Original Article

A Comparison of the Clinical Characteristics of TAFRO Syndrome and Idiopathic Multicentric Castleman Disease in General Internal Medicine: A 6-Year Retrospective Study

Running Head: Clinical Features of TAFRO Syndrome

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ABSTRACT

Background: Although thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome was first described as a variant of idiopathic multicentric Castleman disease, patients with TAFRO syndrome have more aggressive clinical features. Because these patients may present with fever of unknown origin, general physicians need to recognize its characteristic laboratory data and clinical features during hospitalization.

Aims: Herein, we described the features, symptoms, and characteristics of TAFRO syndrome and compared them to those of idiopathic Castleman disease.

Methods: This was a retrospective study of patients with histopathologically confirmed TAFRO syndrome and idiopathic multicentric Castleman disease who were diagnosed and managed between April 2012 and June 2018 in a Japanese university hospital General Medicine Department.

Results: We found that the hospitalizations were significantly longer among patients with TAFRO syndrome compared to those with idiopathic Castleman disease (median: 87 days; range: 34-236 days vs. median: 30 days; range: 13-59 days; $p < 0.01$). Patients with TAFRO syndrome were more likely to present with fever, abdominal pain, and elevated inflammatory markers and be misdiagnosed with an infectious disease during

the first hospital visit. Approximately 40% of patients with TAFRO syndrome had no radiographically enlarged lymph nodes.

Conclusions: TAFRO syndrome may present like an infectious disease with an aggressive clinical course. Our study highlights the importance of placing significance on chief complaints and laboratory data. Physicians need to recognize the clinical and laboratory features of this disease to avoid missing this potentially fatal disorder.

Keywords

TAFRO syndrome, Castleman disease, chief complaints, procalcitonin, immunoglobulin

INTRODUCTION

Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly, (TAFRO) syndrome is a new clinical entity that was first described in 2010 as a variant of idiopathic multicentric Castleman disease (iMCD)[1]. It is a systemic inflammatory disorder characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), and organomegaly (O) with aggressive clinical features as previously described[1-5]. Castleman disease (CD) is a rare and heterogenous lymphoproliferative disorder that was first described over 60 years ago[6]. It is divided into two subtypes; localized or unicentric Castleman disease, and multicentric Castleman disease (MCD). MCD is characterized by organomegaly, elevated serum pro-inflammatory cytokines such as interleukin 6 (IL-6), and polyclonal hypergammaglobulinaemia[7]. Pathologically, MCD is classified into one of the following four categories; hyaline vascular, plasma cell, mixed, or plasma-blastic type, thus making the disease heterogenous[8]. Previously, MCD was considered to occur mainly in association with human herpes virus 8 (HHV-8) infection in immunocompromised patients[9]. However, it was recently reported that HIV-negative and HHV-8 negative MCD were more prevalent, accounting for approximately 50% of cases of MCD in the United States[7]. iMCD was thus further defined by HIV and HHV-8 negative MCD subtypes. Reports of TAFRO syndrome have been described recently in

Western countries among Caucasian populations[10-13]. Although the clinical characteristics are similar in these two disorders, TAFRO syndrome has been described as a clinical entity distinct from iMCD because TAFRO syndrome is usually associated with hypogammaglobulinemia, which is in stark contrast to iMCD, and poor treatment response[14]. However, the boundaries between TAFRO syndrome and other iMCD have not been well defined. These facts signify the importance of recognizing the clinical characteristics of TAFRO syndrome and iMCD given these disorders may be more prevalent and different than previously thought.

Although the clinicopathological characteristics of TAFRO syndrome have been reported previously[15, 16], no studies have clearly described its clinical presentation according to the chief complaint, symptoms, and hospital-related characteristics. Although TAFRO syndrome has been gaining recognition recently, not all generalists are aware of the clinical characteristics and presentations of the disease. Since patients with TAFRO syndrome present with various complaints and symptoms including prolonged fever[17-20], patients may be referred to or admitted to internal medicine services for further investigation. Thus, it is important for internists to recognize the clinical characteristics of TAFRO syndrome given that the disease may be fatal.

The purpose of this study is to help define the boundaries between TAFRO

syndrome and other iMCD, while revealing the laboratory and clinical features of TAFRO syndrome and compare them to those of iMCD, with a focus on the patients' history of present illness, symptoms, and clinical characteristics during hospitalization.

METHODS

Design and study population

This was a retrospective observational study. We included 15 patients who were admitted and diagnosed with TAFRO syndrome or HIV-negative and HHV-8-negative iMCD from April 2012 to June 2018 in the General Medicine Department of Okayama University Hospital, Okayama, Japan. Okayama University Hospital has 813 beds. In this study, all the patients were of Japanese descent. Of the 15 included patients, 8 were diagnosed with TAFRO syndrome and 7 were diagnosed with iMCD. The patients had lymph node biopsies for diagnosis. All patients were treated in our department in conjunction with a team of haematologists. The data were reviewed retrospectively by the physicians after informed consent was obtained from the patients. The study protocol was approved by the institutional review board of Okayama University Hospital.

Diagnostic criteria

The patients' data were reviewed retrospectively to determine whether they were compatible with the proposed diagnostic criteria for TAFRO syndrome and iMCD[21-23]. Patients with TAFRO syndrome were those who met two sets of proposed diagnostic criteria[21, 23]. The diagnostic criteria of TAFRO syndrome proposed by Iwaki et al. includes (1) histopathological lymph node appearance consistent with TAFRO syndrome, e.g., atrophic germinal centres with enlarged endothelial cell nuclei, (2) at least three of the five primary diagnostic criteria including thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly, in the presence of small volume lymphadenopathy without hypergammaglobulinemia, (3) at least one of the following minor criteria: hyper- or normoplasia of megakaryocytes in the bone marrow, or an elevated alkaline phosphatase level without marked elevation of serum transaminases. Thrombocytopenia was defined as a platelet count < 100,000 at least once prior to the diagnosis. Anasarca was defined as the existence of a pleural effusion or ascites on computed tomography (CT). Fever was defined as a body temperature ≧ 38.0℃ at least once prior to the diagnosis. Reticulin fibrosis was identified on bone marrow biopsy. Organomegaly included hepatomegaly (vertical liver span ≧ 15cm) and splenomegaly (vertical span ≧ 10cm). The differential diagnosis included infection,

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin pigmentation) syndrome, autoimmune diseases such as systemic lupus erythematosus, and malignancy, which were ruled out in all patients. The baseline data prior to any treatment were used in the analysis.

Statistical analysis

We used Wilcoxon and Kruskal-Wallis tests to investigate the differences between the continuous data of the two groups. The Fisher's exact test was used to detect significant differences in the categorical data between the two groups. The threshold for significance was $P < 0.05$. All statistical analyses were conducted using JMP Version 13 (SAS Institute, Cary, NC, USA).

RESULTS

Laboratory characteristics

The demographics and laboratory findings are summarized in Table 1. Representative findings with regard to laboratory data are shown in Figures 1 and 2. The median ages of the patients were 43.5 and 48.0 in the TAFRO and the iMCD groups, respectively, and the difference was not significant. In the TAFRO group, 5 (62.5%)

patients were men. White-blood cell counts, D-dimer, blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels were more elevated in the TAFRO group than the iMCD group, but there were no statistically significant differences. Of note, the neutrophil fraction was significantly elevated in the TAFRO group ($p < 0.01$). The total protein and albumin levels were significantly decreased in the TAFRO group with medians of 47 g/L (range: 38-61 g/L) and 19 g/L (11-23 g/L), respectively ($p < 0.01$), whereas total protein levels were markedly elevated in the iMCD group (median: 96 g/L, range: 72-115 g/L). The patients in the TAFRO group had significantly elevated total bilirubin levels with a maximum value of 151.0 μmol/L (median: 17.6 μmol/L, range: 5.5-151.0 μmol/L) with a significant decrease in cholinesterase level (median: 58 U/L, range: 32-80 U/L) ($p < 0.01$). Inflammatory markers including serum ferritin, C-reactive protein (CRP), and procalcitonin (PCT) levels were markedly elevated in the TAFRO group ($p < 0.01$). The median PCT level was elevated up to 6 times that of the level iMCD group (the median 4.76 ng/mL vs. 0.093 ng/mL respectively). No significant differences were observed in the serum soluble interleukin-2 receptor (sIL-2R), IL-6, and vascular endothelial growth factor (VEGF) levels. Correlations between CRP and PCT or ALP are shown in Figure 2. There was no correlation between CRP and PCT in both groups. Among the patients with

TAFRO syndrome, there was a moderate correlation between CRP and ALP levels, although no statistical significance was observed.

Clinical characteristics

Clinical findings including the chief complaints, symptoms, and other disease-specific characteristics identified during the hospitalizations are described in Table 2.

Difference in the lengths of hospitalization between the groups is shown on the graph in Figure 1. The median duration until the diagnosis was made was 10 days (range: 5-47 days) in the TAFRO group and 13 days (range: 11-62 days) in the iMCD group, and the difference was not significant. However, the length of hospitalization was significantly longer in the TAFRO group (median: 87 days, range: 34-236 days) compared with the iMCD group (median: 30 days, range: 13-59 days) ($p < 0.01$). The patients with TAFRO syndrome more commonly presented with fever, abdominal pain, or cough. Interestingly, none of the patients were correctly diagnosed with TAFRO syndrome or iMCD initially. In the TAFRO group, 6 patients (75%) were initially diagnosed and managed as if they had an infectious disease. Other patients were first diagnosed with autoimmune diseases or heart failure. In contrast, the patients with iMCD were first diagnosed with a variety of disorders including infection, autoimmune disease,

malignancy, IgG4-related disease (IgG4-RD), and small bowel obstruction. The reasons for hospitalization in patients with TAFRO syndrome were mostly fever of unknown origin or abdominal pain, whereas the patients with iMCD had various reasons including pleural effusion and generalized fatigue. Regarding the symptoms, almost all patients in the TAFRO group had fever for the duration of their treatments, whereas only 2 patients (28.6%) in the iMCD group exhibited fever in our study population ($p < 0.05$). The fever type was more likely to be remitting and relapsing in the TAFRO group compared with the iMCD group, although statistical significance was not observed. In contrast, all the patients with iMCD presented with intermittent fevers. In our study population, only a few patients in iMCD group had night sweats or weight loss. None of the patients in the TAFRO group had these symptoms. Interestingly, 3 patients (37.5%) in the TAFRO group did not have lymphadenopathy. Anasarca, defined by the presence of pleural effusion and/or ascites, or lower extremity oedema, was significantly more common in the TAFRO group ($p < 0.01$).

As for the treatment regimens, the first-line treatment for patients with TAFRO syndrome was more likely to be methylprednisolone pulse therapy (6/8; 75%). The iMCD patients tended to receive lower-dose prednisolone therapy defined by doses equal to or less than 0.5mg/kg (5/7, 71.4%). The choices for second-line therapy were mainly

tocilizumab (anti-IL-6 monoclonal antibody), rituximab (anti-CD20 monoclonal antibody), or cyclosporine (calcineurin inhibitor) in the TAFRO group. One patient in the group underwent bortezomib therapy as a second-line therapy. All of the patients with TAFRO syndrome required the second-line treatment. In contrast, 2 patients (28.6%) in the iMCD group had no second-line treatment, suggesting that patients with iMCD responded to corticosteroids better than those with TAFRO syndrome. The third-line treatment regimen included mainly tocilizumab or rituximab in both groups. One patient in each group died during the treatment periods.

Factors affecting the length of hospitalization

The results of the linear regression analysis showing the correlation between the length of hospitalization and cholinesterase level is shown in Figure 2. There was a significant negative correlation between the length of hospitalization and the serum cholinesterase level in patients with TAFRO syndrome. There was also a weak correlation between the length of hospitalization and the serum CRP level in patients with TAFRO syndrome, although no statistical significance was observed.

DISCUSSION

Our study is the first retrospective, exploratory analysis to examine the clinical and laboratory differences between TAFRO syndrome and iMCD among patients in the general internal medicine department. Compared to previous studies[21, 24], we focused on clarifying not only the laboratory values, but also the clinical factors including the patients' first complaints, diagnostic information, and detailed data acquired during the hospitalization. Although the study was conducted in the Japanese population and a caution to geographical variation should be made when interpreting the data, our results showed that there was a significant difference in the laboratory data including WBC differentials, platelet counts, immunoglobulins, and inflammatory markers such as CRP and PCT, between the patients with TAFRO syndrome and those with iMCD. As for clinical factors, patients with TAFRO syndrome had significantly longer lengths of hospitalization, which may be a surrogate marker of disease severity. Symptomatically, fever and anasarca were more common in patients with TAFRO syndrome. Patients with TAFRO syndrome patients tended to receive more aggressive treatment regimens, including methylprednisolone pulse therapy. We also found that lower cholinesterase and IgG4 levels at baseline were significantly correlated with longer lengths of hospitalization in the patients with TAFRO syndrome, which may be useful for comprehensive planning and inpatient management among hospitalists.

Previous studies have presented a different perspective for patients with TAFRO syndrome, questioning whether it is a subtype of iMCD or not. A retrospective study suggested that platelet counts, serum Alb, and immunoglobulin levels were significantly decreased, while CRP and ALP were significantly elevated in patients with TAFRO syndrome compared to those with iMCD[21]. These tendencies were also true in our data. Our results also showed that the proportion of neutrophils was significantly increased in patients with TAFRO syndrome. In our study population, 50% of patients with TAFRO syndrome complained of abdominal pain at the first encounter and their serum PCT was also significantly elevated. These facts raise a concern that TAFRO syndrome can easily lead to clinical presentations that mimic abdominal infectious diseases due to hepatobiliary inflammation. Adequate attention should be paid to rule out a known infectious aetiology as noted by the disease definition.

A previous retrospective study from Thailand reported on the clinical presentations of patients with TAFRO syndrome and iMCD[25]. Their findings showed that all the patients with TAFRO syndrome presented with lymphadenopathy. Contrary to that previous report, only about 60% of the patients with TAFRO syndrome in this study

exhibited lymphadenopathy. Because TAFRO syndrome was first characterized by small volume lymphadenopathy, less than 1.5cm in diameter[23], the patients may not have shown obvious lymph node enlargements on the CT scans. Our findings are supported by a previous study that investigated the CT findings of patients with TAFRO syndrome, which found that approximately 20% of the patients did not have lymphadenopathy[16]. This point is important for internists to recognize, because these patients need to be referred for lymph node biopsy even in the absence of apparent lymphadenopathy. Internists should recognize the unique features of lymphadenopathy and lymph node size in patients with TAFRO syndrome, and the fact that lymph node biopsy is essential for making the diagnosis of TAFRO syndrome.

This study showed that the length of hospitalization was significantly longer in patients with TAFRO syndrome. Although there is the premise that the average length of hospitalization in a Japanese acute care bed is 16.3 days[26], which is considerably long compared with that in other countries, the length of hospitalization for patient with TAFRO syndrome is still long. This may reflect the fact that the patients with TAFRO syndrome had more aggressive clinical courses, as shown by the differences in the treatment regimens. Thus, length of hospitalization may be a surrogate marker of disease

severity. Patients with TAFRO syndrome were more likely to have corticosteroid pulse therapy as the first-line therapy, and about 80% of patients received third-line treatments as well. In addition, there was a weak positive correlation between serum CRP and the length of hospitalization. This suggests that cholinergic activity may modulate the systemic inflammatory response[27], and reduced serum cholinesterase levels could predict mortality after sepsis[28]. Our findings also suggest that IgG4 is produced to attenuate systemic inflammation[29]. Thus, decreased cholinesterase and IgG4 levels may reflect the extent of hyper-inflammatory status and a dysregulation of the immunomodulatory process in patients with TAFRO syndrome. Further pathophysiological investigations are required to elucidate the mechanism of action of these molecules.

Our study has a few limitations that needed to be considered when reviewing the results. First, our study was conducted at a single Japanese university hospital, which reduces the generalizability of the results to patients of other ethnicities. Second, because both TAFRO syndrome and iMCD are rare diseases, only 15 patients were included in our study. Thus, this study may lack the power to detect significant associations.

Conclusion

We performed a retrospective analysis to elaborate the clinical and laboratory characteristics of patients with TAFRO syndrome compared to patients with iMCD. There was a significant difference in the laboratory values including platelet count, ALP, immunoglobulin, and inflammatory markers. Patients with TAFRO syndrome were more likely to initially present with abdominal pain and be misdiagnosed with an infectious disease. Internists should recognize these characteristics of TAFRO syndrome so as not to miss the diagnosis of this lethal disease.

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Contributors

YN is the lead author and was involved in all aspects of the study, including manuscript writing and data collection. YH, NF, EK and FO assisted in manuscript editing and methodology development.

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Competing Interests

The authors have no conflicts of interest to report.

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Figure Legends

Figure 1. Characteristic laboratory data comparison of the patients with TAFRO syndrome and idiopathic multicentric Castleman Disease

Difference between C-reactive protein (CRP), procalcitonin (PCT), neutrophil fraction, cholinesterase (ChE), immunoglobulin G (IgG), immunoglobulin G4 (IgG4), and albumin (Alb) levels and length of hospitalization (LOS) between the patients with TAFRO syndrome and iMCD are shown. The mean values and ±SEM are shown in the data. * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly

Figure 2. Correlation between clinical and laboratory factors

A linear regression analysis is presented to elaborate on the correlations between C-reactive protein (CRP) and procalcitonin (PCT), alkaline phosphatase (ALP), and CRP levels; length of hospitalization (LOS) and cholinesterase (ChE) level; and LOS and CRP. The correlations are compared between the TAFRO and the iMCD groups. Blue and red marked areas indicate trust regions. * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.