

TAFRO Syndrome With Kidney Involvement: A Case Series of Patients With Kidney Biopsies



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TAFRO (thrombocytopenia, anasarca, fever, reticulin myelofibrosis/renal insufficiency, and organomegaly) syndrome is a systemic inflammatory disease sharing some features with Castleman disease and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome in relation to abnormal secretions of interleukin 6 and vascular endothelial growth factor. The kidney is a main target organ of TAFRO syndrome but the kidney histopathology associated with TAFRO syndrome is yet to be completely defined. We report 3 TAFRO syndrome cases with different clinical courses in which kidney biopsies were performed. In all 3 cases, kidney biopsies showed similar glomerular lesions of diffuse global swelling of the endothelium and expansion of subendothelial spaces, consistent with severe glomerular endothelial injury. Case 3 showed an additional finding of focal tubulointerstitial injury characterized by marked plasma cell infiltration, which was absent in the other 2 cases. Clinical symptoms in cases 1 and 2, which had lower disease severity scores of TAFRO syndrome, were effectively treated with the administration of corticosteroids or a combination of corticosteroids and cyclosporine A. Case 3, with a higher disease severity score, had an aggressive clinical course that was refractory to corticosteroids and tocilizumab; the patient ultimately died of multiple organ failure. In all 3 cases, kidney biopsy provided indications for the diagnosis process and clinical management of TAFRO syndrome.

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INTRODUCTION

TAFRO syndrome is a life-threatening systemic inflammatory disorder characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin myelofibrosis/renal insufficiency (R), and organomegaly (O). Patients with TAFRO syndrome often exhibit acute, progressive, and critical clinical courses.¹ The clinical symptoms of TAFRO syndrome are similar to those found in patients with idiopathic multicentric Castleman disease, which shows lymphadenopathy, hepatosplenomegaly, and pancytopenia. Excessive production of interleukin 6 (IL-6) and vascular endothelial growth factor (VEGF), which induce endothelial cell injury and vascular permeability, respectively, may be involved in the pathogenesis and progression of organ damage in both TAFRO syndrome and Castleman disease.

The kidney is a well-known target organ of TAFRO syndrome. However, kidney histopathologic findings of TAFRO syndrome are not sufficiently described because severe thrombocytopenia occasionally occurs, making it difficult to perform kidney biopsies in patients with TAFRO syndrome. Accordingly, only a limited number of cases have been reported in relation to clinicopathologic correlations in patients with TAFRO syndrome. We report the kidney histopathologic findings in 3 cases of TAFRO syndrome, which showed different clinical courses.

CASE REPORTS

Case 1

A man in his 30s was referred for a 1-month history of fatigue. He presented with hypertension (blood pressure, 176/117 mm Hg), swelling of the right axillary lymph node, and edema in limbs. Laboratory examination showed the following values: platelet count, 185,000/ μ L; serum C-reactive protein (CRP), 11.6 mg/dL; serum creatinine (Scr), 1.92 mg/dL; estimated glomerular filtration rate (eGFR), 35 mL/min/1.73 m²; serum IL-6, 44.7 pg/mL; and serum VEGF, 1,510 pg/mL. Urinalysis showed urinary protein excretion of 1.81 g/d and a red blood cell count in urinary sediment of more than 100 cells/high-power field. Kidney biopsy was performed on day 2 of hospitalization (Fig 1A-C). TAFRO syndrome was diagnosed based on 3 major and 2 minor criteria, with a severity score of 5 of 12 points.¹ He required hemodialysis for acute kidney injury; however, with oral corticosteroids, serum CRP and Scr levels immediately decreased, followed by his platelet count gradually recovering, with a minimal count of 26,000/ μ L on day 26 (Fig 2A). His platelet count recovered to 200,000/ μ L at 5 months.

Case 2

A man in his 50s was admitted for a 1-month history of low-grade fever. He presented with hypertension (blood

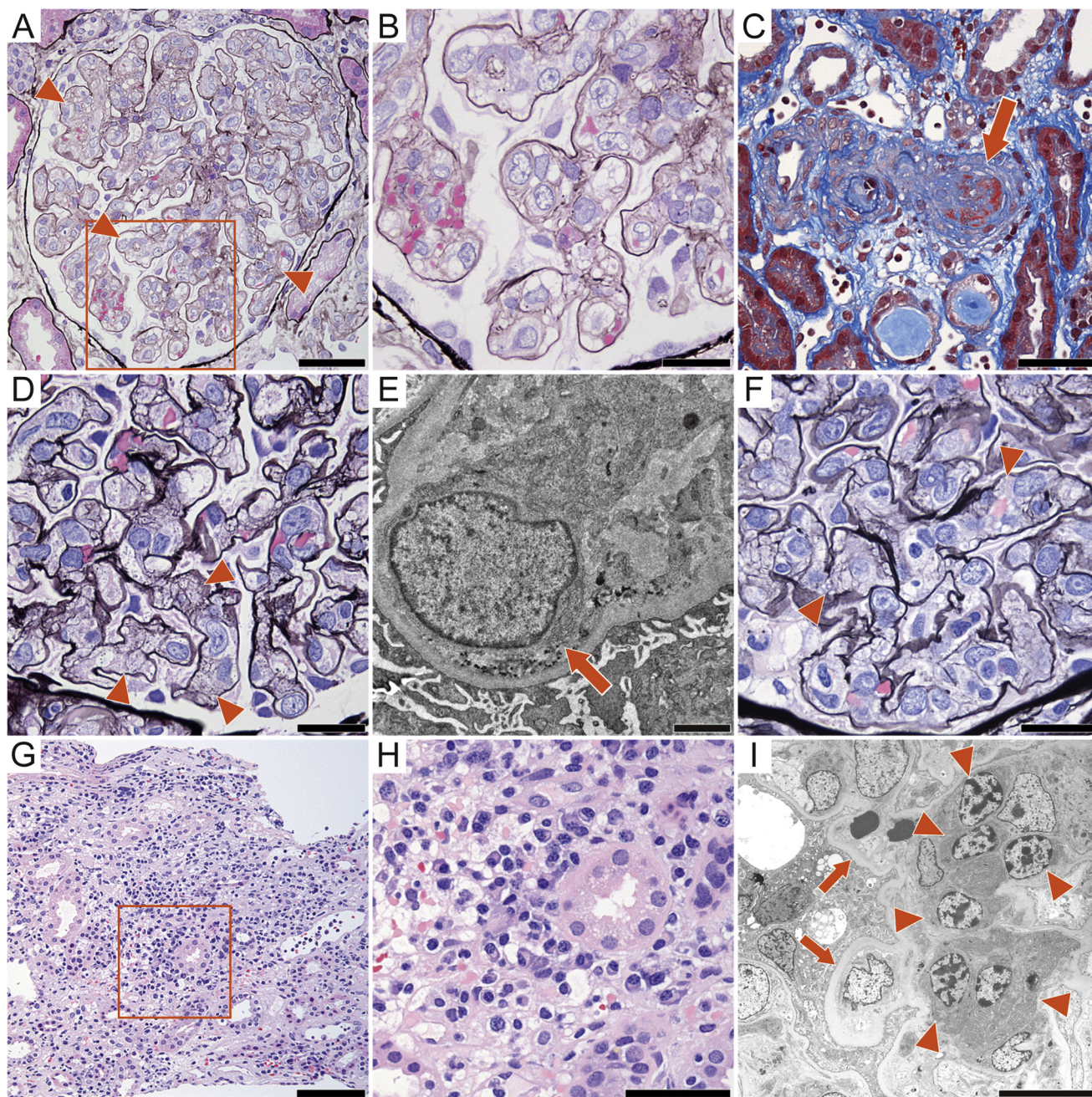


Figure 1. Kidney histopathologic findings in 3 cases of TAFRO (thrombocytopenia, anasarca, fever, reticulin myelofibrosis/renal insufficiency, and organomegaly) syndrome. (A) Glomeruli were diffusely enlarged and glomerular capillaries were globally occluded. Arrowheads indicate focal mesangiolysis and ballooning of glomerular capillary loops (case 1) (periodic acid–silver methenamine-hematoxylin and eosin [PASM-HE] staining; scale bar = 50 μ m). (B) Glomerular capillaries were occluded by enlarged glomerular endothelial cells and infiltrating cells (case 1) (PASM-HE staining; scale bar = 20 μ m). (C) An interlobular artery was occluded by a thrombus, suggesting thrombotic microangiopathy (arrow, case 1). (Masson trichrome staining; scale bar = 50 μ m). (D) Glomerular endothelial cells were diffusely enlarged and focal mesangiolysis (arrowheads) was observed (case 2). (PASM-HE staining; scale bar = 50 μ m). (E) Electron microscopy showed markedly swollen glomerular endothelial cells (arrow) occupying the glomerular capillary (case 2) (scale bar = 2 μ m). (F) Glomeruli were diffusely enlarged and glomerular capillaries were globally occluded by enlarged endothelial cells and infiltrated cells. Arrowheads indicate focal mesangiolysis (case 3). (PASM-HE staining; scale bar = 50 μ m). (G) Focal tubulointerstitial nephritis associated with plasma cell infiltration (case 3). (HE staining; scale bar = 100 μ m). (H) Magnified image shows that large portions of the infiltrating cells were composed of plasma cells (case 3) (HE staining; scale bar = 50 μ m). (I) Electron microscopy showed the widening of the subendothelial space (arrows) and infiltration of plasma cells (arrowheads) into mesangial areas (case 3) (scale bar = 2 μ m).

pressure, 177/109 mm Hg) and moderate edema in limbs with a platelet count of 139,000/ μ L, serum CRP level of 9.54 mg/dL, Scr level of 1.20 mg/dL, eGFR of 50 mL/min/1.73 m², serum IL-6 level of 7.0 pg/mL, and serum VEGF level of 783 pg/mL. Urinalysis showed urinary protein excretion of 1.31 g/d and no significant microscopic hematuria. Kidney biopsy was performed on day 5 of hospitalization (Fig 1D). TAFRO syndrome was diagnosed based on 3 major and 4 minor criteria, with a severity score of 5 of 12 points.¹ Oral corticosteroids combined with cyclosporine A were administered, resulting in a gradual improvement in platelet count, with a minimal count of 12,000/ μ L on day 75. He was discharged on day 118 (Fig 2B). His platelet count recovered to 230,000/ μ L at 5 months

Case 3

A man in his 50s presented with a 1-week history of cough and fever. He showed high body temperature of 38.8 °C and moderate edema in limbs without hypertension on admission. Laboratory examination showed thrombocytopenia (platelet count, 30,000 / μ L), serum CRP level of 26.5 mg/dL, Scr level of 1.10 mg/dL, eGFR of 57 mL/min/1.73 m², and serum IL-6 level of 89.0 pg/mL. Urinalysis showed urinary protein excretion of 0.37 g/g creatinine and no significant microscopic hematuria. Computed tomography showed bilateral pleural effusion, ascites, and enlargement of axillary and inguinal lymph nodes. He had acute kidney injury (Scr, 2.82 mg/dL, and eGFR, 20 mL/min/1.73 m²) and required hemodialysis because of diuretic-resistant volume overload on day 9 of hospitalization (Fig 2C). Kidney biopsy was performed on day 10 after a platelet transfusion (Fig 1E and F). TAFRO syndrome was diagnosed based on 3 major and 3 minor criteria, with a severity score of 9 of 12 points.¹ Corticosteroid therapy did not improve his general condition. Hypotension was observed on day 14, and noradrenaline was administered. Despite additional treatments with intravenous methylprednisolone pulse followed by tocilizumab, his general condition worsened and he died of multiple organ failure on day 24.

DISCUSSION

We have presented 3 cases of TAFRO syndrome with kidney involvement. Kidney histopathology in all 3 cases consistently showed severe glomerular endothelial injury, as evidenced by diffuse global endothelial cell swelling and enlarged subendothelial spaces. The findings of thrombotic microangiopathy (in case 1) and mesangiolysis (in cases 1, 2, and 3) identified in the biopsies further support that the endothelium, especially the glomerular endothelium, is the main target of kidney injury in TAFRO syndrome. In addition to the severe glomerular endothelial injury, the kidney biopsy in case 3, which had a higher disease severity score, also featured focal tubulointerstitial injury associated with plasma cell infiltration, which was absent

in the other 2 cases with lower disease severity scores. To our knowledge, biopsy findings of TAFRO syndrome have been reported in 14 cases, all of which, including our cases, consistently demonstrated findings suggesting marked glomerular endothelial cell injury (Table 1).²⁻¹⁵

Castleman disease and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome are considered to be similar pathologic entities to TAFRO syndrome, and abnormal secretion and biological actions of IL-6 and VEGF may be involved in the pathogenesis of these diseases. In animal experiments, overproduction of IL-6 induces endothelial cell injury, whereas VEGF is known to increase vascular permeability.¹⁶ Approximately 50% and 40% of cases of Castleman disease and POEMS syndrome, respectively, show glomerular endothelial cell injury.^{17,18} Serum IL-6 and VEGF levels increased in most patients with TAFRO syndrome previously diagnosed.¹ In the cases of TAFRO syndrome with kidney involvement presented here, serum IL-6 and VEGF levels were elevated in all 3 cases and in 2 cases (because serum VEGF was not measured in case 3), respectively. These findings are consistent with the hypothesis that IL-6 and/or VEGF are responsible for kidney involvement in TAFRO syndrome, which is mainly attributed to glomerular endothelial injury.

VEGF is constitutively secreted by podocytes and crucially involved in the development and maintenance of the glomerular endothelium.¹⁹ Podocyte-specific VEGF conditional knockout mouse models and patients with preeclampsia or those undergoing anti-VEGF therapy have shown glomerular endothelial damage similar to that in the present cases with TAFRO syndrome.^{19,20} In patients with preeclampsia, increased soluble FLT-1 (VEGF receptor 1) functions as a potential antagonist of VEGF. Although circulating VEGF levels increase in patients with TAFRO syndrome and Castleman disease, some case reports showed that glomerular VEGF expression decreased, which may have led to glomerular endothelial injury.⁷ This is controversial, and further research is needed to clarify the mechanism underlying glomerular endothelial injury in TAFRO syndrome.

Currently, the ideal treatment strategy for patients with TAFRO syndrome is unestablished. High-dose corticosteroids, tocilizumab, siltuximab (anti-IL-6 monoclonal antibody), cytotoxic chemotherapies, and cyclosporine A are commonly used, but these therapies often result in treatment failure and relapse.²¹ Case 1 responded to corticosteroid monotherapy and case 2 was effectively treated by a combination of oral corticosteroids and cyclosporine A.

However, case 3 was refractory to intensive therapy including corticosteroids and tocilizumab, even though the patient's serum IL-6 level was high. Similarly, cases resistant to tocilizumab therapy have been reported.²² This has led to the assumption that humoral factors other than IL-6 are involved in the pathogenesis of TAFRO syndrome.

Table 1. Comparison of Kidney Histopathologic Findings and Treatments Between Reported Cases of TAFRO Syndrome

Reference	Age, y/Sex	Light Microscopy	Immunofluorescence	Electron Microscopy	Treatment	Response to Therapies
Tanaka et al ² (2017)	70/male	Glomerular endothelial cell swelling, double contours of the GBM, mesangiolytic, interstitial edema	Negative	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces	Corticosteroids	Effective
José et al ³ (2017)	61/female	Mesangial expansion, TMA, double contours of the GBM	Not performed	Not performed	Corticosteroids, tocilizumab, rituximab	Effective
Kawashima et al ⁴ (2017)	38/male	Mesangial proliferation, double contours of GBM	IgA, IgM, and C3	Not performed	Corticosteroids	Effective
Mizuno et al ⁵ (2018)	84/male	Glomerular endothelial cell swelling, endocapillary hypercellularity, mesangiolytic	Negative	No EDD, glomerular endothelial cell swelling	Corticosteroids, tocilizumab, plasma exchange,	Effective
Nakamori et al ⁶ (2018)	54/female	Glomerular endothelial cell swelling, mild interstitial inflammation	Negative	No EDD	Corticosteroids	Effective
Noda-Narita et al ⁷ (2018)	80/female	Glomerular endothelial cell swelling, endocapillary hypercellularity, double contours of the GBM	IgM and κ light chain	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces	Corticosteroids, tocilizumab	Effective
Furuto et al ⁸ (2018)	55/female	Mesangial proliferation, double contours of the GBM	IgM	No EDD, mesangial interposition, duplication of the GBM, podocyte foot process effacement	Corticosteroids	Effective
Ito et al ⁹ (2018)	76/female	Endocapillary hypercellularity, double contours of the GBM, mesangial proliferation, massive macrophage infiltration within the glomeruli and tubulointerstitial area	Negative	No EDD, enlarged subendothelial spaces, mesangial interposition, duplication of the GBM, podocyte foot process effacement	Corticosteroids	Effective
Noda et al ¹⁰ (2018)	79/female	Double contours of the GBM, mesangiolytic	Negative	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces	Corticosteroids, rituximab, plasma exchange	Effective
Ozeki et al ¹¹ (2018)	51/female	Glomerular endothelial cell swelling, double contours of the GBM, mesangiolytic, partial infiltration of monocytes and plasma cells into tubulointerstitial lesions	Negative	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces	Corticosteroids	Effective
Nagayama et al ¹² (2019)	48/female	Glomerular endothelial cell swelling, endocapillary hypercellularity, double contours of the GBM, mesangiolytic	Negative	No EDD, enlarged subendothelial spaces, edematous change in mesangial areas, podocyte foot process effacement	Corticosteroids, cyclosporine A, tocilizumab	Effective

(Continued)

Table 1 (Cont'd). Comparison of Kidney Histopathologic Findings and Treatments Between Reported Cases of TAFRO Syndrome

Reference	Age, y/Sex	Light Microscopy	Immunofluorescence	Electron Microscopy	Treatment	Response to Therapies
Leurs et al ¹³ (2019)	28/female	Glomerular endothelial cell swelling, endocapillary hypercellularity, double contours of the GBM, mesangial proliferation, mesangiolytic	IgM, C1q, κ and λ light chains	Subendothelial EDD, podocyte foot process effacement	Corticosteroids	Effective
Saito et al ¹⁴ (2019)	45/female	Glomerular endothelial cell swelling, double contours of the GBM, mesangiolytic	Negative	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces	Corticosteroids, cyclosporine A	Effective
Hashimoto et al ¹⁵ (2019) ⁵	69/male	Mesangial proliferation, double contours of the GBM	IgM and C1q	Subendothelial EDD, enlarged subendothelial spaces, mesangial proliferation, expansion	Corticosteroids, cyclosporine A	Not effective
Case 1	30s/male	Glomerular endothelial cell swelling, endocapillary hypercellularity, mesangiolytic, vascular intimal thickening (TMA)	Negative	Not performed	Corticosteroids	Effective
Case 2	50s/male	Glomerular endothelial cell swelling, endocapillary hypercellularity, mesangiolytic	Negative	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces	Corticosteroids, cyclosporine A	Effective
Case 3	50s/male	Glomerular endothelial cell swelling, endocapillary hypercellularity, mesangiolytic, interstitial nephritis with plasma cell infiltration	Negative	No EDD, glomerular endothelial cell swelling, enlarged subendothelial spaces, podocyte foot process effacement	Corticosteroids, tocilizumab	Not effective

Abbreviations: EDD, electron-dense deposits; GBM, glomerular basement membrane; IgA, immunoglobulin A; TAFRO, thrombocytopenia, anasarca, fever, reticulin myelofibrosis/renal insufficiency, organomegaly; TMA, thrombotic microangiopathy.

Treatments targeting humoral factors, such as plasma exchange and targeted therapies for molecules other than IL-6, may be considered as alternative strategies for some patients with TAFRO syndrome, especially for those showing severe clinical manifestations. Consistent with this idea, successful treatment using rituximab and plasma exchange has been reported in a previous case of TAFRO syndrome.^{2,3}

The factors that determine the prognosis of TAFRO syndrome are unknown. Disease severity scores for TAFRO syndrome are based on the combination of thrombocytopenia, anasarca, fever, reticulin myelofibrosis/renal insufficiency, organomegaly, and other clinically identifiable findings.¹ Despite all 3 cases showing severe glomerular endothelial injury, we could not determine differences in the severity of glomerular lesions. Instead, tubulointerstitial injury with marked plasma cell infiltration was identified only in case 3, which showed a higher disease severity score. Although tubulointerstitial nephritis involved in TAFRO syndrome cases has not been found to be associated with poor prognosis,^{6,9,11} no report has yet described tubulointerstitial infiltration of massive plasma cells. Plasma cell infiltration in the kidney implies that plasma cells infiltrate other organs as well, and this might reflect the severity and poor prognosis of TAFRO syndrome.

In summary, we discussed 3 cases of diagnosed TAFRO syndrome in patients who underwent kidney biopsy and showed different clinical courses. Lesions indicating severe glomerular endothelial cell injury were consistently identified in all 3 cases. Focal tubulointerstitial infiltration of plasma cells was identified in 1 case, which showed an aggressive clinical course. In all cases, kidney biopsy findings provided useful information that supported the diagnosis of TAFRO syndrome and the determination of the treatment strategy. Further accumulation of cases is required to elucidate the pathophysiologic basis of kidney involvement in TAFRO syndrome.

ARTICLE INFORMATION

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REFERENCES

- Masaki Y, Kawabata H, Takai K, et al. Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol*. 2016;103(6):686-692.
- Tanaka M, Tsujimoto H, Yamamoto K, et al. Clinicopathological features of progressive renal involvement in TAFRO syndrome: a case report and literature review. *Medicine (Baltimore)*. 2017;96(40):e8216.
- José FF, Kerbauy LN, Perini GF, et al. A life-threatening case of TAFRO syndrome with dramatic response to tocilizumab, rituximab, and pulse steroids: the first case report in Latin America. *Medicine (Baltimore)*. 2017;96(13):7-10.
- Kawashima M, Usui T, Okada H, et al. TAFRO syndrome: 2 cases and review of the literature. *Mod Rheumatol*. 2017;27(6):1093-1097.
- Mizuno H, Sekine A, Oguro M, et al. Renal histology in a patient with TAFRO syndrome: a case report. *Hum Pathol*. 2018;82:258-263.
- Nakamori A, Akagaki F, Yamaguchi Y, et al. Nephrotic syndrome with thrombocytopenia, lymphadenopathy, systemic inflammation, and splenomegaly. *Intern Med*. 2018;57(8):1123-1129.
- Noda-Narita S, Sumida K, Sekine A, et al. TAFRO syndrome with refractory thrombocytopenia responding to tocilizumab and romiplostim: a case report. *CEN Case Rep*. 2018;7(1):162-168.
- Furuto Y, Hashimoto H, Horiuti H, et al. Membranoproliferative glomerulonephritis-like findings for TAFRO syndrome, associated with an anterior mediastinal tumor: a case report. *Medicine (Baltimore)*. 2018;97(24):e11057.
- Ito S, Uchida T, Itai H, et al. Serial manifestation of acute kidney injury and nephrotic syndrome in a patient with TAFRO syndrome. *Intern Med*. 2018;57(21):3129-3133.
- Noda Y, Saka Y, Kato A, et al. Successful rituximab treatment of TAFRO syndrome with pathological findings of glomerular endothelial damage. *Clin Nephrol Case Stud*. 2018;6(01):16-20.
- Ozeki T, Tsuji M, Yamamoto J, et al. Thrombotic microangiopathy on kidney biopsy in a patient with TAFRO syndrome. *CEN Case Rep*. 2018;7(2):243-247.
- Nagayama Y, Yamano M, Yagame M, et al. TAFRO syndrome as a cause of glomerular microangiopathy: a case report and literature review. *BMC Nephrol*. 2019;20(1):1-9.
- Leurs A, Gnemmi V, Lionet A, et al. Renal pathologic findings in TAFRO syndrome: is there a continuum between thrombotic microangiopathy and membranoproliferative glomerulonephritis? A case report and literature review. *Front Immunol*. 2019;10:1489.
- Saito H, Tanaka K, Fujiwara M, et al. Pathological findings of progressive renal involvement in a patient with TAFRO syndrome. *CEN Case Rep*. 2019;8(4):239-245.
- Hashimoto K, Sano T, Honma Y, et al. An autopsy case of TAFRO syndrome with membranoproliferative glomerulonephritis-like lesions. *CEN Case Rep*. 2019;8(1):48-54.

16. Garibotto G, Sofia A, Procopio V, et al. Peripheral tissue release of interleukin-6 in patients with chronic kidney diseases: Effects of end-stage renal disease and microinflammatory state. *Kidney Int.* 2006;70(2):384-390.
17. Xu D, Lv J, Dong Y, et al. Renal involvement in a large cohort of Chinese patients with Castleman disease. *Nephrol Dial Transplant.* 2012;27(suppl 3):119-125.
18. Nakamoto Y, Imai H, Yasuda T, et al. A spectrum of clinicopathological features of nephropathy associated with POEMS syndrome. *Nephrol Dial Transplant.* 1999;14(10):2370-2378.
19. Estrada CC, Maldonado A, Mallipattu SK. Therapeutic inhibition of VEGF signaling and associated nephrotoxicities. *J Am Soc Nephrol.* 2019;30(2):187-200.
20. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol.* 2019;15(5):275-289.
21. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. *Blood.* 2018;132(20):2115-2124.
22. Simons M, Apor E, Butera JN, et al. TAFRO syndrome associated with EBV and successful triple therapy treatment: case report and review of the literature. *Case Rep Hematol.* 2016;2016:1-7.
23. Meguri Y, Asada N, Nakasako Y, et al. A case report of TAFRO syndrome successfully treated by immunosuppressive therapies with plasma exchange. *Ann Hematol.* 2019;98(2):537-539.