




# Severe systemic inflammation mimicking TAFRO syndrome following COVID-19

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## Abstract

TAFRO syndrome is a rare systemic inflammatory disease. Its pathogenesis mainly involves excessive cytokine secretion and autoimmune dysfunction. Although its etiology is unclear, some viral infections have been reported to cause it. Here, we report a case of severe systemic inflammation mimicking TAFRO syndrome that arose after COVID-19. A 61-years-old woman suffered from a continuous fever, ascites, and edema after contracting COVID-19. She developed progressive thrombocytopenia, renal failure, and elevated C-reactive protein levels. She was tentatively diagnosed with multisystem inflammatory syndrome in adults (MIS-A) and received steroid pulse therapy. However, she exhibited worsening fluid retention and progressive renal failure, which are not typical of MIS-A. A bone marrow examination showed reticulin myelofibrosis and an increased number of megakaryocytes. Although a definitive diagnosis of TAFRO syndrome was not made according to current diagnostic criteria, we determined that her symptoms were clinically consistent with those of TAFRO syndrome. Combination therapy, including steroid pulse therapy, plasma exchange, rituximab, and cyclosporine, improved her symptoms. There are pathological similarities between hyperinflammation that arises after COVID-19 and TAFRO syndrome in terms of the associated cytokine storms. COVID-19 may have triggered the development of systemic inflammation mimicking TAFRO syndrome in this case.

**Keywords** TAFRO syndrome · COVID-19 · Cytokine storm · Interleukin-6

## Introduction

TAFRO syndrome is a systemic inflammatory disease characterized by thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, and organomegaly [1, 2]. Although the etiology of TAFRO syndrome is unclear, its pathogenesis mainly involves excessive cytokine secretion and autoimmune dysfunction [3]. Multicentric Castleman disease (MCD) is another inflammatory disorder, which is characterized by polyclonal lymphadenopathy resulting from a cytokine storm driven by interleukin (IL)-6 [4, 5]. Human herpes virus-8 (HHV-8) can cause MCD, which is categorized as HHV-8-associated MCD [4]. On the other hand, it is unclear whether viral infections can cause TAFRO syndrome [3]. A previous report suggested that viral infections, such as Epstein-Barr virus infections, may occasionally be involved in the development of TAFRO syndrome [6].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019

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(COVID-19) pandemic. Although COVID-19 is known to exhibit pulmonary manifestations, it also harms other organ systems through cytokine storms, endothelial cell damage, and thrombo-inflammation, in addition to direct viral toxicity [7, 8]. COVID-19 can produce hematological, cardiovascular, renal, gastrointestinal, endocrinological, and neurological manifestations [7]. Additionally, several studies have described autoimmune diseases, such as systemic lupus erythematosus, antiphospholipid syndrome, and Guillain–Barre syndrome, occurring after COVID-19 [9–12]. However, no cases of TAFRO syndrome that arose after COVID-19 have been reported. Here, we describe a case of severe systemic inflammation mimicking TAFRO syndrome that arose after COVID-19.

## Case report

A 61-years-old female with no relevant medical history was admitted to our hospital because of a continuous fever, which had developed after COVID-19. She had received her third vaccination against COVID-19 four months before contracting COVID-19. She had received the Pfizer-BioNTech BNT162b2 vaccine for all three vaccinations. Three weeks before admission, she developed a fever and was diagnosed with COVID-19 based on a polymerase chain reaction (PCR) test. Three days after being diagnosed with COVID-19, her fever subsided. However, seven days after being diagnosed with COVID-19, she developed a fever again, accompanied by right hypochondrial pain. The laboratory tests performed on admission to the previous hospital showed a decreased platelet count ( $10.0 \times 10^4/\mu\text{L}$ ) and an elevated C-reactive protein (CRP) level (14.8 mg/dL). At that time, an antigen test for SARS-CoV-2 was negative. She was tentatively diagnosed with cholecystitis and treated with antibiotics. Although the abdominal pain resolved, the fever persisted, as did the high CRP level. A transthoracic echocardiogram revealed a small amount of pericardial effusion, which led to a suspicion of pericarditis. However, she developed renal impairment and was transferred to our hospital to undergo hemodialysis and further examination to obtain a diagnosis.

On admission to our hospital, she did not have a fever, as it had been treated with a non-steroid anti-inflammatory drug, but exhibited pitting edema and ascites. There were no skin eruptions, conjunctivitis, or abnormal neurological findings. Laboratory tests revealed progressive thrombocytopenia ( $8.4 \times 10^4/\mu\text{L}$ ), renal failure (serum creatine, 4.7 mg/dL), an elevated CRP level (13.6 mg/dL), and a high D-dimer level (58.1  $\mu\text{g/dL}$ ). A PCR test of a nasal swab for SARS-CoV-2 was negative. Other laboratory test results are shown in Table 1. Her cytokine levels, including those of IL-6 (41.8 pg/mL), vascular endothelial growth factor (VEGF, 4230 pg/mL), and the soluble IL-2 receptor (2735 U/mL),

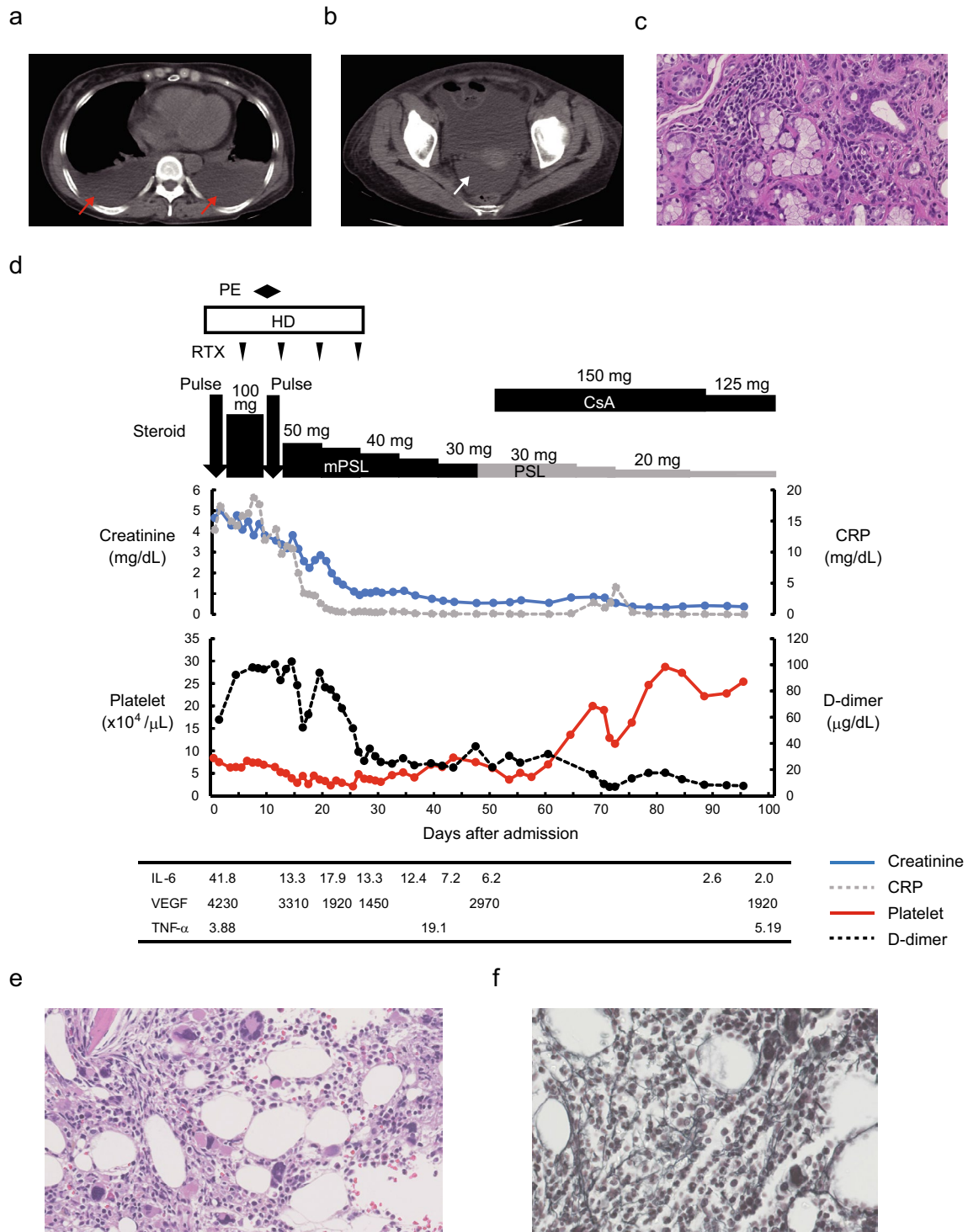
**Table 1** Laboratory data on admission

Test	Value	Reference range
WBC	11,700	3300–8600/ $\mu\text{L}$
RBC	3.32	$4.35\text{--}5.55 \times 10^6/\mu\text{L}$
Hemoglobin	9.8	13.7–16.8 g/dL
Hematocrit	29.2	40.7–50.1%
Reticulocytes	6.0	$2.0\text{--}27.0 \times 10^4/\mu\text{L}$
Platelets	8.4	$15.8\text{--}34.8 \times 10^4/\mu\text{L}$
Neutrophils	86	38.5–80.5%
Monocytes	5	2.0–10.0%
Eosinocytes	1	0–8.5%
Lymphocytes	8	16.5–49.5%
Aspartate aminotransferase	43	13–30 U/L
Alanine aminotransferase	17	10–42 U/L
Lactate dehydrogenase	183	124–222 U/L
Total bilirubin	1.0	0.40–1.50 mg/dL
Creatinine	4.65	0.65–1.07 mg/dL
Blood urea nitrogen	59.9	8.0–20.0 mg/dL
C-reactive protein	13.6	0.0–0.14 mg/dL
Ferritin	343	16.0–239.0 ng/mL
Immunoglobulin G	878	861–1747 mg/dL
sIL-2R	2735	122–496 U/mL
Interleukin-6	41.8	< 7.0 pg/mL
Interleukin-10	< 2	$\leq 5.0$ pg/mL
VEGF	4230	$\leq 115$ pg/mL
TNF- $\alpha$	3.88	0.75–1.66 pg/mL
IFN- $\gamma$	< 0.1	$\leq 0.1$ IU/mL
Anti-nuclear antibodies	Negative	Negative
Anti-SS-A antibodies	$\geq 240$	< 7.0 U/mL
HHV-8 DNA	< 20	< 20 copies/ $10^6$ WBC
SARS-CoV-2 antibodies	4.8	< 1.0

WBC white blood cells, RBC red blood cells, sIL-2R soluble interleukin-2 receptor, VEGF vascular endothelial growth factor, TNF tumor necrosis factor, IFN interferon, SS-A Sjögren's syndrome-A, HHV human herpes virus, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

were elevated. Computed tomography revealed pleural effusion, pericardial effusion, and ascites without lymphadenopathy or splenomegaly (Fig. 1a and b). She was positive for anti-Sjögren's syndrome type A antigen (SS-A) antibodies ( $\geq 240$  U/mL). A labial salivary gland biopsy exhibited a focus score of 1.3 [13]. Although her histological salivary gland manifestations were compatible with Sjögren's syndrome, she had no glandular manifestations. Therefore, she was not diagnosed with Sjögren's syndrome (Fig. 1c) [14, 15]. A tentative diagnosis of multisystem inflammatory syndrome in adults (MIS-A) was made, based on the patient's clinical course; i.e., her symptoms arose after a COVID-19, and steroid pulse therapy was initiated.

After the steroid pulse therapy, she continued to exhibit high CRP levels, and her ascites deteriorated (Fig. 1d).



**Fig. 1** **a, b** Computed tomography (CT) findings seen at admission. The red arrows indicate the bilateral pleural effusion. The white arrow indicates ascites in the Douglas fossa. **c** The microscopic features of the salivary gland biopsy specimen. Focal inflammatory cell infiltration was seen around the intralobular conduit. **d** The patient's clinical course and cytokine levels (including her interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and tumor necrosis

factor- $\alpha$  (TNF- $\alpha$ ) levels). PE: plasma exchange; HE: hemodialysis; RTX: rituximab; CsA: cyclosporin A; mPSL: methylprednisolone; PSL: prednisolone; CRP: C-reactive protein. **e-f** Microscopic features of the bone marrow biopsy specimen. Increased numbers of megakaryocytes (**e**) and reticulin fibers (**f**) were seen. Hematoxylin and eosin staining ( $\times 400$ , **e**) and silver impregnation staining ( $\times 400$ , **f**)

Therefore, TAFRO syndrome was suspected since the small amount of pericardial fluid, the absence of skin eruptions, and the patient's worsening fluid retention and progressive renal failure were not typical of MIS-A. A bone marrow biopsy showed increased levels of megakaryocytes and reticulin fibers (Fig. 1e and f). Finally, we determined that her symptoms were clinically consistent with those of TAFRO syndrome [1]. Her TAFRO syndrome was classified as severe. Her age and elevated D-dimer level suggested a poor prognosis [16].

As the first round of steroid pulse therapy did not improve her symptoms, rituximab (375 mg/m<sup>2</sup>, once a week for four weeks) was administered (Fig. 1d). In addition, plasma exchange was performed to remove cytokines in addition to the steroid pulse therapy and rituximab, as described previously [17]. Two weeks after admission, dysarthria and right hemiplegia developed. Magnetic resonance imaging revealed a cerebral infarction in the left corona radiata (Fig. 2a). The patient's prolonged high D-dimer levels suggested that her cerebral infarction had probably been caused by a hypercoagulable state induced by TAFRO syndrome. Recombinant thrombomodulin was administered intravenously for the hypercoagulable state. After anticoagulation therapy, including a change from recombinant thrombomodulin to oral edoxaban, no re-infarction or cerebral bleeding occurred. Three weeks after admission, the patient's elevated CRP levels and renal insufficiency had been ameliorated. Hemodialysis was withdrawn three weeks after the initial dose of rituximab had been administered. Although the patient's fluid retention improved, her platelet count did not increase (Fig. 1d). The administration of cyclosporine A improved her thrombocytopenia. Three months after being diagnosed, she was discharged without fluid retention (Fig. 2b and c).

## Discussion

COVID-19 sometimes causes a hyperinflammatory response, induced by an excessive reaction to the virus, and produces immune-mediated manifestations [18]. Such inflammatory responses can result in various systemic inflammatory autoimmune diseases. In our case, after the patient's initial symptoms of COVID-19 had subsided the fever recurred and her high CRP levels persisted despite a negative PCR test result for SARS-CoV-2. She was initially diagnosed with MIS-A based on the presence of thrombocytopenia; elevated CRP levels; elevated IL-6 levels; and pericardial effusion, which was probably due to pericarditis. However, her thrombocytopenia, renal failure, and ascites worsened after corticosteroid therapy for MIS-A. These clinical findings and her bone marrow histology resulted in a provisional diagnosis of TAFRO syndrome. She was treated based on this diagnosis, which improved her thrombocytopenia, renal failure, and ascites. This is the first reported case of severe systemic inflammation mimicking TAFRO syndrome to arise after COVID-19.

Many patients are asymptomatic or have mild symptoms after being infected with SARS-CoV-2. On the other hand, in 20% of cases COVID-19 may become severe or even critical. Most of these severe cases are caused by hyperresponsiveness of the immune system [11]. A hyperinflammatory response can cause cytokine storm syndrome, in which IL-6 plays a major role [11, 18]. In cytokine storm syndrome induced by COVID-19 or other conditions, such as an adverse effect of chimeric antigen receptor T-cell (CAR-T) therapy, the IL-6 level is elevated, and IL-6 blockade by tocilizumab ameliorates the condition [18–21]. Interferon- $\gamma$ , IL-1, tumor necrosis factor, and VEGF levels are also elevated in cytokine storms. Cytokine storms can lead to the prolonged activation of signaling pathways and induce inflammatory cell death, which can result in more cytokines being produced and generate a positive feedback loop between cytokine release and cell death [19, 22]. Thus,



**Fig. 2** **a** Magnetic resonance imaging (MRI) findings observed at the onset of a cerebral infarction in the left corona radiata (arrow); **b–c** The CT findings seen at seventy days after admission. The pleural effusion (**b**) and ascites (**c**) had improved



cytokine storms can cause various inflammatory diseases, such as acute respiratory distress syndrome (ARDS), multi-system inflammatory syndrome (MIS), and hemophagocytic syndrome [18, 19, 22].

In addition to ARDS in the acute phase, a hyperinflammatory state can occur in multiple systems 4–6 weeks after a SARS-CoV-2 infection, which is termed MIS-C in children and MIS-A in adults [23, 24]. MIS was first reported in pediatric cases as MIS-C [23, 25]. MIS-C involves the cardiovascular and gastrointestinal systems. A similar state of multisystem hyperinflammation has been reported in adults as MIS-A [26]. Although the pathophysiology of MIS-A remains unclear, a case definition has been proposed [27]. In our case, symptoms derived from a hyperinflammatory state occurred two weeks after a COVID-19 infection. Based on the patient's inflammatory status after COVID-19, she was initially diagnosed with MIS-A. However, little cardiac illness was seen. In addition, skin rashes, conjunctivitis, and neurological abnormalities were absent. Although her CRP and IL-6 levels were elevated, her symptoms differed from those of typical MIS-A [24, 26–28].

The pathogenesis of TAFRO syndrome mainly involves a cytokine storm, in which IL-6 and VEGF predominate [3, 29]. Although the molecular mechanism underlying TAFRO syndrome is not fully understood, cytokines and autoimmune cells stimulate effector cells, producing many cytokines through a positive feedback loop, which results in a cytokine storm [2, 3]. TAFRO syndrome and MCD are related diseases. MCD is also characterized by the overexpression of IL-6. In HHV-8-associated MCD, the viral homolog of IL-6 drives symptoms accompanied by a cascade of other cytokines, including human IL-6 [30]. Although the pathogen that causes TAFRO syndrome has not been established, some studies have suggested that viral and bacterial infections may be associated with the development of TAFRO syndrome [3]. COVID-19 also induces cytokine storms, which involve IL-6 and VEGF. Therefore, COVID-19 may be able to trigger TAFRO syndrome. A previous report suggested that COVID-19 may become severe in patients with TAFRO syndrome [31]. Another report indicated that TAFRO syndrome can develop after vaccination against COVID-19 and have a fatal outcome [32]. Here, we report a case of severe inflammation mimicking TAFRO syndrome that arose after COVID-19. Further evaluations are warranted to elucidate whether the COVID-19-induced overexpression of IL-6 can directly cause TAFRO syndrome.

Previous reports have not adequately discussed whether systemic inflammation that causes TAFRO syndrome-like manifestations following COVID-19 should be called TAFRO syndrome. When diagnosing TAFRO syndrome, infectious diseases need to be excluded. Although our patient developed fluid retention, renal failure, and

thrombocytopenia, a PCR test for COVID-19 performed at this time was negative. Since TAFRO syndrome is a clinical term, we diagnosed her with TAFRO syndrome according to the diagnostic criteria [1]. However, there are several sets of diagnostic criteria for TAFRO syndrome, and a previous study proposed three categories of TAFRO syndrome: idiopathic MCD (iMCD)-TAFRO, possible iMCD-TAFRO, and TAFRO without iMCD or other comorbidities [29, 33]. Within this classification, our patient would be classified as having TAFRO without iMCD or other comorbidities. In the latter classification, COVID-19 cytokine storm syndrome was listed as an exclusion criterion. However, COVID-19 cytokine storm syndrome and TAFRO syndrome share a similar pathogenesis, involving excessive cytokine levels, and it is difficult to precisely distinguish between them. Although there is no established treatment for cytokine storms that occur after COVID-19, our case suggests that severe systemic inflammation mimicking TAFRO syndrome that arises after COVID-19 may be successfully treated according to the treatment strategies for TAFRO syndrome. Further studies are required to define the differences between COVID-19 cytokine storm syndrome and TAFRO syndrome.

COVID-19 can trigger the new onset of various autoimmune diseases [34]. In addition, COVID-19 can be severe in patients with autoimmune diseases, including Sjögren's syndrome [35, 36]. Our patient was positive for anti-SS-A antibodies, and her salivary gland histological findings were compatible with Sjögren's syndrome. Although she was not diagnosed with Sjögren's syndrome because she had no symptoms associated with the condition, she may have been predisposed to Sjögren's syndrome. Patients with TAFRO syndrome occasionally present similar manifestations to severe Sjögren's syndrome [37, 38]. Therefore, a predisposition to autoimmune conditions, such as positivity for anti-SS-A antibodies, may be a risk factor for developing TAFRO syndrome after COVID-19.

In conclusion, our case suggests that manifestations mimicking TAFRO syndrome can occur after COVID-19. There are pathological similarities between hyperinflammation that arises after COVID-19 and the development of TAFRO syndrome. In this case, COVID-19 may have triggered the development of TAFRO syndrome by inducing a cytokine storm.

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**Data availability** The data supporting this study's findings are not publicly available due to the need to protect patient privacy, but are available on reasonable request from the corresponding author, HH.

## Declarations

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the relevant institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from the patient.

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