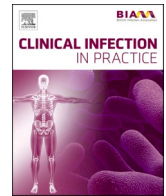




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Case Reports and Series

Severe coronavirus disease 2019 in a patient with TAFRO syndrome: A case report

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ABSTRACT

Background: TAFRO syndrome, a subtype of idiopathic multicentric Castleman disease, is an acute or subacute systemic inflammatory disease that causes fever, generalized oedema (pleural effusion or ascites), and thrombocytopenia and is associated with renal impairment, anaemia, and organomegaly (hepatosplenomegaly and lymph node enlargement). Coronavirus disease 2019 (COVID-19)-associated hyperinflammation is caused by dysregulation of proinflammatory cytokines. Cytokine storm syndrome is common to both COVID-19 and TAFRO syndrome.

Case report.

A 66-year-old man with TAFRO syndrome was admitted because of worsening renal function, right pleural effusion, and ascites. He was taking 20 mg prednisolone orally and 25 mg cyclosporin A orally twice daily. Despite administration of maximum oxygenation and remdesivir, the patient developed acute respiratory distress syndrome (ARDS) and was transferred to the intensive care unit.

Results: Chest radiography showed bilateral lung infiltration. COVID-19 was confirmed with a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2. Chest and abdominal computed tomography showed massive ground-glass opacities in both lungs, slight right pleural effusion, hepatomegaly, splenomegaly, and ascites.

Conclusion: To the best of our knowledge, this is the first report of COVID-19 in a patient with TAFRO syndrome. Despite receiving a moderate dose of a corticosteroid and a monoclonal antibody against the IL-6 receptor, our patient developed severe pneumonia, suggesting that strong immunomodulatory therapy in the antiviral phase of COVID-19 may promote viral growth and induce ARDS.

Introduction

TAFRO syndrome, first reported in Japan in 2010, is a rare systemic inflammatory disease characterised by thrombocytopenia, anasarca, fever, bone marrow fibrosis, renal dysfunction, and organomegaly (Masaki et al., 2020). The annual incidence of TAFRO syndrome in Japan is estimated to be 0.9–4.9 per million individuals, and the nationwide prevalence is approximately 860–7240 cases (Masaki et al., 2020). Although several pathological findings of lymph nodes in TAFRO syndrome resemble those in idiopathic multicentric Castleman disease (iMCD), TAFRO syndrome takes an acute or subacute clinical course, with milder lymph-node swelling and a lower platelet count than that in

iMCD (Masaki et al., 2020). iMCD comprises a heterogeneous group of lymphoproliferative disorders characterised by excessive systemic inflammatory features. The clinical manifestations of iMCD may be attributed to excessive proinflammatory hypercytokinaemia with elevated levels of interleukin 6 (IL-6).

The majority of patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain asymptomatic or experience mild symptoms. However, some develop delayed acute respiratory distress syndrome (ARDS), presumably due to cytokine storms (Hsu et al., 2021). Risk factors for severe coronavirus disease 2019 (COVID-19) include hypertension, diabetes, cardiovascular disease, and chronic lung disease (Masaki et al., 2016); however, limited data are available

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Fig. 1. Chest and abdominal computed tomography images at the onset of acute respiratory distress syndrome. A. Massive ground-glass opacities in both lungs and right pleural effusion. B. Hepatosplenomegaly. C. Slight ascites in Douglas' pouch (white arrow).

regarding the relationship between autoimmune diseases, including TAFRO syndrome, and COVID-19 severity.

Here, we report a case of severe COVID-19 pneumonia in a patient with TAFRO syndrome receiving moderate-dose corticosteroids and sarilumab, a monoclonal antibody against IL-6 receptor, for several months prior to COVID-19 onset.

Case report

A 66-year-old man diagnosed with TAFRO syndrome 2 years previously was admitted to our hospital because his renal function, right pleural effusion, and ascites had worsened over the past 2 months. He had a cough that had started 4 days before admission without dyspnoea on admission. He was taking prednisolone 20 mg orally, cyclosporine A (CyA) 50 mg orally twice daily, and sarilumab 200 mg subcutaneously fortnightly and had been hospitalised recurrently for his unstable renal function. He was an ex-smoker with no history of diabetes or cardiovascular disease and his body mass index was 22.44. Physical examination on admission revealed a body temperature of 38.2 °C, blood pressure of 167/107 mmHg, pulse of 101 beats per minute, respiratory rate of 24 breaths per minute, and blood oxygen saturation of 91% on room air. He presented with systemic cyanosis and crackles in the lower lobes of both lungs on auscultation, and routine chest radiography showed bilateral massive lung infiltration (Fig. 1A). According to the 2019 update of the 2015 disease severity classification for TAFRO syndrome (Masaki et al., 2020), his disease was slightly severe. The rheumatologist suspected COVID-19, and the patient's polymerase chain reaction test result was positive for SARS-CoV-2. Chest and abdominal computed tomography showed massive ground-glass opacities in both lungs, slight right pleural effusion, hepatomegaly, and ascites (Fig. 1B-D). Haematology revealed neutrophil, lymphocyte, and platelet counts of 153×10^9 cells/L (reference range, $14.4\text{--}62.1 \times 10^9$ cells/L), 5.4×10^9 cells/L ($9.4\text{--}41.4 \times 10^9$ /L), and 5.8×10^9 /L ($13.8\text{--}30.9 \times 10^9$ /L), respectively. Blood biochemistry revealed serum triglyceride and creatinine levels of 308 mg/dL (50–149 mg/dL) and 1.07 mg/dL (0.62–1.07 mg/dL), respectively, and an estimated glomerular filtration rate of 51.39 mL/min (≥ 60 mL/min). The soluble IL receptor 2 level was 751 U/mL (122–496 U/mL). The patient's COVID-19-associated hyperinflammation score (cHIS) was 3 (≥ 2 indicates hyperinflammation and poor outcome) (Jordan et al., 2020).

Despite administration of oxygen and remdesivir, his respiratory condition deteriorated, and he developed ARDS. He was transferred to the intensive care unit (ICU) and underwent endotracheal intubation on day 2 of hospitalisation. CyA and sarilumab were continued at the same dose, and the prednisolone dose was increased to 25 mg twice daily intravenously on the rheumatologist's advice. His respiratory condition gradually improved with intensive care that included circulatory and respiratory support. He was extubated on day 5 and transferred to the infectious disease ward; however, on day 6, chest infiltration relapsed, and his respiratory condition worsened again. He received high-flow

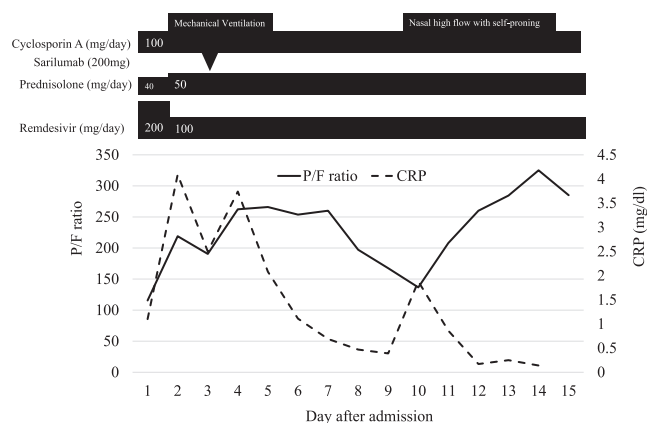


Fig. 2. The patient's clinical course after admission. P/F ratio, partial pressure of arterial oxygen (PaO₂) to fraction of inspiratory oxygen (FiO₂) ratio.

nasal oxygen therapy combined with self-prone positioning while awake and recovered from COVID-19. Subsequently, he was moved to a rehabilitation ward for respiratory rehabilitation and was discharged on day 90. The time courses of partial pressure of arterial oxygen to fraction of inspired oxygen ratio and C-reactive protein level are shown in Fig. 2.

Discussion

To the best of our knowledge, this is the first report of severe COVID-19 in a patient with TAFRO syndrome. The effect of autoimmune diseases on COVID-19 susceptibility and prognosis is unclear. Patients with autoimmune disease are more likely to require ICU admission and develop severe respiratory failure; however, mortality is not increased (Freites Nuñez et al., 2020). Currently, no data are available on COVID-19 severity in patients with TAFRO syndrome receiving immunomodulation. TAFRO syndrome is usually treated with corticosteroids. Other immunomodulatory agents such as CyA, rituximab, cyclophosphamide, and tocilizumab are sometimes prescribed in cases refractory to corticosteroids (Hsu et al., 2021). In patients with autoimmune diseases and COVID-19, adherence to medication regimens to prevent autoimmune disease flares is strongly recommended (Liu et al., 2021). As robust immune reactions contribute to the pathogenesis of both disease conditions, the treatment strategies for autoimmune diseases and COVID-19 are similar. Pharmacotherapy for COVID-19 is divided into an antiviral window and an immunomodulatory window (Masaki et al., 2016). In the latter phase, immunomodulatory drugs such as corticosteroids and biologics, which are also used to treat TAFRO syndrome, are effective in suppressing hyperinflammation (Masaki et al., 2016). Unlike other autoimmune diseases, TAFRO syndrome, a subtype of iMCD whose hallmark is cytokine storm syndrome (CSS), is characterised by hyperinflammation similar to that in COVID-19. In patients with COVID-19,

hyperinflammation is caused by dysregulation of proinflammatory cytokines including IL-6 and Janus kinases (JAK) / signal transducer and activator of transcription (Luo et al., 2020). Most experts recommend continuing glucocorticoids regardless of SARS-CoV-2 infection status in patients with autoimmune disease (Landewé et al., 2020; American College of Rheumatology, 2021). However, some experts recommend stopping immunosuppressants, non-IL-6 biologics, and JAK inhibitors. In our patient, although all immunomodulatory drugs were continued with a slight increase in the glucocorticoid dose, and the patient finally recovered, baricitinib should have been added to prevent ARDS because baricitinib has been shown to be superior to remdesivir alone in improving clinical symptoms, reducing recovery time, and accelerating oxygen-saturation improvement in patients receiving high-flow oxygen (Kalil et al., 2021). Moreover, JAK is the cytokine associated with both COVID-19 and iMCD.

Several studies have reported the potential benefit of steroids and anti-IL-6 agents in patients with COVID-19. In patients hospitalised with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among patients receiving invasive mechanical ventilation or oxygen alone (Horby et al., 2021). In critically ill patients with COVID-19 receiving organ support in ICUs, treatment with the IL-6-receptor antagonists tocilizumab and sarilumab improved outcomes, including survival (Gordon et al., 2021). However, no study has evaluated the effects of immunosuppressive drugs alone. Although most previous studies were retrospective cohort studies or case series, and there is significant heterogeneity among studies, many studies suggest increased disease severity and mortality among solid-organ-transplant recipients with COVID-19 (Fung and Babik, 2021). Our patient with TAFRO syndrome developed severe COVID-19 pneumonia while receiving high-dose corticosteroid and monoclonal antibody against IL-6 receptor. Previous studies have shown that in some viral infections, corticosteroid administration in the early phase of the disease suppresses the production of inflammatory and antiviral cytokines (especially interferon 1) and promotes viral replication (Shimba and Ikuta, 2020; Thomas et al., 2014). Two reports showed that early initiation of corticosteroid therapy (within the first week of illness) increased the length of hospital stay and need for invasive ventilation in SARS and Middle East respiratory syndrome, respectively (Lee et al., 2004; Arabi et al., 2018), which is consistent with the findings in our case. Thus, strong immunomodulatory therapy in the antiviral phase of COVID-19 may promote viral growth and induce ARDS in patients with TAFRO syndrome. As hyperinflammation plays a pivotal role in the clinical course of severe COVID-19 and iMCD, treatment guidelines for managing CSS are needed.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Oshima, Dr. Kanamori, Dr. Baba, and Dr. Tokuda are staff members of an endowed course by the Kyosei Medical Research Institute.]

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Ethical approval

This study complied with the Declaration of Helsinki and was approved by the Institutional Ethical Board of Tohoku University Hospital and the written informed consent was obtained.

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