CASE REPORT

TAFRO syndrome successfully treated with tocilizumab: A case report and systematic review

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Abstract

Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome is considered as a unique clinicopathologic variant of multicentric Castleman’s disease and is recently reported in Japan. This entity represents a severe inflammatory state leading to organ failures such as severe liver dysfunction seen in our case, and can be treated by immunosuppressive agents, steroids, and cyclosporine shown in several case reports. A systematic review and our case suggest the potential utility of tocilizumab as a treatment for TAFRO syndrome.

Introduction

Castleman’s disease (CD), a rare lymphoproliferative disease originally described in 1956, is divided into unicentric or multicentric (MCD). In terms of histopathological features, MCD is categorized into four variants: hyaline-vascular (HV), plasma cell (PC), mixed, and plasmablastic [1,2]. MCD is a systemic lymphadenopathy consisting of a heterogeneous group of disorders with various etiologies. Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome is considered as a unique clinicopathologic variant of MCD recently reported in Japan [3,4]. It is characterized by a constellation of symptoms (and is named accordingly), as TAFRO. The pathogenesis of the disorder remains unclear, but there are previous reports of TAFRO patients who responded to immunosuppressive therapies [5–7], although there were some refractory cases with fatal outcomes. Here, we report a patient with TAFRO syndrome and severe liver damage who was successfully treated with tocilizumab (TCZ).

Case report

A 49-year-old Japanese woman with hypertension presented with a 2-d history of mild fever and abdominal pain. Physical examination revealed a distended abdomen and epigastric tenderness. The computed tomography (CT) scan revealed hepatomegaly and ascites. Laboratory results included severe thrombocytopenia and anasarca. The computed tomography (CT) scan revealed hepatomegaly and ascites. Laboratory results included severe thrombocytopenia (2.0 × 10^10/l), coagulation abnormalities (fibrin degradation products 33.1 μg/ml, and D-dimer 9.8 μg/ml), and elevated C-reactive protein (CRP 21.9 mg/dl) (Table 1). She was immediately admitted, and meropenem was initiated for presumptive peritonitis and related disseminated intravascular coagulation. The ascites revealed a high serum-to-albumin ascites gradient (above 1.1 g/dl), which suggested portal hypertension. On hospital day 3, hypoxia developed, and pulmonary edema was suspected from the ground-glass pattern on CT of the lung fields bilaterally. Because of the high level of the soluble IL-2 receptor (2105 U/ml), bone marrow aspiration, and skin biopsy were performed to test for potential hematological etiologies, such as intravascular lymphoma; however, no abnormalities were found. Normal immunoglobulin and complement and absence of antibody and antineutrophilic cytoplasmic antibody made the diagnosis of a collagenous disease, such as systemic lupus erythematosus or the vasculitis syndromes, less likely. As the degree of abdominal pain increased gradually, opioids were given to control pain. Anuria developed, and respiratory and liver function deteriorated. Continuous hemodiafiltration in the intensive care unit was initiated on day 4. A biopsy of some slightly enlarged, palpable lymph nodes was performed. Some diseases potentially responsive to steroids, such as malignant lymphoma and CD, were suspected, and intravenous methylprednisolone (1000 mg for 3 d) was given before the lymph node biopsy results were obtained. However, the fever and elevated direct bilirubin and transaminases did not improve. There was no evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection because HBV surface antigen, HBV core antibody, and anti-HCV antibody were not detected on admission. Histopathological examination of the lymph nodes revealed paracortical hyperplasia with vascular proliferation and atrophic germinal centers, which are seen in HV-type CD. Bone marrow biopsy histology included the presence of micromegakaryocytes and mild reticulin fibrosis (Figures 1 and 2). Tests for antibody to human immunodeficiency virus (HIV) and human herpes virus 8 (HHV-8) PCR were negative, and the serum IL-6 and vascular endothelial growth factor (VEGF) levels in admission blood samples were significantly elevated (83.4 and 84.5 pg/ml, respectively). The constellation of symptoms and signs (including thrombocytopenia, anasarca, bone marrow reticulin fibrosis, renal...
dysfunction, and organomegaly) and histopathological findings established the TAFRO syndrome diagnosis. On day 8, mechanical ventilation was required for deteriorating respiratory failure, and weekly TCZ (anti-IL-6 receptor antibody) therapy (8 mg/kg) was initiated. Hyperbilirubinemia (direct bilirubin dominant) became progressively worse and severe jaundice developed during the following few days. We speculated that increasing total bile acid was associated with impairment of biliary excretion caused by damage to hepatocytes. Around day 15 (TCZ day 7), the liver damage and inflammatory markers started to improve, with total and direct bilirubin peaks of 12.6 and 10.9 mg/dl, respectively. She was extubated, and on day 28, total bile acid was normal. TCZ was administered consistently every 2 weeks and intravenous methylprednisolone was gradually tapered until discontinuation on day 149. On day 66, it was determined that renal replacement therapy was not needed because her urine volume increased and her abdominal girth decreased gradually after administration of TCZ. During the current admission, transfer to the intensive care unit occurred three times for severe complications including acute hemorrhagic rectal ulcer and coagulase negative staphylococci sepsis, but she was discharged to home, ambulatorily, on day 166. Repeated CT before discharge showed that hepatomegaly and ascites had almost disappeared. Her platelet counts, transaminase (AST/ALT), serum creatinine, and CRP levels at discharge all improved (32.0/210/4/104/ml, 57 IU/l, 46 IU/l, 0.95 mg/dl, and 0.01 mg/dl, respectively. Supplementary data 1). TCZ treatments have continued every 2 weeks on an outpatient basis, and at the time of this writing there have been no clinical sequelae. Initial symptoms and liver dysfunction were completely resolved 10 months after disease onset. The serum IL-6 level increased once to more than 1800 hpg/ml at day 30, but then gradually decreased after initiating TCZ therapy (Figure 3).

Discussion

Recently, MCD can be subdivided into HHV-8 associated MCD and HHV-8 negative MCD because HHV-8 drives the hypercytokinemia in immunodeficiency state and might contribute the onset of MCD [2,8–10]. Suda et al. and Kojima et al. also reported that, unlike in Western, idiopathic MCD in Japan is not associated with HHV-8 [8–10]. Kojima et al. showed that Japanese patients were categorized into two distinct clinicopathologic groups: idiopathic plasmacytic lymphadenopathy (IPL), and non-IPL [9]. IPL-type MCD is histologically characterized by normal germinal

| Table 1. Laboratory data. |
|---------------------------|
| Variable | Reference range | On admission |
| Erythrocyte count (per mm³) | 3,800,000–4,800,000 | 4,3400,000 |
| Hemoglobin (g/dl) | 11.5–14.5 | 12.0 |
| White-cell count (per mm³) | 3000–9000 | 15,000 |
| White-cell differential count (%) | | |
| Neutrophils | 38–77 | 86 |
| Band forms | 0–8 | 0 |
| Lymphocytes | 15–53 | 8 |
| Monocytes | 0–13 | 6 |
| Eosinophils | 0–6 | 0 |
| Basophils | 0–2 | 0 |
| Platelet count (per mm³) | 160,000–360,000 | 20,000 |
| Prothrombin time (s) | 11.6–14.0 | 15.9 |
| Activated partial thromboplastin time (s) | 30.3–45.4 | 50.1 |
| Fibrinogen (mg/dl) | 182–366 | 994 |
| Antithrombin (%) | 79–117 | 63 |
| Fibrin degradation products (µg/ml) | 0–5 | 33.1 |
| D-dimer (µg/ml) | 0–1 | 9.8 |
| Creatinine (mg/dl) | 0.45–0.8 | 2.2 |
| Urea nitrogen (mg/dl) | 7–20 | 44 |
| Total bilirubin (mg/dl) | 0–1.2 | 1.9 |
| Aspartate aminotransferase (U/l) | 10–35 | 94 |
| Alanine aminotransferase (U/l) | 7–42 | 45 |
| Alkaline phosphatase (U/l) | 110–360 | 1073 |
| Lactate dehydrogenase (IU/l) | 120–240 | 350 |
| Sodium (mEq/l) | 136–146 | 137 |
| Potassium (mEq/l) | 3.4–4.9 | 4.0 |
| Chloride (mEq/l) | 96–108 | 102 |
| C-reactive protein (mg/dl) | 0.0–0.2 | 21.9 |
| Albumin (g/dl) | 4–5 | 1.8 |
| IgG (mg/dl) | 870–1700 | 1003 |
| IgA (mg/dl) | 110–410 | 159.6 |
| IgM (mg/dl) | 35–220 | 37.4 |
| C3 (mg/dl) | 63–155 | 91.8 |
| C4 (mg/dl) | 10–40 | 21.7 |
| CH50 (U/ml) | 28–50 | 49.3 |
| Antinuclear antibody | Negative at 1:40 and 1:160 dilution | |
| Antineutrophil cytoplasmic antibody | Negative | Negative |
| IgG4 (mg/dl) | 4.8–105 | 13.0 |
| IL-6 (pg/ml) | 0–4 | 83.4 |
| Vascular endothelial growth factor (pg/ml) | 0–38.3 | 84.5 |
| Soluble IL-2 receptor (U/ml) | 135–500 | 2105 |
| Human herpes virus 8 | Negative | Negative |
| Human immunodeficiency virus | Negative | Negative |

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centers and sheet-like infiltration of PCs in the interfollicular areas of lymph nodes, and is accompanied by polyclonal hyperimmunoglobulinemia. On the other hand, non-IPL-type MCD has mixed-type or, less frequently, HV-type CD histology, and marked thoracoabdominal fluid. It is frequently associated with female predominance and older age. TAFRO syndrome has recently been seen in an increasing number of case reports or series. For example, Takai et al. [3] reported three TAFRO syndrome
patients, and one had HV-type lymph node histology, consistent with non-IPL-type MCD. TAFRO syndrome diagnostic criteria include blood count abnormalities, systemic inflammation, renal dysfunction, myelofibrosis, immunologic disorders, antinuclear antibodies, rare polyclonal hypergammaglobulinemia, and elevation of serum IL-6 and VEGF [11]. The histology is mixed-type, or less frequently HV-type, CD [7]. Careful diagnosis is needed to distinguish TAFRO syndrome from a great variety of other diseases, including HIV infection, IgG4-related disease, PC dyscrasias, autoimmune disorders, and malignant lymphoma. Patients have thrombocytopenia; therefore, idiopathic thrombocytopenic purpura, systemic lupus syndrome, and other hematopoietic malignancies need to be ruled out. Pleural effusions and ascites may lead to secondary respiratory failure with pulmonary edema. A multidisciplinary approach including mechanical ventilator support and dialysis is sometimes required. Although the clinical course in many cases is relatively benign, some patients progress rapidly [5–7].

The etiology of TAFRO syndrome remains mostly unknown and optimal treatment standards have not been determined. There are several reported cases that were successfully treated with methylprednisolone, cyclosporine, and rituximab, leading to remission in accordance with the treatment of idiopathic MCD. These drugs can inhibit systemic inflammatory activation and improve organ damage. However, it is reported that most patients with idiopathic MCD experience relapse during steroid tapering [2]. Rituximab is only partially effective and typically does not provide long-term disease control. Over the last decade, treatment directly targeting IL-6 has been used for idiopathic MCD. TCZ is a humanized monoclonal antibody targeting the IL-6 receptor that is approved for clinical use in Japan. TCZ binds with soluble and membrane-bound interleukin-6 receptors, thereby hindering IL-6 from exerting its proinflammatory effects [12]. Nishimoto et al. have demonstrated its effectiveness for inducing and maintaining remission in idiopathic MCD patients [13].

We subsequently conducted a systematic and extensive search for cases of TAFRO syndrome that was treated with TCZ. We used the search strategy of “TAFRO syndrome” AND “tocilizumab”, and also looked into the articles if details might have been related to our interest. To our knowledge, there are only 11 reported cases of TAFRO syndrome treated with TCZ in PubMed and Ichushi (Japan Medical Abstracts Society) [6,7,14–22] (Table 2, detailed clinical courses are shown in Supplementary data 2). These 11 cases including three cases reported in conference abstracts and our case were hereby summarized. Ages ranged 15–78, with the median of 49.5-years old, and seven out of 12 cases were female. The information of IL-6 level was obtained in 10 cases and averaged at 31.9 pg/ml. Among these cases, eight cases reached complete remission (defined as the improvement of all symptoms) and four cases required additional agents or change of treatment. At least five of them survived more than 1 year with complete remission by administration of TCZ. No adverse effect related to TCZ was reported. We also tried to get beneficial information from the relevant pharmaceutical company, but no additional information was obtained.

These reported cases with the current case suggested that TCZ could be an effective treatment for the idiopathic MCD variant of the TAFRO syndrome. Among these cases, corticosteroid (methylprednisolone and/or prednisolone) therapy was used in combination with TCZ. Besides these drugs, rituximab was applied in five cases [14–16,20,22]. Cholestatic liver damage occurred with disease progression in the current case; to our knowledge, the mechanisms involved remain unknown. Several reports exist of marked sinusoidal dilatation in liver biopsies of CD patients [23]. We speculate that sinusoidal endothelial impairment from the hypercytokinemia induces secondary hepatocyte damage; subsequently, impairment of biliary excretion into bile capillaries could occur. It could be hypothesized that control of the hypercytokinemia is indispensable for stopping this cyclical mechanism of liver damage.
Table 2. Characteristics of reported cases of TAFRO syndrome treated with tocilizumab.

| References       | Age | Sex  | Symptoms on admission                                      | IL-6 (pg/ml) before treatment | VEGF (pg/ml) before treatment | Initial treatment | Response to TCZ therapy and need for change treatment | Outcome         |
|------------------|-----|------|------------------------------------------------------------|-------------------------------|------------------------------|-------------------|-----------------------------------------------------|-----------------|
| Kubokawa et al.  | 15  | Male | Fever                                                      | 29                            | NS                           | GC (pulse) + TCZ  | CR, no                                              | Alive (1 year)  |
| Kawabata et al.  | 47  | Female | Fever, right subcostal pain, general malaise             | 21.9                          | NS                           | GC (pulse) + TCZ  | CR, no                                              | Alive (2.5 years) |
| Iwaki et al.     | 43  | Female | Fever, dyspnea                                            | 45.6                          | 665                          | GC (pulse) + R + TCZ | CR, no                                              | Alive (3 months) |
| Tedesco et al.   | 21  | Female | Fever, left subcostal pain, general malaise                | 19.4                          | NS                           | GC + TCZ          | PR, yes (R + CVP)                                   | Alive (1 month) |
| Konishi et al.   | 77  | Female | Fever, edema                                               | 26.9                          | NS                           | GC + TCZ          | PR, yes (RCyA)                                      | Alive (1.5 years) |
| Tatekawa et al.  | 56  | Male  | Fever, dyspnea, abdominal distension                      | 8.1                           | 244                          | GC + TCZ          | PR, yes (+Thal)                                     | Alive (2 years)  |
| Awano et al.     | 78  | Female | Fever, epigastric pain                                     | 18                            | 69.4                         | GC (pulse) + TCZ  | CR, no                                              | Death with relapse (within 13 months) |
| Ishii et al.     | 50  | Male  | Fever, lymphadenopathy, abdominal distension               | 21                            | 184                          | GC + TCZ          | CR, no                                              | Alive (NS)       |
| Nagai et al.     | 56  | Male  | Fever, epigastric pain                                     | NS                            | NS                           | GC (pulse) + TCZ  | PR, yes (+R)                                        | Alive (2 months) |
| Hamasaki et al.  | 50  | Male  | Fever, epigastric pain                                     | NS                            | NS                           | GC (pulse) + TCZ  | CR, no                                              | Alive (3 months) |
| Kondo et al.     | 40  | Female | Fever                                                      | 45.6                          | NS                           | GC (pulse) + R + TCZ | CR, no                                              | Alive (6 months) |
| Sakai (present study) | 49 | Female | Fever, right subcostal pain, general malaise             | 83.4                          | 84.5                         | GC (pulse) + TCZ  | CR, no                                              | Alive (1.5 years) |

GC, glucocorticosterone; TCZ, tocilizumab; R, rituximab; CVP, cyclophosphamide, vincristine, and predonisolone; Thal, thalidomide; NS, not stated; CR, complete remission (defined the improvement of all symptoms); PR, partial remission (defined the improvement of partial symptoms).
In conclusion, we treated a TAFRO syndrome patient who was refractory to methylprednisolone and subsequently responded to TCZ treatment. Severe liver damage developed, and the patient would not have survived if TCZ administration had been delayed. Although systemic inflammation induces hepatomegaly and hyperbilirubinemia, the pathological mechanisms resulting in the TAFRO syndrome remain unknown. We speculate that a hypercytokinemia leads to hepatocyte and, subsequently, biliary excretion disorders. It is apparent from this patient’s course that the hepatomegaly and bile secretory failure of the TAFRO syndrome can be reversed by TCZ administration. Accumulation of similar cases and further research will help clarify the diagnostic criteria, pathogenesis, and optimal therapeutic regimen for treatment of the TAFRO syndrome.

Informed consent

The written consent to publish this case report was obtained from the patient.

Conflict of interest

None.

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Supplementary material available online