomography at the initial admission to our hospital. A chest X-ray film showed bilateral pleural effusion (a). Computed tomography showed cardiac effusion, pleura effusion (b), ascites, splenomegaly (c), and kidney enlargement (d).
Component (C) 3, C4, or fibrinogen. Electron microscopy showed endothelial swelling (Fig. 8) and slight tubule epithelial changes. No particular basement membrane changes, dense deposits, or fibrils were found.

Her nephrotic syndrome was persistent with other general symptoms, including fatigue and fever; her serum creatinine level reached 1.67 mg/dL (eGFR 26.0 mL/min/1.73 m²).

Oral prednisolone therapy (40 mg/day, 0.8 mg/kg/day) was initiated. Her urinary protein level decreased to 0.7 g/gCr after a week, and many of her other problems were relieved: anasarca was reduced, her CRP level decreased to 0.05 mg/dL, her platelet count was $8.9 \times 10^{13}$ μL, and her serum creatinine returned to 0.43 mg/dL (eGFR 114.9 mL/min/1.73 m²).

**Figure 2.** Multiple lymphadenopathy and splenomegaly were observed on positron emission tomography-computed tomography. Positron emission tomography-computed tomography with [18F]-fluorodeoxyglucose (FDG) revealed lymphadenopathy with the strong uptake of FDG in the deep cervical lymph nodes (a arrows), the paratracheal lymph nodes (b arrows), the subaortic lymph nodes (c arrow), the splenic hilar and the arterial lymph nodes (d arrowhead). The maximum diameter of the subaortic lymph nodes was 35 mm (c arrow). The slight uptake of FDG was also observed in the enlarged spleen (d arrow) and in the axillary lymph nodes (e arrows).

**Figure 3.** The histological findings in the left axillary lymph node (×40). The germinal centers were atrophic with the expansion of the interfollicular zone (×40, Hematoxylin and eosin staining).

**Figure 4.** The histological findings in the left axillary lymph node (×400). The proliferation of highly dense endothelial venules was seen in both the germinal centers and in the interfollicular zone. Relatively few mature plasma cells were seen (×400 Hematoxylin and eosin staining).
without urine casts. Still, her blood pressure was approximately 150/90 mmHg with the administration of olmesartan medoxomil (an antihypertensive agent). Cilnidipine was added, and her blood pressure fell to around 125/60 mmHg. The dose of prednisolone was gradually reduced to 2.5 mg. It is possible that the patient’s blood pressure had some influence on her urinary protein level. At the onset of her 

Discussion

The diagnostic criteria for TAFRO syndrome were not published when the patient in the present case developed nephrotic syndrome and underwent biopsy. According to the 2015 diagnostic criteria for TAFRO syndrome (2), this case met all of the three major categories (anasarca, thrombocytopenia, and systemic inflammation) and three of the four minor categories (Castleman disease [CD]-like features on lymph node biopsy, mild organomegaly, and progressive renal insufficiency). Iwaki et al. proposed the diagnostic criteria for TAFRO-iMCD based on their clinicopathological analysis of TAFRO syndrome (6). Kidney involvement was not mentioned in the criteria. However, this case fulfilled all of the major criteria: four of the five TAFRO symptoms (thrombocytopenia, anasarca, fever, and organomegaly), the absence of hypergammaglobulinemia, and small volume lymphadenopathy in addition to the histopathological criteria and one of the two minor criteria: high levels of serum alkaline phosphatase without markedly elevated serum transaminase.

On the other hand, renal insufficiency was defined as a glomerular filtration rate of <60 ml/min/1.73 m² in the 2015 diagnostic criteria for TAFRO syndrome (2). Based on this classification, the case was classified as grade 3: slightly se-
symptoms, her blood pressure was continuously high, while prednisolone improved her proteinuria and urinary casts. We assume that her proteinuria was mainly caused by inflammation from TAFRO syndrome, and not by hypertension.

We did not observe reticulin fibrosis in the bone marrow samples in this case. A bone marrow biopsy would have been needed to observe reticulin fibrosis.

In summary, we presented a case of nephrotic syndrome that was later diagnosed as TAFRO syndrome. A kidney biopsy showed endothelial swelling, which could have been due to small vessel lesions. The accumulation of a greater number of case studies is needed, and the kidney biopsy findings of such cases should be investigated in order to clarify the pathogenesis of kidney involvement.

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

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Compliance with Ethical Standards
Disclosure: The authors declare no conflicts of interest in association with the present study.

This article does not contain any studies with human participants or animals.

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