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Case Report

TAFRO syndrome with a fatal clinical course following BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccination: A case report

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ABSTRACT

TAFRO syndrome is a rare disorder that manifests as thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly. Although this disease often follows a severe clinical course, the cause remains unknown. The coronavirus disease 2019 (COVID-19) pandemic is a major global problem. Vaccination against COVID-19 has been successful; however, there are concerns about severe adverse events. Herein, we report a rare presentation of TAFRO syndrome triggered by the COVID-19 vaccine with a fatal clinical course. A 42-year-old Japanese man presented to our hospital complaining of fever lasting for 2 weeks that occurred a day after receiving the BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine. The patient had a low platelet count, ascites, reticulin myelofibrosis, renal failure, and lymphadenopathy and was diagnosed with TAFRO syndrome. Despite administering several immunosuppressive drugs, the condition did not improve. The patient repetitively developed and eventually died of bacteremia caused by multidrug-resistant Klebsiella pneumoniae. We highlight the first reported case of TAFRO syndrome after COVID-19 vaccination.

1. Introduction

TAFRO syndrome, first reported in 2010 [1], is a rare disease characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin myelofibrosis, renal dysfunction (R), and organomegaly (O), including hepatosplenomegaly and lymphadenopathy [2]. Initially, TAFRO syndrome was thought to be a subtype of idiopathic multicentric Castleman disease, which is a rare heterogeneous systemic disorder characterized by systemic inflammation, multicentric lymphadenopathy with characteristic histopathological features, and organ dysfunction due to elevated pro-inflammatory cytokines, including interleukin-6 (IL-6) [3, 4].

The coronavirus disease 2019 (COVID-19) pandemic has been a worldwide concern since 2019. Vaccines including BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) have been administered worldwide to prevent this pandemic. Although vaccination is usually effective and safe, some people experience severe side effects. Side effects such as local injection site reaction, anaphylaxis, fever, and fatigue are common; however, those caused by autoantibodies, such as thrombosis with thrombocytopenia syndrome, Guillain-Barre syndrome, and idiopathic thrombocytopenic purpura (ITP) [5], are rare but severe. Moreover, cytokine release syndrome, including multisystem inflammatory syndrome in adults (MIS-A) [6] and systemic capillary leak syndrome (SCLS) [7], have also been reported as rare side effects of COVID-19 vaccination.

Here, we report a case of TAFRO syndrome following BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccination.

2. Case report

A 42-year-old Japanese man with no relevant medical history presented to our hospital with a chief complaint of persistent fever after the
second dose of BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine. The patient was in the usual state of health until the first vaccination, but the patient noticed a loss of appetite and general malaise the next day. From the day after the second vaccination, high fever (>38 °C) occurred. Fever, loss of appetite, and general malaise persisted for 2 weeks, followed by abdominal fullness and weight gain; hence, the patient presented to our hospital.

On admission, the patient’s temperature was 37.2 °C, blood pressure was 125/86 mmHg, pulse rate was 98 beats/min, respiratory rate was 16 breaths/min, and oxygen saturation was 98% on room air. Initial laboratory investigations revealed the following: white blood cell count, 8.06 \times 10^3/\text{mm}^3 (71.5% neutrophils, 8.5% lymphocytes, and 9.5% monocytes); hemoglobin level, 14.5 g/dL; platelet count, 10 \times 10^9/\text{mm}^3; C-reactive protein level, 23.9 mg/dL; albumin level, 2.8 g/dL; ferritin level, 539 ng/mL, erythrocyte sedimentation rate, 42 mm/1 hour; and soluble interleukin 2 receptor level, 1400 U/mL. There were no electrolyte or aminotransferase abnormalities, and renal function was normal. Human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C virus antibody were negative. Urine dipstick examination results were normal. Additional data showed immunoglobulin G level of 553 mg/dL, immunoglobulin G4 level of 24.2 mg/dL, immunoglobulin A level of 48 mg/dL, and immunoglobulin M level of 30 mg/dL. The results of immunoelectrophoresis showed α1-globulin levels of 12.0%, α2-globulin levels of 14.9%, β-globulin levels of 11.7%, and γ-globulin levels of 9.5%. Rheumatoid factor level of <5.0 IU/mL, antinuclear antibody level of <40, antineutrophil cytoplasmic antibody level of <1.0 U/mL, double-stranded DNA level of <10 IU/mL, anti-Sm antibody level of <1.0 U/mL, anti SS-A/B antibody level of <1.0 U/mL, anti-ribonucleoprotein antibody level of <2.0 U/mL. Contrast-enhanced computed tomography (CT) revealed pleural effusion (Fig. 1a and Fig. 1b), ascites, periporal edema, mild hepatosplenomegaly, and mild lymphadenopathy (mediastinal and retroperitoneal, approximately 6 mm in short-axis diameter). Blood, sputum and urine cultures and interferon-gamma release assays were negative. Echocardiography did not reveal vegetation on the valves, and positron emission tomography-CT scan showed no lymphadenopathy that could be biopsied. Moreover, random skin biopsy was negative, while bone marrow examination showed reticulin myelofibrosis. Additional laboratory tests revealed an IL-6 level of 47.5 pg/mL, vascular endothelial growth factor of 5520 pg/mL, and a positive result for platelet-associated IgG (PAIgG). Based on these clinical features and examination results, the patient was diagnosed with TAFRO syndrome.

Twelve days after admission, we started intravenous methylprednisolone pulse therapy (1000 mg/day) for 3 days, followed by prednisolone 1 mg/kg daily (70 mg/day). Despite starting steroids, laboratory abnormalities and the patient’s condition continued to worsen. Even after adding tocilizumab 8 mg/kg on the 16th day, anasarca increased, while platelet count and renal function decreased. On the 22nd, 32nd, 40th, and 55th days, we treated the patient with four doses of weekly rituximab 375 mg/m². Since daily platelet transfusion was required, we added intravenous immunoglobulin therapy from the 68th day to the 72nd day and tocilizumab 8 mg/kg again on the 75th day. While platelet count gradually improved to around 1.0 \times 10^3/\text{mm}^3 without daily transfusion, anasarca did not decrease. We performed abdominal paracentesis and removed 5 L of ascites every other day. Fetal bacteremia caused by multidrug-resistant bacteria occurred several times. On the 91st day, the patient developed fever, and blood culture revealed bacteremia caused by multidrug-resistant Klebsiella pneumoniae. Despite using susceptibility-based antibiotics including Cefmetazole, levofloxacin, imipenem, tigecycline, and colistin, the patient’s condition did not improve, and eventually, the patient died on the 94th day of hospitalization (Fig. 2). An autopsy was performed the day after the death. The autopsy revealed ascites, pleural effusion, hepatomegaly, splenomegaly, and myelofibrosis in the bone marrow. Retroperitoneal lymphadenopathy showed only inflammatory changes and no atypical lymphocytes, and it did not show any depostions of amyloid proteins.

3. Discussion

To the best of our knowledge, this is the first case of TAFRO syndrome in a healthy person associated with BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccines, as described in the scientific literature. Unfortunately, the patient had an extremely fatal clinical course despite multiple immunosuppressive treatments.

We diagnosed the patient with TAFRO syndrome because three major and two minor criteria of the 2015 diagnostic criteria for TAFRO syndrome [2] were met. Major criteria include anasarca, thrombocytopenia, and systemic inflammation such as fever of unknown etiology or serum C-reactive protein concentration >2 mg/dL or both. Minor criteria include reticulin myelofibrosis, mild organomegaly, and progressive renal insufficiency. Even if the patient fulfills these characteristics, several diseases need to be ruled out to diagnose TAFRO syndrome.
syndrome, such as malignancies including lymphoma, autoimmune disorders including systemic lupus erythematosus and ANCA-associated vasculitis, and infectious disorders including acid-fast bacterial infection, rickettsial disease, Lyme disease, and severe fever with thrombocytopenia syndrome. Moreover, it is necessary to rule out POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome, IgG4-related disease, hepatic cirrhosis, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome before the diagnosis of TAFRO syndrome [2], which we have conducted and confirmed through the examination results during hospitalization. In addition, autopsy examination of the retroperitoneal lymphadenopathy did not show Castleman’s disease-like features such as hyaline vascular, hypervascular, and/or plasmacytic pathology [8], as described in the diagnostic criteria for TAFRO syndrome [2]. We speculate that the biopsy results may have been masked by the administration of steroids in the diagnostic criteria for TAFRO syndrome [2]. We considered that the hyperinflammatory state caused by COVID-19 vaccination could contribute to such a condition.

In conclusion, a previously healthy man developed TAFRO syndrome a day after COVID-19 vaccination. Therefore, physicians should be aware that COVID-19 vaccines may cause various hyperinflammatory states, leading to TAFRO syndrome. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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