【 CASE REPORT 】

# Complete Resolution of a Case of TAFRO Syndrome Accompanied by Mediastinal Panniculitis, Adrenal Lesion, and Liver Damage with Hyperbilirubinemia

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**Abstract:**

TAFRO syndrome is a systemic inflammatory, lymphoproliferative disorder, but the pathophysiology of the disease is unknown. It is typically characterized by thrombocytopenia, anasarca, a fever, reticulin fibrosis, renal dysfunction, and organomegaly. However, other manifestations have been also reported. We encountered a 43-year-old man with TAFRO syndrome who showed mediastinal panniculitis, liver damage, and adrenal lesions in addition to the core signs. He achieved complete remission with combination therapy of corticosteroids, tocilizumab, and cyclosporin, and remission was maintained even after drug discontinuation at 15 months. Atypical manifestations and complete remission of TAFRO syndrome were remarkable features of our case.

**Key words:** TAFRO syndrome, liver damage, adrenal lesion, tocilizumab, cyclosporin, complete resolution

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## Introduction

TAFRO syndrome is a systemic inflammatory, lymphoproliferative disorder that was originally reported in 2010 (1) and is now classified as a subtype of multicentric Castleman disease (MCD). The signs and symptoms common to TAFRO (which give it its name) are thrombocytopenia, anasarca, fever, reticulin fibrosis, renal dysfunction, and organomegaly; however, other conditions, such as membranoproliferative glomerulonephritis-like glomerulopathy with nephrotic syndrome (2), hemolytic anemia (3), acquired hemophilia (4), and hepatitis (5, 6), have been also reported. Although interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) have been proposed to have pathogenic roles in TAFRO syndrome, whether or not these also contribute to the development of these other conditions is unclear. Several immunosuppressive, anti-inflammatory, and cytotoxic drugs have been reported to be effective for treating TAFRO syndrome. However, each case has a unique clinical course and treatment response, and there is therefore no well-established treatment strategy for TAFRO syndrome.

We encountered a case of TAFRO syndrome associated with mediastinal panniculitis, adrenal lesions, and liver damage, in addition to the core signs and symptoms. The patient was successfully treated with a combination of corticosteroids (CS), cyclosporine (CyA), and tocilizumab (TCZ) and achieved complete remission. Complete remission was maintained even after the discontinuation of all medications.

## Case Report

A 43-year-old man developed the acute onset of chest and abdominal pain 10 days before presentation at our hospital. He had no notable medical history and his health status had been normal until the onset of these symptoms. He underwent a series of medical tests at a different hospital. Blood tests revealed elevation of the white blood cell count

**Table 1.   Laboratory Date on Admission.**

| <Hematology> | | <Biochemistry> | | <Biochemistry> | |
|---|---|---|---|---|---|
| WBC | 15,600 /μL | Total protein | 5.4 g/dL | Ferritin | 731 ng/mL |
| Neutrophil | 86.0 % | Albumin | 2.4 g/dL | IL-6 | 46.7 pg/mL |
| Lymphocyte | 6.0 % | Total bilirubin | 0.9 mg/dL | VEGF | 852 pg/mL |
| Monocye | 8.0 % | AST | 28 IU/L | ANA | <×40 |
| Eosinophil | 0 % | ALT | 36 IU/L | PR3-ANCA | 10.4 U/mL |
| Basophil | 0 % | ALP | 579 IU/L | MPO-ANCA | <1.0 U/mL |
| Atypical-Lymphocyte | 0 % | γ-GTP | 153 IU/L | IgA | 277.1 mg/dL |
| Red blood cell | 508×10⁴ /μL | Cretine kinase | 79 IU/L | IgG | 1,125.7 mg/dL |
| Hemoglobin | 14.5 g/dL | LDH | 334 IU/L | IgM | 95.5 mg/dL |
| Platelet | 22.5×10⁴ /μL | Blood urea nitorogen | 8.0 mg/dL | M-protein | undetected |
| | | Creatinine | 1.11 mg/dL | C3 | 38.1 mg/dL |
| <Coagulation> | | Na | 136 mEq/L | C4 | 6.7 mg/dL |
| PT | 50.0 % | K | 137 mEq/L | | |
| APTT | 32.9 sec | Cl | 138 mEq/L | <Marker of Infection> | |
| Fibrinogen | 469 mg/dL | Glucose | 99 mEq//L | HBs-Ag | negative |
| D dimer | 7.0 μg/mL | C-ractive protein | 27.4 mg/dL | HCV-Ag | negative |
| FDP | 20.3 μg/mL | soluble IL-2R | 1,353 IU/L | HIV-Ab | negative |
| Solubule fibrin | 5.0 μg/mL | | | Anti-EB-IgM VCA | <×10 |
| Antithrombin III | 59 % | <Urinary analysis> | | Anti-EB-IgG VCA | ×80 |
| | | Protein | 30 mg/dL | Anti-EBNA IgG Ab | ×10 |
| | | Occult blood | negative | Anti-CMV IgM | <×10 |
| | | Suger | negative | Anti-CMV IgG | <×10 |
| | | β2MG | 1,535 μg/mL | | |

PT: prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, AST: aspartate aminotransferase, ALT: alanine aminotranseferase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transeptidase, LDH: lactate dehydrogenase, solubel IL-2R: soluble interleukin 2 receptor

(12,600/μL) and C-reactive protein (CRP; 14.1 mg/dL); all other results were within normal limits. Abdominal computed tomography (CT) showed only swelling of the left adrenal gland, which was not considered to be consistent with his symptoms. A fever and abdominal distension also developed after admission, and broad-spectrum antibiotics were administered. His condition worsened despite antibiotics, and he was referred to our hospital for a further investigation.

On admission, the patient complained of general fatigue and abdominal pain and was febrile and mildly dyspneic (respiratory rate: 24 breaths/minute; oxygen saturation: 94% on ambient air). A physical examination revealed swelling of the cervical lymph nodes, abdominal distention with tenderness, and bilateral pitting leg edema. Laboratory tests (Table 1) showed elevations in white blood cells, CRP, alkaline phosphatase (ALP), lactate dehydrogenase, and serum creatinine. The percentage activity of prothrombin time and albumin level were also decreased. The platelet counts, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, and bilirubin level were within their normal ranges. Schistocytes were not detected. The serum IL-6 and VEGF levels were increased to 46.7 pg/mL (reference range, <4.0 pg/mL) and 852 pg/mL (reference range, <38.3 pg/mL), respectively. M-protein was not detected by electrophoresis of protein. Serological studies revealed no specific findings for connective tissue diseases, vasculitis, hepatitis

B, hepatitis C, Epstein-Barr virus, or cytomegalovirus. A urinalysis showed mild proteinuria of 30 mg/dL without hematuria or abnormal casts. A bone marrow examination showed no morphological abnormality, and a flow cytometric analysis of the bone marrow did not reveal any signs of clonal proliferation.

CT of the thorax and abdomen revealed multiple lymphadenopathies, an anterior mediastinal lesion, massive ascites, a low-density area around the portal vein (periportal collar sign), subserosal edema of the gallbladder, increased attenuation in the mesentery around the adrenal glands, and bilateral swelling of the adrenal glands (Fig. 1). Blood and urine cultures were sterile. Biopsies were performed of the bone marrow, a cervical lymph node, and the mediastinal lesion.

Over the next few days, the urinary output steadily decreased, and the anasarca worsened. The serum creatinine value increased to 1.78 mg/dL, and the platelet counts decreased to 90,000/μL. The values of ALP, AST, and ALT also steadily increased to 788 IU/L, 45 IU/L, and 37 IU/L, respectively, without any signs of obstruction of the common bile duct. The total bilirubin level was around 0.7 mg/dL at this time. On day 5, we diagnosed him with TAFRO syndrome and started therapy with CS (methylprednisolone pulse therapy at a dose of 1,000 mg for three consecutive days and then 80 mg of prednisolone daily) and TCZ (8 mg/kg, weekly). Within a few days, the high-grade fever had resolved, but the platelet count had decreased to below
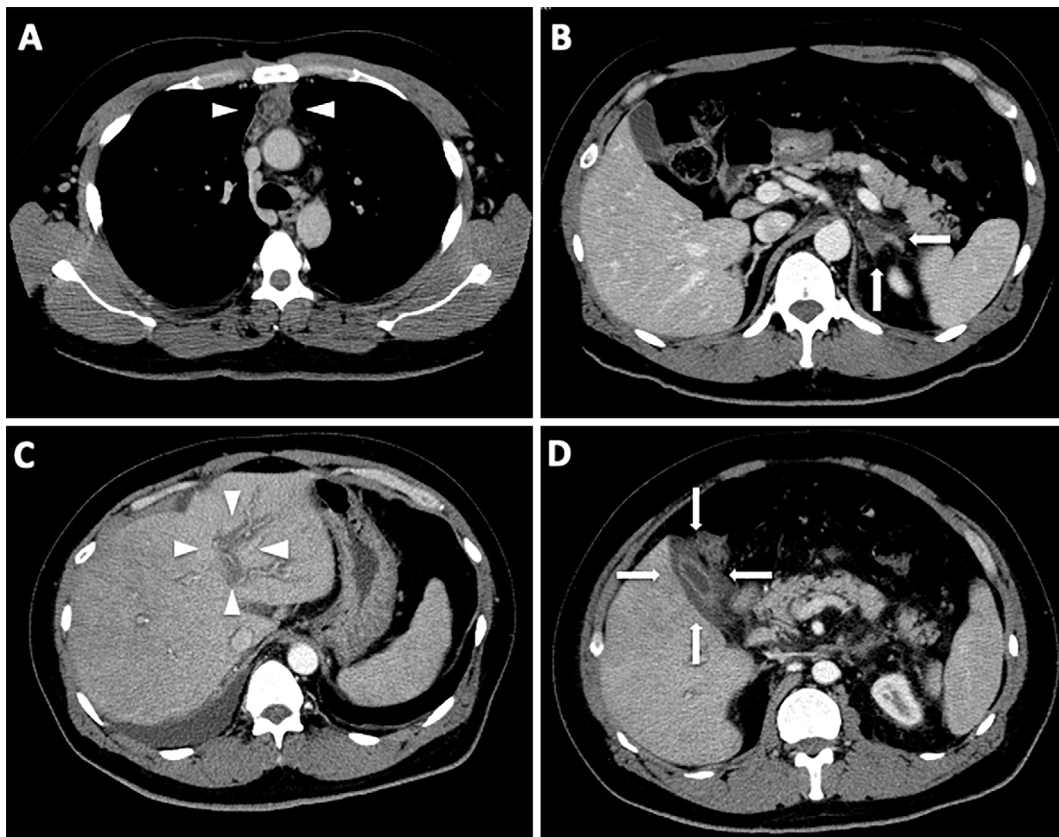
**Figure 1.   Imaging findings at admission. Computed tomography showed (A) an anterior mediastinal mass (arrowheads), (B) swollen adrenal gland and increased attenuation in the mesentery around the adrenal glands (white arrows), (C) periportal collar sign (arrowhead), and (D) subserosal edema of the gallbladder (white arrows).**

50,000/μL. The abdominal distension and kidney dysfunction continued to deteriorate, and the patient became anuric on day 8. As urinary protein was negative and no abnormal casts were detected, we suspected that glomerulonephritis was unlikely. Given the acute deterioration of the kidney function, elevation of β2 microglobulin, and systemic symptoms, we suspected interstitial nephritis and/or acute tubular necrosis as the cause of his acute kidney injury and continued anti-inflammatory and supportive treatment.

At the same time, liver damage, represented by increased levels of AST and ALT (over 200 IU/L), also appeared (Fig. 2). The total bilirubin levels also gradually increased to 6.2 mg/dL on day 15. Hemodialysis was started on day 8, and CyA was added on day 9, with the dose adjusted to keep the plasma concentration between 800 and 1,000 ng/mL at peak and under 250 ng/mL at trough. The serum creatinine level continued to rise until day 22. Histological findings were as follows (Fig. 3): the bone marrow showed hyperplasia of megakaryocytes, reticulin fibrosis, and no evidence of monotonous cell proliferation. The cervical lymph nodes demonstrated atrophy of lymph follicles, hyperplasia of microvessels, and infiltration of plasma cells among follicles. There was no evidence of monoclonal proliferation by κ/λ *in situ* hybridization, and immunostaining revealed no expression of latency-associated nuclear anitigen-1, which is associated with human herpesvirus 8-associated Castleman

disease, or Epstein-Barr virus-encoded small RNA, which is often seen in angioimmunoblastic T cell lymphoma. These histological findings of the bone marrow and lymph nodes were consistent with mixed-type MCD (7). The mediastinal lesion showed fatty tissue with infiltration of inflammatory cells, which was consistent with panniculitis. The clinical and histological findings met all major and minor diagnostic criteria of TAFRO syndrome (Table 2).

The patient's condition gradually improved after combination therapy with CS, TCZ, and CyA and hemodialysis. The fever resolved first, and then the abdominal distension due to ascites gradually resolved. The laboratory data, including ALP, AST, ALT, and bilirubin, also improved simultaneously. After the symptoms had resolved, elevation of AST, ALT, and ALP without bilirubin elevation occurred, but this may have been a side effect of CyA, as it resolved with CyA cessation (Fig. 2). On day 31, renal replacement therapy was terminated, and the patient was discharged on day 60 with CS and TCZ treatment. CT to check for improvement in the mediastinal and adrenal lesions was not repeated because the patient did not give his consent.

In the following nine months, he experienced no recurrence during CS tapering, and TCZ was discontinued because a skin rash occurred after injection. We planned to continue a maintenance dose of CS, but he stopped treatment with 3 mg prednisolone at 15 months after the disease
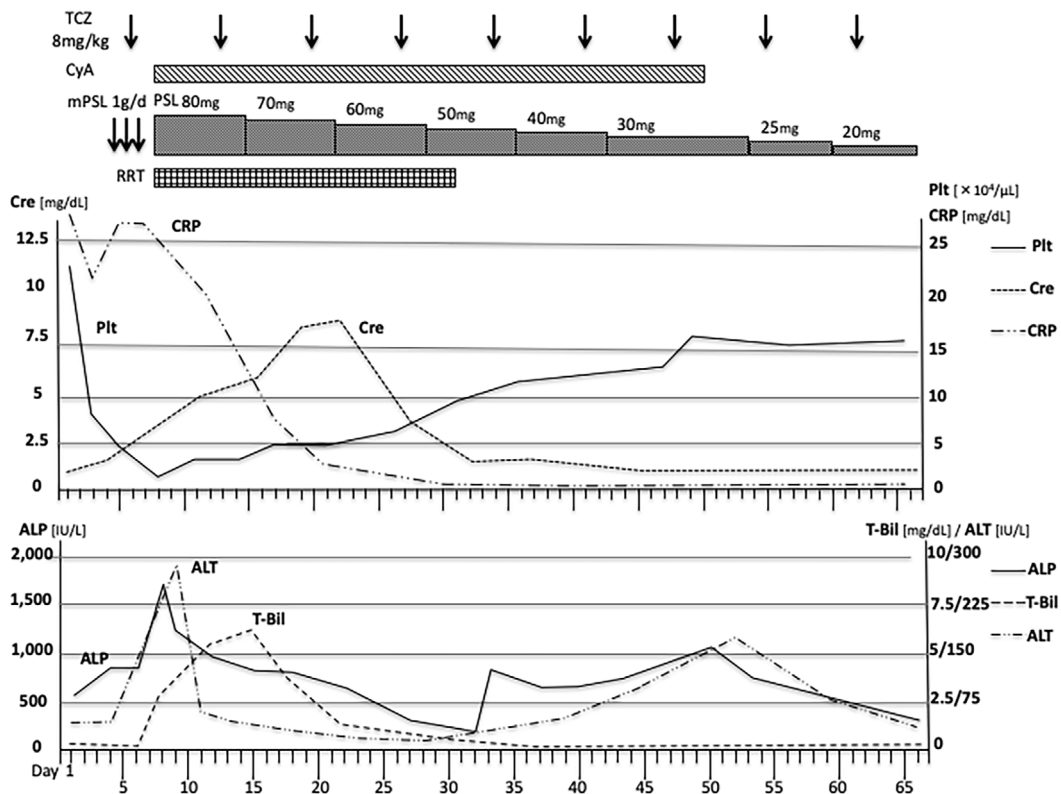
**Figure 2.** Clinical course. ALT and T-Bil increased in sync with worsening of TAFRO symptoms and resolved with combination therapy. Elevation of ALT and ALP from day 33 improved after CyA cessation. ALP: alkaline phosphatase, ALT: alanine aminotransferase, Cre: serum creatinine, CRP: C-reactive protein, CyA: cyclosporine, mPSL: methylprednisolone, Plt: platelet, PSL: prednisolone, RRT: renal replacement therapy, T-Bil: total bilirubin, TCZ: tocilizumab
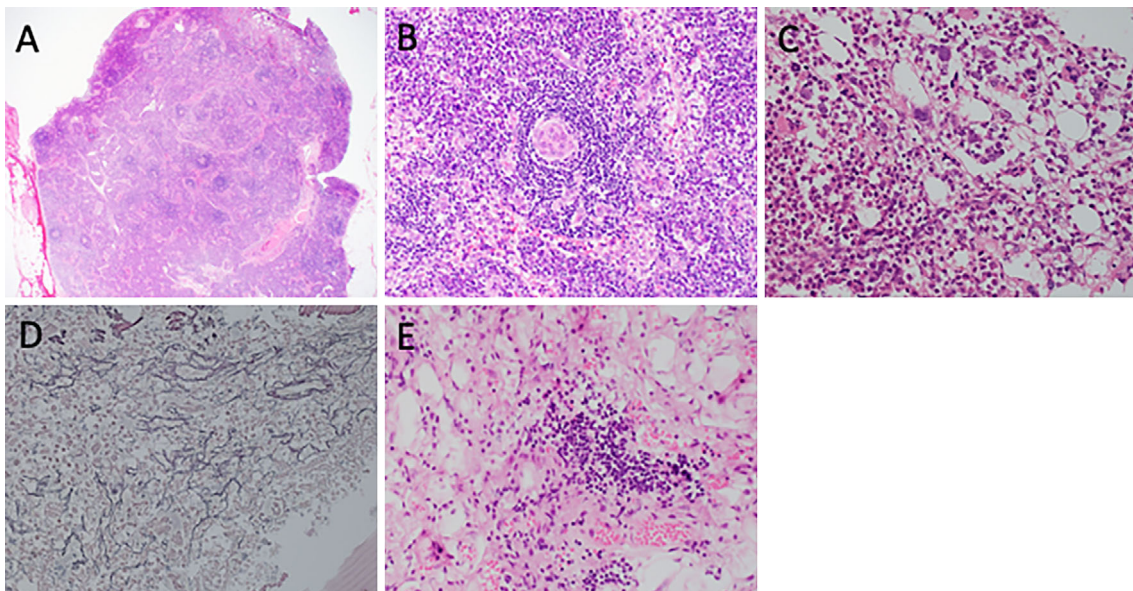


**Figure 3.** Histopathological findings. (A). A cervical lymph node showed scattered lymphoid follicles with atrophic germinal centers [Hematoxylin and Eosin (H&E) staining ×20]. (B) Plasma cells had infiltrated among lymphoid follicles in the lymph node (H&E staining, ×200). (C, D) Hypercellular bone marrow with increased numbers of megakaryocytes and mild reticulin fibrosis. These findings were compatible with mixed-type Castleman's disease (C, H&E staining, ×200; D, silver impregnation staining, ×200). (E) The mediastinal lesion showed fatty tissue infiltrated by inflammatory cells, including plasma cells and lymphocytes (H&E staining, ×400).

**Table 2.  Diagnostic Criteria of TAFRO Syndrome.**

| A diagnosis of TAFRO syndrome requires all three major categories and at least two of four minor categories |
| --- |

**A. Major categories**

(1) Anasarca, including pleural effusion, ascites and general edema

(2) Thrombocytopenia; platelet count ≤ 100,000/μL, without myelosuppressive treatment

(3) Systemic inflammation, defined as fever of unknown etiology above 37.5°C and/or serum C-reactive protein concentration ≥ 2 mg/dL

**B. Minor categories**

(1) Castleman disease-like features on lymph node biopsy

(2) Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow

(3) Mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy

(4) Progressive renal insufficiency

**C. Disease to be exclude**

(1) Malignancies, including lymphoma, myeloma, mesothelioma, etc

(2) Autoimmune disorders, including systemic lupus erythematosus (SLE), Sjögren's syndrome, ANCA-associated vasculitis, etc.

(3) Infectious disorders, including acid fast bacterial infection, rickettsial disease, Lyme disease, severe fever with thrombocytopenia syndrome, etc.

(4) POEMS syndrome

(5) Hepatic cirrhosis

(6) Thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS)

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onset. No recurrence occurred afterward, and he maintained complete resolution without any drugs.

## Discussion

The concept of TAFRO syndrome was first proposed in 2010 (1). It is now classified as a type of idiopathic MCD because of the similar histological features of the lymph nodes and the role of IL-6 and VEGF in the pathophysiology of both diseases. However, whether or not they share a common etiology is still under debate (7, 8). Our patient showed the typical clinical features of TAFRO syndrome, and the histological findings of his lymph nodes were compatible with those of idiopathic MCD. TAFRO syndrome can also cause various manifestations other than the typical symptoms, and this case was complicated with mediastinal panniculitis, adrenal lesions, and liver damage with hyperbilirubinemia.

The histology of the anterior mediastinal lesion was consistent with panniculitis of fatty tissue with infiltration of inflammatory cells. Five cases of TAFRO syndrome with anterior mediastinal lesion have been reported (9-13). In all cases, including ours, the tissue showed inflammation with various inflammatory cells. Although the swelling of the mediastinal lymph nodes is a common sign of unicentric Castleman disease (11), it occurs less commonly in TAFRO syndrome (2, 14). Recently, a new concept wherein lymph node swelling and histopathological features of iMCD are reactive changes to elevated IL-6 and/or other circulating factors was proposed (15). Under this concept, we assume that mediastinal panniculitis is representative of systemic inflammation and/or hypercytokinemia.

The bilateral lesions of the adrenal glands were another remarkable feature of this case. Abnormal adrenal gland findings on abdominal CT can have various causes, including hemorrhaging, infarction, bacterial infection, malignancy, and autoimmune inflammation. In the present case, the clinical findings, such as bilateral lesions, CT findings consistent with the inflammatory process, no evidence of infection, and the ineffectiveness of antibiotics, suggested that malignancy or bacterial infection was unlikely. There have been two reported cases of TAFRO syndrome with adrenal gland lesions (16, 17). The suspected etiology of adrenal gland lesions in the reported cases were necrosis (16) and hemorrhaging (17), although their pathogenesis was not fully clarified. Nara et al. (17) reported that retroperitoneal inflammation might affect the adrenal glands because bilateral thickening of Gerota's fascia was observed. In our case, there were no hemorrhagic findings on repeated CT. However, the increased attenuation in the mesentery around the adrenal glands was consistent with the inflammatory process. We therefore concluded that retroperitoneal inflammation had affected the adrenal glands.

Some cases with the not-otherwise-specified (NOS) type of MCD have also been reported to have adrenal lesions (18, 19). The CT features of the adrenal lesion in patients with NOS-MCD are reported to include a mass with peripheral rim enhancement and peritoneal thickening, findings that differed from those in the present case. In that study, lymphoid tissue around the adrenal gland was suspected as the origin of peritoneal thickening, according to the histological study (19). In our case, however, whether or not the lymphoid tissue was the origin of inflammation was unclear, as a histological examination was not conducted.

In addition to the core TAFRO signs and symptoms, elevation of ALP is also a common abnormality; however, liver damage and hyperbilirubinemia have not been mentioned in review papers (2, 14, 20). There are two reports of cases with hyperbilirubinemia (12, 21), but a liver biopsy was not conducted in either. Seven reports described cases with liver

damage without hyperbilirubinemia and mentioned liver histology in patients with TAFRO syndrome (5, 6, 22-24); five studies reported no specific histological findings, one reported interface hepatitis with infiltration of inflammatory cells (6), and the remaining study reported lobular hepatitis with no steatosis (5). In our present case, CT showed the periportal collar sign and subserosal edema of the gallbladder. These findings are often seen in acute hepatitis, cholangitis, or severe congestion. Although laboratory tests were not diagnostic for a specific etiology, we chose not to perform a liver biopsy because of the risk of bleeding. The drugs administered before the onset of liver damage were antibiotics and antacids. Liver damage occurred after the discontinuation of the antibiotics and resolved without the discontinuation of the antacids. Therefore, drug-induced liver injury was unlikely as the cause of liver damage. The liver enzyme and bilirubin levels fluctuated simultaneously with TAFRO symptoms; therefore, we concluded that liver damage with hyperbilirubinemia can be a component of TAFRO syndrome. We considered hepatitis or intrahepatic cholangitis to be the major cause of the liver injury, rather than cholestasis with interstitial edema caused by vascular hyperpermeability or hypoalbuminemia, for several reasons. First, vascular hyperpermeability and hypoalbuminemia are quite common events with TAFRO syndrome, but liver damage is rarely reported, even in cases with severe systemic anasarca, indicating that the severity of vascular leakage or congestion is not related to the occurrence of liver damage. Second, the panniculitis in the mediastinal tissue and retroperitoneal inflammation around the adrenal gland suggested systemic inflammation of the connective tissue of the whole body. We therefore suspected that the liver damage was a partial sign of TAFRO syndrome that was also caused by the systemic inflammatory process. IL-6 is thought to cause this inflammation, but it is also possible that IL-6 affects hepatocytes, resulting in liver damage, as in MCD (25).

We consider that systemic inflammation and hypercytokinemia caused not only TAFRO symptoms, but rare manifestations such as the panniculitis of the anterior mediastinum, adrenal lesion, and liver damage. However, we cannot clearly explain why several uncommon symptoms occurred in this TAFRO patient. This may be a reflection of the heterogenicity of TAFRO syndrome or iMCD, and the accumulation of further cases is needed.

Immunosuppressive and anti-inflammatory therapies are standard for TAFRO syndrome. CS suppress the inflammatory processes regulated by cytokines and chemokines, including IL-6 and VEGF, which play crucial roles in TAFRO syndrome, and have been used as the first treatment in most reported cases (2, 12). If steroid monotherapy does not demonstrate sufficient efficacy, additional treatment is required. CyA, anti-IL-6 drugs (TCZ and siltuximab), the anti-CD20 drug rituximab, thalidomide, bortezomib plus sirolimus, the anti-IL1 drug anakinra, and lymphoma-based cytotoxic therapy have been reported to be effective (2, 14). A recent review recommends an anti-IL-6 agent as second-line therapy (15).

We first administered high doses of CS and TCZ, after which the high-grade fever and elevated CRP improved. However, the pleural effusion, ascites, and kidney dysfunction continued to deteriorate, prompting us to add CyA. We cannot determine which drug was most effective; instead, we speculate that suppression of multiple inflammatory cascades by combination therapy was essential. There are no available data for predicting the treatment efficacy of each drug, and a patient can sometimes show a dramatic and long-lasting response if given the right agents. We therefore recommend combination therapy or switching drugs if necessary.

The patient experienced no recurrence after discontinuation of CyA and TCZ, and CS was tapered and terminated 15 months after the disease onset. A few studies have reported that treatment of TAFRO syndrome can be discontinued (23, 26, 27), but whether or not complete resolution of TAFRO syndrome is common is unclear. TAFRO syndrome is diagnosed by the combination of clinical and pathological features, and disease-specific findings have not yet been reported. Furthermore, the varied responses to treatment indicate a diverse etiology of TAFRO syndrome.

We described a case of TAFRO syndrome with unusual manifestations of mediastinal panniculitis, adrenal lesions, and liver damage. Notably, once the TAFRO syndrome completely resolved, this state was maintained without drugs.

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