A Case of TAFRO syndrome after COVID-19 vaccination

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Abstract

Here we report a case of TAFRO syndrome developed after the COVID-19 mRNA vaccination. Universal vaccination is important, however, the possibility of various complications after COVID-19 vaccination, including TAFRO syndrome, should be considered.

Introduction

The TAFRO syndrome, a rare systemic disease characterized by thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly, was first reported in Japan in 2010. It is classified as a subtype of idiopathic multicentric Castleman's disease (iMCD) because the pathological findings of lymph nodes in TAFRO syndrome are similar to those of iMCD. iMCD is a lymphoproliferative disorder with three distinct subtypes: POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell proliferation, and skin change) syndrome, TAFRO syndrome, or iMCD-not otherwise specified (iMCD-NOS) [1]. TAFRO syndrome is distinct from POEMS syndrome or iMCD-NOS, as it does not accompany human herpesvirus 8 infection, immunoglobulin overproduction, or polyneuropathy. TAFRO syndrome often presents with progressive clinical symptoms and can be fatal.

COVID-19 vaccination is recommended to reduce the number of COVID-19 infected population and lower the risk of becoming severe. However, some serious adverse events have been reported after COVID-19 vaccination, such as anaphylaxis, thrombosis with thrombocytopenia syndrome, Guillain-Barre syndrome, and myocarditis [2-5]. Although these complications are not frequent, these incidents may lead people to avoid vaccination and the pandemic to the worse.

Here, we report a case of TAFRO syndrome that developed after the first injection of a COVID-19 mRNA vaccine.

Case Presentation

A 45-year-old man was transferred to our hospital for the evaluation of renal dysfunction and anasarca. After the first dose of the COVID-19 mRNA vaccine (Moderna), he developed fever and macrohematuria for 3 to 4 days and developed edema and abdominal distension from the day after the first COVID-19 mRNA vaccination. Six days after vaccination, his symptom was persisted and he was detected renal dysfunction (eGFR 39.2 mL/min/1.73 m^2, serum Creatinine 1.59 mg/dL), elevated C-reactive protein value (22.4 mg/dL), and proteinuria.

On admission to our hospital, the patient was 171.0 cm tall and weighed 80.0 kg (weight gain of 7 kg in 1 week), with a blood pressure of 142/73 mmHg, pulse rate of 60 /min, and body temperature of 37.3 degree. He complained of epigastric pain, dyspnea, and bilateral pitting edema of the lower extremities. Oxygen saturation was 92% in room air. Electrocardiography was normal, and echocardiogram revealed normal left ventricular systolic function. Laboratory data revealed elevated levels of C-reactive protein (22.6 mg/dL) and renal dysfunction (eGFR 49 ml/min/1.73 m^2). The platelet count was 9.1×10^3 /μL (Table 1). The PCR test results for COVID-19 were negative.

Bilateral pleural effusions and a slight accumulation of ascites were detected on computed tomography (CT) (Figure 1). There was no abnormal uptake on gallium scintigraphy. Levels of IL-6 and VEGF in pleural effusion and ascites were significantly elevated (Table 2).

Bone marrow biopsy showed hyperplastic and increased megakaryocytes, and reticular fiber hyperplasia was partially observed by silver staining.

We performed renal biopsy for the definitive diagnosis of renal injuries. Light microscopy showed diffuse hypercellularity with thrombotic microangiopathy (TMA) lesions of the glomeruli. There was diffuse and global endothelial cell enlargement due to cytoplasmic swelling, with a large number of inflammatory cells (Figure 2a). The partial dissolution of the mesangial matrix (mesangiolysis) is also shown (Figure 2b). Endothelial cell swelling occluding the capillary lumen with loss of fenestrations and expansion of the subendothelial space was observed by electron microscopy (Figure 2d,2e). Immunoperoxidase staining for CD34 and CD68 was positive (Figure 2f,2g). Immunofluorescence analysis revealed negative staining for IgG, IgA, IgM, C3, and C1q.

Overall, this patient fulfilled three major categories (thrombocytopenia, anasarca, and systemic inflammation) and three minor categories (renal insufficiency, organomegaly, and myelofibrosis). Thus, the patient was diagnosed with TAFRO syndrome. After second high-dose steroid pulse therapy with 500 mg methylprednisolone for 3 days, followed by prednisolone 40 mg/day, anasarca, systematic inflammation and renal injuries were improved (C-reactive protein <0.1 mg/dL, eGFR 67 ml/min/1.73 m^2). The platelet count increased to the normal range on the 31st day of admission. Eleven months after discharge, the patient had never relapsed under PSL treatment (5 mg/day).

Discussion

We encountered a case of TAFRO syndrome that developed immediately following the first COVID-19 mRNA vaccination. To the best of our knowledge, this is the first reported case of TAFRO syndrome following a COVID-19 mRNA vaccination. Various side effects of the COVID-19 vaccination have been reported worldwide. Braun *et al* . reported a case of cerebral venous thrombosis and thrombotic thrombocytopenia syndrome [2]. Lim *et al* . reported myocarditis after mRNA COVID-19 vaccination [3]. Cases of kidney injury, such as IgA nephropathy [4], minimal change disease [5-7], and IgG4-related disease [8], following mRNA vaccination have accumulated in current research.

Ubara *et al* . reported the renal histology of TAFRO syndrome as glomerular endotheliopathy that is representative of endothelial cell swelling, mesangiolysis, mesangial loosening (loss of mesangial matrix staining),

and GBM double contour and thickening. Electron microscopy shows loss of mesangial architecture and endothelial space as well as loss of endothelial cell fenestrations [6]. In the present case, these findings, except for endothelial cell fenestrations, were detected, confirming the diagnosis of TAFRO syndrome.

Previous reports have suggested that vaccination may trigger an autoimmune response due to antigenic mimicry, as well as activation of quiescent auto-reactive T and B cells [10]. These reports suggest that the COVID-19 mRNA vaccine stimulates the immune system and causes autoimmune reactions.

TAFRO syndrome is a systemic inflammatory disorder and a subtype of HHV-8 negative MCD [11]. Although the etiology has not been revealed, it has been demonstrated that hypercytokinemia related to IL-6 and stimulation of VEGF contributes to the pathophysiological mechanisms of TAFRO syndrome [12,13]. It is suggested that the abnormal autoimmune response induced by COVID-19 mRNA vaccination caused the overproduction of cytokines, such as IL-6 and VEGF, in the present case.

The pathophysiology of TAFRO syndrome has not yet been clarified; however, it often presents with progressive clinical symptoms and can be fatal. We should be considered as one of the rare side reactions of the COVID-19 vaccine and should be diagnosed earlier. Further studies are needed to reveal the mechanisms of the immune response in developing severe side effects following COVID-19 mRNA vaccination.

Conclusion Universal vaccination against COVID-19 is important for lowering the risk of spreading COVID-19 infection. Several complications, such as renal, hematological, and heart diseases, have been reported; however, its pathogenesis is unclear. The possibility of various complications after COVID-19 vaccination, including TAFRO syndrome, should be considered.

Authorship list

Hitomi Hirose (HH) = Original draft preparation. Hitoshi Suzuki (HS) = Conceptualization and editing the manuscript. Yukako Umezawa (YU), Masako Iwasaki (MI), Hiromitsu Fukuda (HF), and Hisatsugu Takahara (HT) = Data collection, validation. Shigeki Tomita (ST) = Histopathological analysis and editing the manuscript. Yusuke Suzuki (YS) = Supervision.

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

Consent

In accordance with the journal's patient consent policy, written informed consent was obtained from the patient to publish this report.

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Figure legends

Figure.1 Computer tomography showed bilateral pleural effusions and ascites but no organomegaly.

Figure.2 Renal histological analysis.

a. There were diffuse and global endothelial cell enlargement by cytoplasmic swelling with large numbers of inflammatory cells.**b.** Mesangiolysis. Partial dissolution of the mesangial matrix (arrow head). **c.** Endothelial cell swelling (arrow head).**d.** Endothelial cell swelling occluding the capillary lumen (star) with loss of fenestrations (triangle), and expansion of the subendothelial space (diamond). Fibrin deposition was observed (white arrow). **e.** Expansion of the subendothelial space was observed.**f,g.** Immunoperoxidase staining for CD34 (f) and CD68(g) was positive.

Table 1 Laboratory data on admission

Complete blood cell count	reference range	Complete blood cell count	reference range	Complete blood cell coun
White blood cell (/μL)		19,000		(4,000˜8,000)
Neutrophil (%)		87.4		(45˜60)
Eosinophil (%)		0.2		(1˜5)
Lymphocyte (%)		4.3		(25˜45)
Hemoglobin (g/dL)		13.7		(14˜18)
Platelet ($\times$104/μL)		9.1		(15˜35)
Coagulation test		Coagulation test		Coagulation test
APTT (s)		33.2		(30.2)
PT (%)		77		(70˜100)
PT-INR		1.19		(0.9˜1.1)
D-dimer (μg/mL)		25.58		(0˜1)
Blood chemistry		Blood chemistry		Blood chemistry
Albumin (g/dL)		1.9		(3.9 4.9)
AST (IU/L)		16		(13 33)
ALT (IU/L)		14		(8 42)

LDH (IU/L)	309	(124˜222)
CPK (IU/L)	66	(60˜287)
ALP (IU/L)	111	(38˜113)
u-GT (IU/L)	44	(10˜47)
UN (mg/dL)	31	(8˜22)
Creatinine (mg/dL)	1.29	(0.61˜1.04)
Urinary acid (mg/dL)	9.2	(2˜7)
Na (mmol/L)	141	(138˜146)
K (mmol/L)	3.8	(3.6˜4.9)
Cl (mmol/L)	108	(99˜109)
IgG (mg/dL)	602	(870˜1700)
IgA (mg/dL)	158	(110˜410)
IgM (mg/dL)	25	(35˜220)
IgE (mg/dL)	1759.0	(0˜232)
C3 (mg/dL)	141	(65˜135)
C4 (mg/dL)	34	(13˜35)
CH50 (U/mL)	69	(32˜49)
C-reactive protein (mg/dL)	22.6	(0˜0.3)
BNP (pg/mL)	248.7	(0˜18.4)
IL-6(pg/mL)	17.2	(0˜4)
Urinalysis	Urinalysis	Urinalysis
Sediment		
RBC(/HPF)	20-29	<1-4
WBC(/HPF)	10-19	<1-4
Cast		
Granule cylinder	1+	
Tubular epithelium	1+	
Urinalysis	Urinalysis	Urinalysis
Protein(g/gCre)	0.67	<0.15
NAG(IU/L)	120.5	(0.97˜4.17)
β2 microglobulin(μg/L)	22,500	(0˜230)

Abbreviations: APTT; Activated partial thromboplastin time; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; ALP, alkaline phosphatase; BUN, urea nitrogen; Na, sodium; K, potassium; Cl, chlorine; BNP, brain natriuretic peptide, IL-6; interleukin-6, RBC red blood cells; WBC, white blood cells; NAG, N-acetyl-β-d-glucosaminidase

Table 2 Analysis of pleural effusion and ascites

Pleural effusions reference range	Pleural effusions reference range	Pleural effusions reference range
sIL2-R (IU/mL)	2130	(157˜474)
IgG (mg/dL)	371	(870˜1700)
IgA (mg/dL)	78	(110˜410)
IgM (mg/dL)	12	(33˜190)
IL-6 (pg/mL)	707	(0˜4)
Ascites	Ascites	Ascites
sIL2-R (IU/mL)	1580	(157˜474)
IgG (mg/dL)	247	(870˜1700)
IgA (mg/dL)	49	(110˜410)
IgM (mg/dL)	7	(33˜190)

IL-6 (pg/mL)	249	(0~4)

Abbreviations: sIL2-R, serum soluble interleukin 2 receptor; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M, IL-6; interleukin-6, VEGF;, vascular endothelial growth factor

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