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An Autopsy Case of TAFRO Syndrome with Type II Respiratory Failure

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 66-year-old
Final Diagnosis: TAFRO syndrome
Symptoms: Appetite loss • dyspnea • general fatigue
Medication: —
Clinical Procedure: Biopsy
Specialty: Hematology

Objective: Rare disease

Background: TAFRO syndrome (thrombocytopenia, anasarca, fever, myelofibrosis, renal dysfunction, and organomegaly) is a systemic inflammatory disorder. The histological features of TAFRO syndrome are not fully understood and few autopsy cases have been reported.

Case Report: A 66-year-old man with type II respiratory failure was diagnosed with TAFRO syndrome. He was initially treated with tocilizumab. Although some improvements were observed, his condition worsened, and the medication was switched to rituximab. His condition remained steady for 1 year with intermittent artificial ventilation. However, he died due to exacerbation of respiratory failure about 20 months after diagnosis. An autopsy revealed mucous fluid retention in the spaces between the axis cylinder and the myelin sheath of peripheral nerves and among the peripheral nerves, suggesting that this retention contributed to neurodegeneration with demyelination. Skeletal muscles, including respiratory muscles, were highly atrophic, which could have led to type II respiratory failure.

Conclusions: Fluid accumulation other than pleural effusion and ascites could occur in intra-organs at a cellular level.

MeSH Keywords: Edema • Giant Lymph Node Hyperplasia • Nerve Degeneration • Respiratory Insufficiency

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926721

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Background

TAFRO syndrome is a systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever, myelofibrosis, renal dysfunction, and organomegaly [1]. The first 3 cases of TAFRO syndrome were reported in 2010 [2], and Masaki et al. proposed diagnostic criteria for TAFRO syndrome and a disease severity classification system in 2015 [3], which were further updated in 2019 [4]. However, the histological features of TAFRO syndrome are not fully understood. Indeed, few studies have reported histological findings other than kidney and lymph node involvement. Moreover, few autopsy cases have been published. Here, we report an autopsy case of TAFRO syndrome complicated with type II respiratory failure due to peripheral nerve disorder. This is a follow-up report of our previous study [5].

Case Report

A 66-year-old man with complaints of dyspnea and general fatigue was admitted to our hospital. He had experienced pitting edema in both legs 4 years prior to admission, with no other symptoms. Pleural effusion and ascites were documented at a different hospital. Biopsy of enlarged axillary lymph nodes and bone marrow were performed at another hospital 1 year prior to the present admission, but no definitive diagnosis was made. Upon worsening of his general condition, he was referred and admitted to our hospital.

He was conscious and oriented on admission. His body temperature was 37.7°C, blood pressure 140/80 mmHg, pulse rate 50/min, respiratory rate 20/min, and oxygen saturation 92% without supplemental oxygen administration. After admission, we re-evaluated pathological tissues obtained from the previous medical institution. Left axillary lymph nodes showed interfollicular expansion, atrophic germinal centers, and arborized blood vessels (Figure 1A, 1B). We also noted infiltration of small lymphocytes and plasma cells, and confirmed the finding of non-monoclonality of infiltrating plasma cells [5]. Increased megakaryocytes and reticular fibers were observed in the bone marrow biopsy (Figure 1C, 1D). We made the diagnosis of TAFRO syndrome based on patient history, laboratory data (Table 1), computed tomography (CT) showing bilateral pleural effusion and moderate lymphadenopathy, results of pathological evaluations, and other findings reported previously [5]. Results of blood gas analysis and a respiratory function test revealed type II respiratory insufficiency and restrictive impairment (%VC: 30.1%, FEV1.0%: 93.5%).

Treatment with tocilizumab was initiated, achieving gradual improvements in general condition as well as laboratory findings such as thrombocytopenia and renal dysfunction; however, respiratory function did not sufficiently improve. He was discharged on day 35. Administration of tocilizumab once every other week was continued in an outpatient setting, every 3 weeks from day 148, and once every 4 weeks beginning on day 211 (Figure 2). Then, the patient was re-admitted on day 267 due to exacerbation of thrombocytopenia and renal dysfunction. Suspecting that TAFRO syndrome had worsened, the frequency of tocilizumab administration was increased back to bi-weekly administration. His overall condition improved and he was discharged on day 283. However, general fatigue progressed and a worsened respiratory state was confirmed on day 286, resulting in re-hospitalization. Gradual worsening of ability to perform activities of daily living (ADL) was also noted. Despite pulse therapy with methylprednisolone (1000 mg/day for 3 days) on day 288, his respiratory condition worsened further, and he was placed on an artificial respirator. At this point, we switched to rituximab 500 mg (375 mg/m^2), and laboratory values improved and respiratory status also improved somewhat. A tracheotomy was performed on day 314, after which intermittent ventilation was needed. He was discharged on day 442, since his general condition (other than respiratory status) was satisfactory. While previous studies reported that respiratory failure was related to myasthenia gravis in some cases of Castleman's disease [6,7], anti-acetylcholine receptor antibodies were negative in our patient. A previous nerve conduction study of our patient [5] revealed axonal involvement and demyelination changes, leading us to suspect peripheral nerve disorder.

Despite respiratory discomfort and worsened ADL, the patient's overall condition was generally stable for several months with rituximab treatment every 4 weeks. However, he was re-admitted on day 584 due to worsening of general fatigue and appetite loss. Mild fluid accumulation without consolidation in the right chest was observed on CT. Laboratory findings showed slight CRP elevation and worsened renal function. Thrombocytopenia was observed 3 days after re-admission. Cultures of sputum and urine were negative. Suspecting that TAFRO syndrome had worsened, rituximab was administered earlier than the scheduled (roughly 2 weeks after the previous administration) but was not effective. The patient and his family wished no further treatment. His general condition gradually worsened and he died on day 611.

An autopsy revealed pleural effusions (left: 40 mL, hemorrhagic due to bronchopneumonia; right: 1000 mL, serosity) and ascites (1500 mL, serosity). Parenchyma of the left lung was increased in weight (left 675 g, right 430 g) and had marked bronchopneumonia, but the condition did not appear critical enough to have cause respiratory failure. We then sought to determine the cause of type II respiratory failure. Peripheral nerves were degenerated (neurodegeneration) with demyelinating and edematous changes. Spaces around the peripheral

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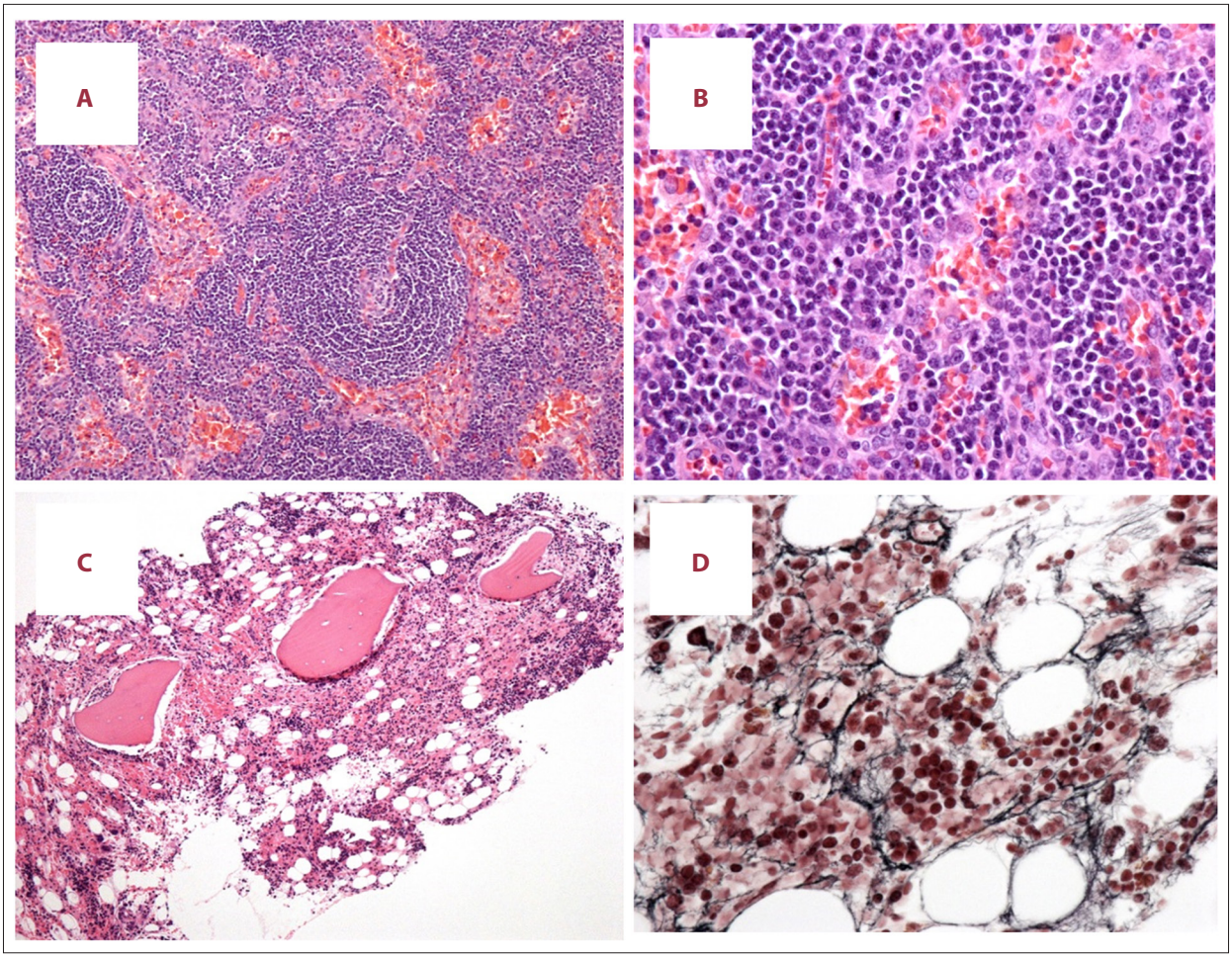

Figure 1. Histological findings on biopsy (our previous study [5]). (**A**) Histological appearance of left axillary lymph node with hematoxylin and eosin stain. Many lymphoid follicles with unclear atrophic germinal centers and expansion of interfollicular zone were apparent. Original magnification ×100. (**B**) A peripheral mantle layer was developed with a concentric cellular distribution. Original magnification ×200. (**D**) Arborized blood vessels were present and we noted infiltration of small lymphocytes and plasma cells in the interfollicular zone. Original magnification ×400. (**C**) Increase in megakaryocytes of the bone marrow was evident by hematoxylin and eosin stain. Original magnification ×200. (**D**) Silver impregnation stain confirmed an increase in reticular fibers. Original magnification ×400.

nerves of the skeletal muscle (e.g., breathing muscle) were positive for Alcian Blue staining and negative for hyaluronidase staining (Figure 3A, 3B). Retention of mucus was suspected between the axis cylinder and myelin sheath, but no lymphocyte accumulation was observed in those areas. Retention of mucus among peripheral nerves was also suspected. Little staining was observed with Klüver-Barrera staining (Figure 3C, 3D). Overall, highly atrophic skeletal muscles, including respiratory muscles (Figure 3E), atrophic lymph nodes, notable high endothelial venules (Figure 4A, 4B), atrophic white pulps of the spleen, and notable red pulps were observed. A membranoproliferative glomerulonephritis-like appearance was noted across the kidney. Lobular formation with mesangial proliferation was found in almost all glomeruli, and many glomeruli showed crescent formation (Figure 4C, 4D).

Discussion

TAFRO syndrome was defined at a Japanese consensus meeting in 2012 [1], and its diagnostic criteria were first proposed in 2016 and updated in 2019 [4]. Our patient fit all major (anasarca, thrombocytopenia, and systemic inflammation) and minor categories. In terms of disease severity, his condition was slightly severe (grade 3) with 3 points for anasarca, 2 points for thrombocytopenia, and 1 point each for fever and renal insufficiency.

Renal dysfunction associated with TAFRO syndrome varies in severity, with some patients requiring hemodialysis [8–11]. In the present case, while renal function worsened as the disease progressed, treatment with tocilizumab and rituximab

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Table 1. Laboratory findings on first admission.

White blood cells (/μL)	2950
Red blood cells (×10⁴/μL)	343
Hemoglobin (g/dL)	10.4
Hematocrit (%)	33.3
MCV (fL)	97.1
Platelet counts (×10⁴/μL)	4.3
Albumin (g/dL)	3.3
AST (IU/L)	15
ALT (IU/L)	13
LDH (IU/L)	53
ALP (IU/L)	206
BUN (mg/dL)	50
Creatinine (mg/dL)	1.55
eGFR (mL/min/1.73 m²)	37.2
Na (mEq/L)	137
K (mEq/L)	5.4
CL (mEq/L)	99
IL-6 (pg/ml)	4.97
VEGF (pg/ml)	151
PT-T (sec)	14.2
PT-INR	1.26
APTT (sec)	43.1
FDP (μg/mL)	3.9
D-dimer (μg/mL)	1.9

CRP (mg/dL)	0.17
IgG (mg/dL)	2168
IgA (mg/dL)	418
IgM (mg/dL)	39
C3 (mg/dL)	44
C4 (mg/dL)	17.7
CH50 (IU/L)	33
Antinuclear antibody	Negative
Thyroglobulin antibody (IU/mL)	495.7
Thyroid peroxidase antibody (IU/mL)	148.1
PAIgG (ng/10⁷ cells)	20.9
Acetylcholine receptor antibody	Negative
HHV-8 DNA PCR	Negative
Analysis of blood gases	
pH	7.31
pCO_2 (mmHg)	62
pO_2 (mmHg)	58.5
HCO_2 (mmol/L)	30.5
Urine test	
Protein	+/–
Glucose	Negative
Urinary sediment	
RBC (/HPF)	1–4
WBC (/HPF)	<1

AST – aspartate aminotransferase; ALT – alanine aminotransferase; LDH – lactate dehydrogenase; ALP – alkaline phosphatase; VFGF – vascular endothelial growth factor; PAIgG – platelet-associated IgG; HHV-8 – human herpes virus 8.

achieved some improvement. Histological findings on autopsy revealed a membranoproliferative glomerulonephritis-like appearance, which has also been reported in previous cases of TAFRO syndrome [9,11,12].

The patient had type II respiratory failure. A nerve conduction study confirmed that he had peripheral nerve disorder with axonal involvement and demyelinating changes. In autopsy, histological findings revealed that spaces between the axis cylinder and myelin sheath of peripheral nerves in skeletal muscles were positive for Alcian Blue staining and negative for hyaluronidase staining, and retention of mucous fluid was suspected. This and the Klüver-Barrera staining of peripheral nerves confirmed neurodegeneration with demyelination of peripheral nerves, which were consistent with results of the nerve conduction study. Overall, skeletal muscles, including respiratory muscles, were highly atrophic. This could have led to his type II respiratory failure, which worsened and was eventually fatal. Since type II respiratory failure developed early on, we speculate that the nerve disorder could have also developed from an early stage of the disease.

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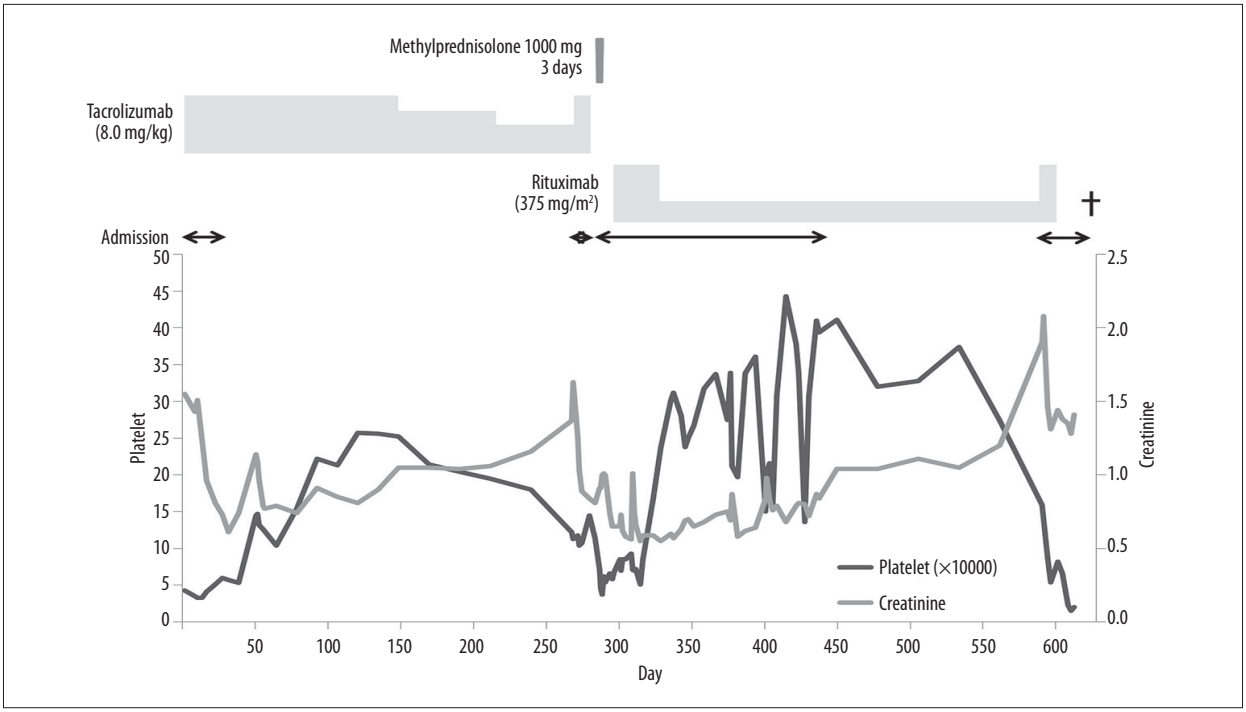
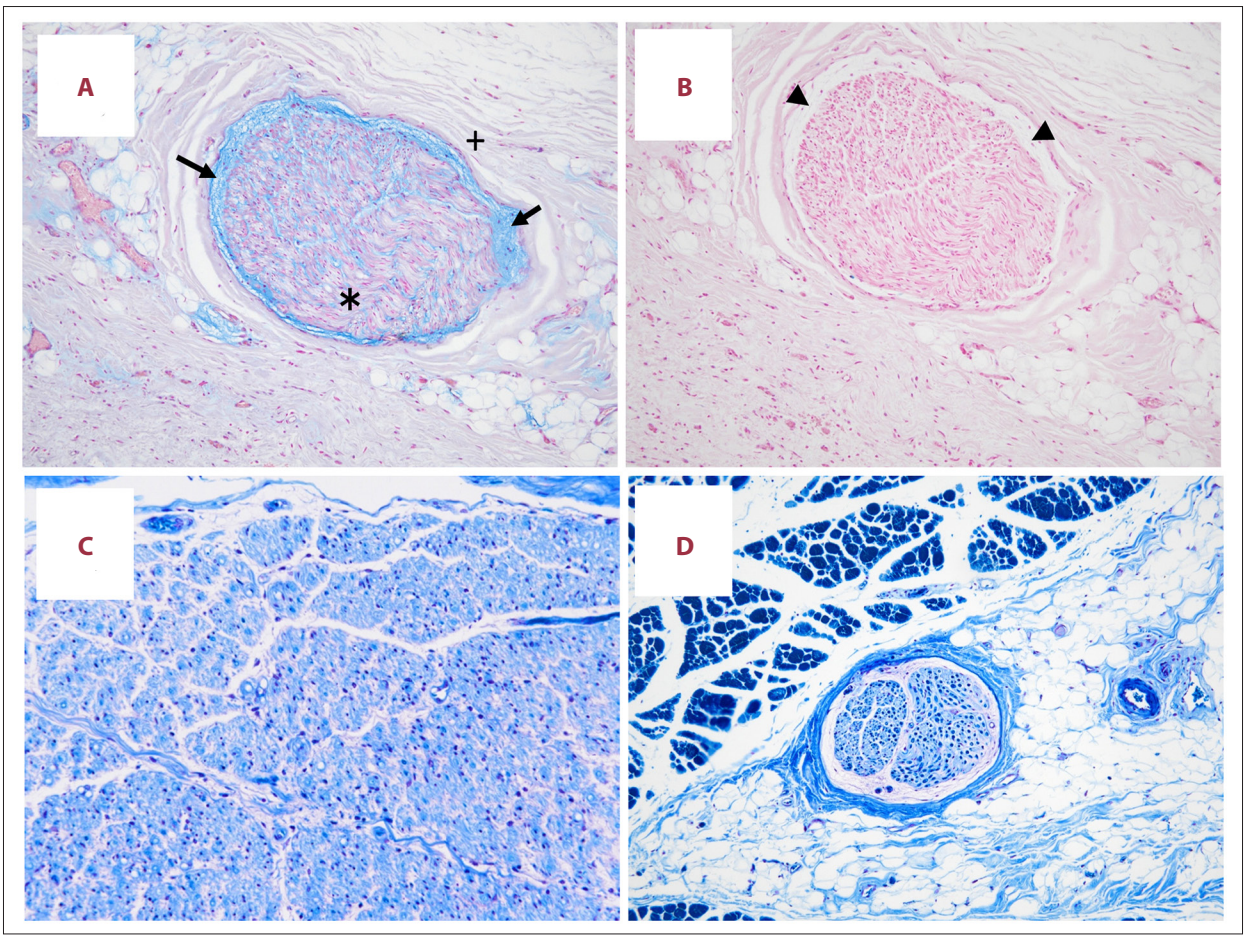


Figure 2. Clinical course.



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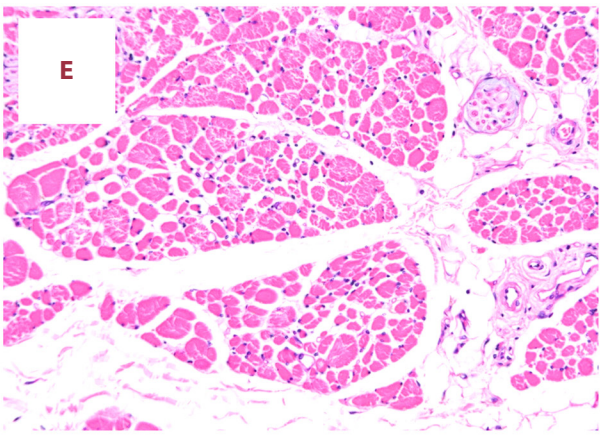

Figure 3. Histological findings on autopsy. (**A**) Alcian Blue staining and (**B**) hyaluronidase staining of peripheral nerves. Spaces that were positive for Alcian Blue staining (arrows) and negative for hyaluronidase staining (arrow head) were observed around the peripheral nerves. Retention of mucus was observed around and among the peripheral nerves of the peripheral nerves. * Axis cylinder. + myelin sheath. Original magnification ×20. (**C, D**) Klüver-Barrera staining of proximal peripheral nerves revealed demyelination. Original magnification ×20 for (**C**) and ×10 for (**D**). (**E**) Hematoxylin and eosin staining of respiratory muscles. Highly atrophic changes were observed. Original magnification ×10.

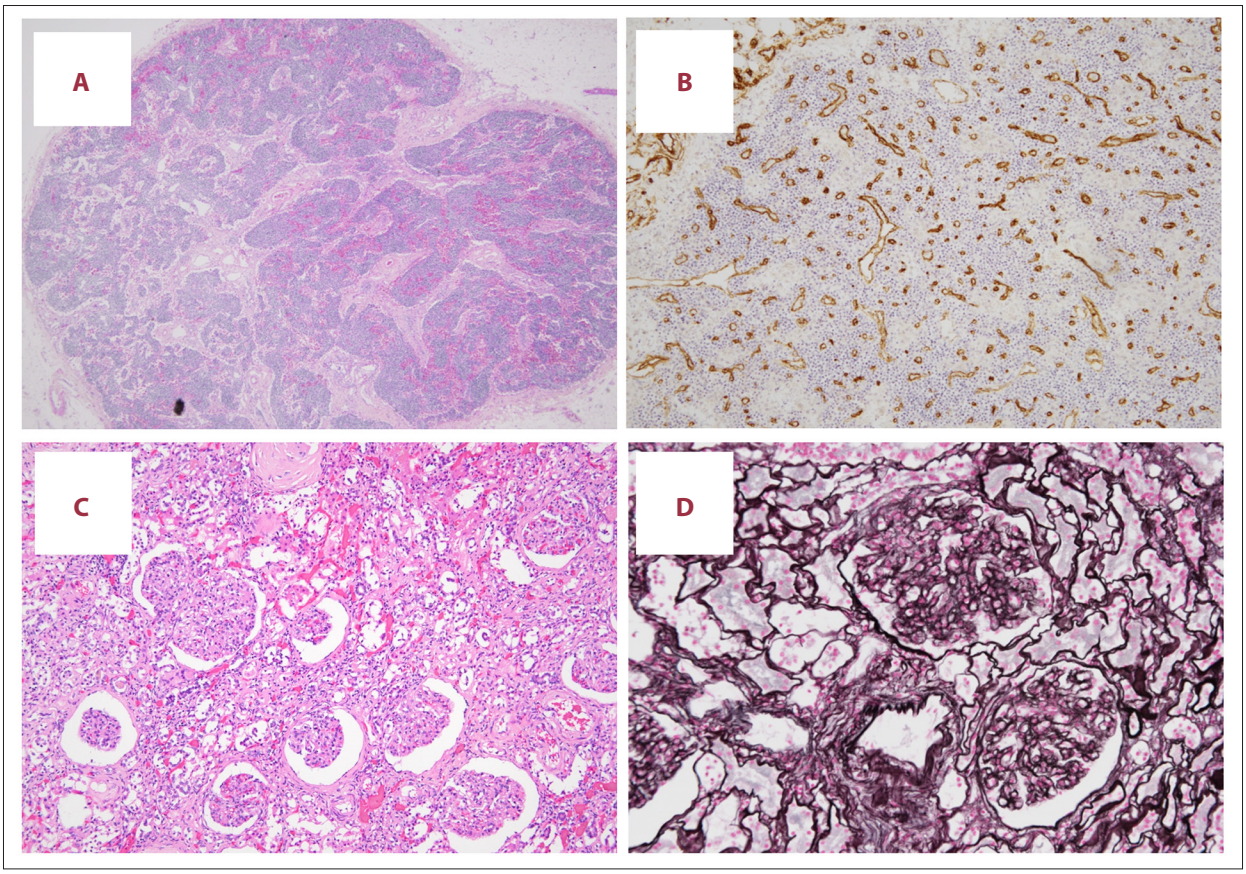

Figure 4. (**A**) Hematoxylin and eosin staining of lymph nodes (original magnification ×4) and (**B**) CD34 immunostaining of lymph nodes (original magnification ×10). Overall, lymph nodes were atrophic, and high endothelial venules were relatively notable. (**C, D**) Renal histological findings include a membranoproliferative glomerulonephritis-like appearance. (**C**) Hematoxylin and eosin staining (original magnification ×10) and (**D**) periodic acid methenamine silver staining (original magnification ×20). Almost all glomeruli showed lobular formation with mesangial proliferation. Many large glomeruli showed crescent formation.

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A possible differential diagnosis was POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes) syndrome [13]. Restrictive lung disease with neuromuscular weakness has been reported in some cases of POEMS syndrome [14]. However, as the patient did not have monoclonality for plasma cells or skin changes, the patient was unlikely to have POEMS syndrome. Both TAFRO syndrome and POEMS syndrome resemble Castleman's disease in some respects. For instance, POEMS syndrome includes peripheral neuropathy in the disease definition. Thus, these diseases might be related in the context of neurodegeneration.

While fluid accumulation, such as pleural effusion and ascites, is one of the characteristics of TAFRO syndrome, few reports have described fluid retention in other intra-organs. In a previously reported case of TAFRO syndrome, the patient developed chronic and asymmetric edema of the optic disc and serous retinal detachment [15]. In our patient, mucous fluid retention was observed in the spaces between the axis cylinder and the myelin sheath of peripheral nerves and among the peripheral nerves. This may suggest the existence of a subpopulation of TAFRO syndrome cases in which fluid accumulation is not limited to pleural effusion and ascites, but also occurs in other intra-organs on a cellular level. However, while tocilizumab treatment did not have a sufficient effect on some patients [16,17], treatment of our case led to a modest improvement of respiratory failure and peripheral nerve disorder. Thus, we cannot rule out the possibility that another disease was involved in the retention of mucous fluid and neurodegeneration.

Conclusions

We described an autopsy case of TAFRO syndrome complicated by type II respiratory failure with atrophic changes in respiratory muscles due to neurodegeneration. Histological findings revealed mucous fluid retention around the peripheral nerves in skeletal muscles, and we speculate this could have contributed to neurodegeneration with demyelination. Further accumulation of cases will be necessary to determine the association of TAFRO syndrome with peripheral nerve disorder and fluid retention.

Department and Institution where work was done

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Conflicts of interest

None.

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