RESEARCH ARTICLE

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TAFRO Syndrome Without Pathology Supporting Castleman Disease: To Be Treated as Idiopathic Multicentric Castleman Disease-TAFRO or a Distinct Disease Entity?

Castleman Hastalığını Destekleyen Patolojisi Olmayan TAFRO Sendromu: İdiyopatik Multisentrik Castleman Hastalığı-TAFRO Olarak mı Yoksa Ayrı Bir Hastalık Varlığı Olarak mı Tedavi Edilmeli?

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Abstract

Objective: TAFRO syndrome, entailing thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly, was previously considered a subtype of idiopathic multicentric Castleman disease (iMCD-TAFRO), with the diagnosis requiring pathology supporting Castleman disease. However, lymph node biopsies may be difficult for TAFRO patients (TAFRO without pathological evidence: TAFRO-w/op-iMCD), and sometimes these biopsies do not confirm iMCD (TAFRO-w/o-iMCD). We aimed to compare the clinical features and prognosis of TAFRO subgroups.

Materials and Methods: We retrospectively analyzed the cases of 50 iMCD-TAFRO and 11 TAFRO-w/o-iMCD patients treated from May 2015 to April 2024.

Results: The groups showed no significant differences in clinical presentation or laboratory data. Both groups of patients were treated with iMCD-targeted strategies addressing cytokine storms. With a median follow-up of 21.4 (range: 0.5-107.0) months, there were no significant differences between iMCD-TAFRO and TAFRO-w/o-iMCD patients in 3-month response rate (72.1% vs. 88.9%, p=0.525), 6-month response rate (70.0% vs. 83.3%, p=0.849), or best overall response rate (77.6% vs. 90.0%, p=0.645). The estimated 3-year progression-free survival rate (65.8% vs. 90.0%, log-rank p=0.163) and the estimated 3-year overall survival rate (77.0% vs. 100%, log-rank p=0.145) were also not significantly different. Cox univariate analysis showed that decreased estimated glomerular filtration rate (<60 mL/min/1.73 m^2) was associated with an increased risk of disease progression (hazard ratio: 4.133, 95% confidence interval: 1.561-10.940, p=0.004).

Conclusion: iMCD-TAFRO and TAFRO-w/o-iMCD could be considered overlapping entities and these patients should be treated promptly, targeting cytokine storms with similar strategies for each group of patients.

Öz

Amaç: Trombositopeni, anazarka, ateş, retikülin fibrozu ve organomegaliyi içeren TAFRO sendromu, daha önce idiyopatik multisentrik Castleman hastalığının (iMCD-TAFRO) bir alt tipi olarak kabul ediliyordu ve tanı için Castleman hastalığını destekleyen patoloji gerekiyordu. Ancak, lenf nodu biyopsileri TAFRO hastaları için zor olabilir (patolojik kanıt olmayan TAFRO: TAFRO-w/op-iMCD) ve bazen bu biyopsiler iMCD'yi doğrulamaz (TAFRO-w/o-iMCD). TAFRO alt gruplarının klinik özelliklerini ve prognozunu karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Mayıs 2015 ile Nisan 2024 tarihleri arasında tedavi edilen 50 iMCD-TAFRO ve 11 TAFRO-w/o-iMCD hastasının olguları retrospektif olarak analiz edildi.

Bulgular: Gruplar klinik sunum veya laboratuvar verilerinde anlamlı bir fark göstermedi. Her iki hasta grubu da sitokin fırtınalarını ele alan iMCD hedefli stratejilerle tedavi edildi. 21,4 (aralığı: 0,5-107,0) aylık medyan takip süresiyle iMCD-TAFRO ve TAFRO-w/o-iMCD hastaları arasında 3 aylık yanıt oranında (%72,1'e karşı %88,9, p=0,525), 6 aylık yanıt oranında (%70,0'a karşı %83,3, p=0,849) veya en iyi genel yanıt oranında (%77,6'ya karşı %90,0, p=0,645) anlamlı bir fark görülmedi. Tahmini 3 yıllık ilerleme içermeyen sağkalım oranı (%65,8-%90,0, log-rank p=0,163) ve tahmini 3 yıllık genel sağkalım oranı (%77,0-%100, log-rank p=0,145) da anlamlı şekilde farklı değildi. Tek değişkenli Cox analizi, glomerüler filtrasyon hızının (<60 mL/dk/1,73 m^2) düşük olmasının, hastalık progresyonu riskinde artış ile ilişkili olduğunu göstermiştir (hazard oranı: 4,133, %95 güven aralığı: 1,561-10,940, p=0,004).

Sonuç: iMCD-TAFRO ve TAFRO-w/o-iMCD örtüşen durumlar olarak kabul edilebilir ve bu hastalar hemen tedavi edilmeli, her hasta grubu için benzer stratejilerle sitokin fırtınaları hedeflenmelidir.

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Abstract

Keywords: TAFRO syndrome, Idiopathic multicentric Castleman disease, Lymph node biopsy, Treatment

Öz

Anahtar Sözcükler: TAFRO sendromu, İdiyopatik multisentrik Castleman hastalığı, Lenf nodu biyopsisi, Tedavi

Introduction

TAFRO syndrome, first proposed in 2010, was described as an inflammatory disorder characterized by thrombocytopenia, anasarca (edema, pleural effusion, and ascites), fever, reticulin fibrosis and/or renal insufficiency, and organomegaly (hepatosplenomegaly and lymphadenopathy) [1]. Since its first recognition, cases of TAFRO syndrome have been reported globally [2,3,4,5]. While the prevailing opinion held that TAFRO syndrome was a distinct subtype of idiopathic Castleman disease (iMCD), referred to as iMCD-TAFRO, some authorities argued that TAFRO syndrome and iMCD may not constitute separate entities but may rather exist on a spectrum of related disorders. Takai [6] emphasized that the distinction between TAFRO syndrome and iMCD-TAFRO was not clinically meaningful and may lead to confusion, as TAFRO syndrome exhibited homogeneous clinical, laboratory, and prognostic features irrespective of the presence or absence of Castleman disease (CD)-like histology. Similarly, Masaki et al. [7] highlighted the overlapping characteristics of TAFRO syndrome with and without iMCD. This ongoing debate underscores the complexity of accurately classifying these conditions, which frequently present with severe cytokine storms characterized by elevated circulating cytokine levels, acute systemic inflammatory symptoms, and multiorgan dysfunction, potentially leading to multiorgan failure or even death unless treated adequately and promptly [8]. A deeper understanding of the pathophysiology of cytokine storms would support the development of treatments aimed at cytokine neutralization and other anti-inflammatory agents.

According to the criteria proposed by Iwaki et al. [9] for iMCD-TAFRO and the international diagnostic criteria for iMCD [10], lymph node histology consistent with CD was strictly required for diagnosing iMCD-TAFRO. However, lymph node biopsies pose challenges for TAFRO patients due to the absence of apparent lymphadenopathy and the high risk of bleeding associated with thrombocytopenia. Despite considerable efforts, in these cases biopsies may not provide conclusive pathological findings that align with the iMCD spectrum. Without a definitive pathological diagnosis of CD, treatment may be delayed, leading to poor outcomes. Therefore, it was essential to clarify whether these cases should also be treated as iMCD-TAFRO.

These challenges led to the proposal by Nishimura et al. [11] of a new classification for TAFRO syndrome with three categories: 1) iMCD-TAFRO, as described above, with lymph node histopathology consistent with CD; 2) TAFRO syndrome with no lymph node biopsy performed and no other comorbidities (TAFRO without pathological evidence: TAFRO-w/op-iMCD); and 3) TAFRO syndrome with lymph node histopathology not consistent with iMCD or other comorbidities (TAFRO without iMCD or other co-morbidities: TAFRO-w/o-iMCD). Fujimoto et al. [12] noted that iMCD-TAFRO and TAFRO-w/op-iMCD did not differ significantly in clinical presentation, laboratory findings, or survival prognosis, suggesting that they could be considered as the same entity and should be treated promptly using similar treatment strategies. However, there was a paucity of research on patients with TAFRO-w/o-iMCD. These patients underwent lymph node biopsy under challenging circumstances and the histopathological features were not consistent with CD or other comorbidities, resulting in serious challenges for diagnosis and further treatment.

To address these questions and characterize the features of patients with TAFRO-w/o-iMCD more accurately, following the classification established by Nishimura et al. [11]. We aimed to determine whether the two groups of patients could be considered as reflecting the same disease entity and whether we could treat patients with TAFRO-w/o-iMCD with a treatment strategy similar to that used for iMCD-TAFRO, which targets cytokine storms.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and received prior approval from the Institutional Review Board and the Ethics Committee of Peking Union Medical College Hospital (Beijing, China; approval no: I-23PJ1862, date: 2023-11-07). The requirement for informed consent was waived due to the retrospective nature of the study.

Patient Groups

This retrospective single-center study included patients diagnosed with iMCD-TAFRO and TAFRO-w/o-iMCD at Peking Union Medical College Hospital from May 2015 to April 2024. The diagnostic criteria for TAFRO syndrome require all three major categories and at least two of four minor categories [13]. The major categories are as follows: 1) with anasarca, including pleural effusion, ascites, and general edema; 2) thrombocytopenia (platelet count of ≤100,000/μL) without myelosuppressive treatment; and 3) systemic inflammation, defined as fever of unknown etiology above 37.5 °C and/or serum C-reactive protein concentration ≥2 mg/dL. The minor categories are as follows: 1) CD-like features on lymph node

biopsy; 2) reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow; 3) mild organomegaly, including hepatomegaly, splenomegaly, and lymphadenopathy; and 4) progressive renal insufficiency. Patients with malignancies (including lymphoma, myeloma, mesothelioma, etc.), autoimmune disorders, infectious disorders, POEMS syndrome, IgG4-related disease, hepatic cirrhosis, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome were excluded. Among these differential diagnoses, autoimmune disorders were a particularly challenging issue. To address this, a comprehensive evaluation was conducted including detailed clinical assessments, laboratory testing for disease-specific autoantibodies, and renal biopsies in cases of significant renal injury. This rigorous diagnostic process was carried out with a multidisciplinary approach to ensure accuracy and reliability. According to the classification criteria proposed by Nishimura et al. [11] in 2021, these cases were further categorized into one of three categories: iMCD-TAFRO, TAFRO-w/op-iMCD, or TAFRO-w/o-iMCD. In this study, we included only patients with iMCD-TAFRO and TAFRO-w/o-iMCD.

Assessment and Outcomes

Treatment response assessment in this study included symptomatic and biochemical responses according to the consensus guidelines of the Castleman Disease Collaborative Network [8], and overall response was defined based on the symptomatic and biochemical responses. Overall complete response (CR) was defined as the combined complete biochemical (high-sensitivity C-reactive protein, hemoglobin, albumin, and estimated glomerular filtration rate [eGFR]) and symptomatic (fever, fatigue, anorexia, and weight loss) responses. The eGFR was calculated using the standard equation proposed by the Chronic Kidney Disease Epidemiology Collaboration. Overall partial response (PR) was defined as improvement in all four symptomatic inflammation-related responses and >50% improvement in all biochemical parameters. Overall progressive disease (PD) was defined as >25% deterioration in laboratory test results and aggravation of any of the four inflammation-related symptoms. Overall stable disease was defined as the absence of PR, CR, or PD. "Response" was determined in patients who achieved at least PR during the follow-up period.

Follow-up information was obtained from medical record systems and via telephone contact until 30 April 2024. Our primary outcomes were the response rate at 3 months, the response rate at 6 months, and the best overall response rate observed during the treatment period. Secondary outcomes were the 3-year estimated progression-free survival (PFS), 3-year estimated overall survival (OS) rates, and 3-month mortality rate. PFS was defined as the time from diagnosis until the first disease progression or death resulting from any cause. OS was defined as the time from treatment initiation to the last follow-up or death.

Statistical Analysis

The characteristics of iMCD-TAFRO and TAFRO-w/o-iMCD cases were compared using Mann-Whitney U tests or Student's t-tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. The time-to-event OS and PFS endpoints were described using Kaplan-Meier plots and survival functions were compared using the log-rank test. Univariate Cox regression was performed to analyze factors potentially influencing disease progression. Statistical significance was defined as a two-tailed value of $p<0.05$ for all analyses. Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.2.0 (GraphPad Software Inc., La Jolla, CA, USA).

Results

Patients' Demographic, Clinical, and Laboratory Features

A total of 68 patients were diagnosed with TAFRO syndrome within the studied time period and 7 patients diagnosed with TAFRO-w/op-iMCD were excluded from the analysis, as the aim of the study was to compare iMCD-TAFRO with TAFRO-w/o-iMCD. Thus, 61 patients were included in this study, comprising 50 patients with iMCD-TAFRO and 11 patients with TAFRO-w/o-iMCD. Histopathologically, among the 50 cases of iMCD-TAFRO, 42% were classified as the mixed subtype, 36% as the hyaline vascular subtype, and 22% as the plasmacytic subtype. The 11 patients with TAFRO-w/o-iMCD displayed reactive lymph node hyperplasia without specific pathological changes sufficient for the diagnosis of CD or other comorbidities.

Clinical profiles and laboratory data at diagnosis are presented in Table 1. The median age at diagnosis was 46.5 (range: 20-69) years for the iMCD-TAFRO patients and 45 (range: 22-71) years for the TAFRO-w/o-iMCD patients. The sex distribution was comparable between the groups, with 34 (68.0%) iMCD-TAFRO patients and 8 (72.7%) TAFRO-w/o-iMCD patients being male. Clinical manifestations were largely consistent between the groups. All patients experienced fatigue, anasarca, and organomegaly. Hemodialysis was required for 11 (22.0%) iMCD-TAFRO patients and 1 (9.1%) TAFRO-w/o-iMCD patient, with no statistically significant difference between the groups. None of the patients met the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH) [14].

Compared to iMCD-TAFRO, the patients with TAFRO-w/o-iMCD had similar laboratory findings, including anemia (median hemoglobin: 90.5 g/L vs. 85.5 g/L, p=0.840), thrombocytopenia (median platelet count: $67.5x10^9$/L vs. $54.5x10^9$/L, p=0.130), hypoalbuminemia (median albumin: 27.00 g/L vs. 28.50 g/L, p=0.610), and elevated serum creatinine (median: 136.5 µmol/L vs. 147.0 µmol/L, p=0.299).

Table 1. Clinical and laboratory findings of patients with iMCD-TAFRO and TAFRO-w/o-iMCD.

	iMCD-TAFRO (n=50)	TAFRO-w/o-iMCD (n=11)	p
Age at diagnosis, years, median (range)	46.5 (20-69) (n=50)	45 (22-71) (n=11)	0.937
Sex, male, n (%)	34 (68.0) (n=50)	8 (72.7) (n=11)	1.000
Histopathology, n (%)			
Hyaline vascular	18 (36.0) (n=50)		
Plasmacyte	11 (22.0) (n=50)		
Mixed	21 (42.0) (n=50)		
Clinical manifestations, n (%)			
Fatigue	50 (100) (n=50)	11 (100) (n=11)	1.000
Anasarca	50 (100) (n=50)	11 (100) (n=11)	1.000
Fever (>38 °C)	42 (84.0) (n=50)	9 (81.8) (n=11)	1.000
Organomegaly	50 (100) (n=50)	11 (100) (n=11)	1.000
Renal insufficiency with hemodialysis	11 (22.0) (n=50)	1 (9.1) (n=11)	0.578
Laboratory data, median (IQR)			
Hemoglobin, g/L	85.50 (75.50-97.50) (n=50)	90.50 (76.25-108.75) (n=11)	0.840
Platelets, x10^9/L	54.50 (26.80-75.50) (n=50)	67.50 (50.75-82.25) (n=11)	0.130
Albumin, g/L	28.50 (26.00-32.00) (n=50)	27.00 (24.00-31.00) (n=11)	0.610
Serum creatinine, µmol/L	147.00 (94.00-235.00) (n=50)	136.50 (115.50-201.25) (n=11)	0.299
eGFR of <60 mL/min/1.73 m^2, n (%)	35 (70.0) (n=50)	7 (63.6) (n=11)	0.958
ALP, U/L	156.00 (111.00-235.00) (n=48)	171.00 (125.00-200.00 (n=11)	0.170
IgG, g/L	12.93 (10.26-16.55) (n=48)	10.84 (10.72-14.74) (n=10)	0.393
ESR, mm/h	48.50 (21.50-84.30) (n=50)	43.00 (34.00-64.00) (n=10)	0.631
hsCRP, mg/L	67.59 (20.96-102.70) (n=50)	85.22 (37.14-113.55) (n=11)	0.959
IL-6, pg/mL	12.70 (7.55-24.00) (n=50)	25.70 (16.30-36.50) (n=10)	0.120
VEGF, pg/mL	1895.00 (544.00-3271.00) (n=40)	1654.00 (1286.50-3284.50) (n=7)	0.590
Bone marrow biopsy findings, n (%)			
Increased megakaryocytes	20 (42.6) (n=47)	6 (60) (n=10)	0.512
Myelofibrosis	17 (36.2) (n=47)	4 (40) (n=10)	1.000

iMCD: Idiopathic multicentric Castleman disease; TAFRO-w/o-iMCD: TAFRO syndrome with lymph node histopathology not consistent with iMCD or other comorbidities; eGFR: estimated glomerular filtration rate; ALP: alkaline phosphatase; Ig: immunoglobulin; ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; VEGF: vascular endothelial growth factor; IQR: interquartile range.

Reference ranges: Hemoglobin, male 120-160 g/L, female 110-150 g/L; platelets, 100-350x10^9/L; albumin, 35-52 g/L; serum creatinine, male 59-104 µmol/L, female 45-84 µmol/L; ALP: 50-135 U/L; IgG: 7-17 g/L; ESR: 0-20 mm/h; hsCRP: 0-3 mg/L; IL-6: 0-5.9 pg/mL; VEGF: <600 ng/L.

Markers of inflammation were pronounced in both groups, with similar levels of high-sensitivity C-reactive protein (median: 85.22 mg/L vs. 67.59 mg/L, p=0.959), erythrocyte sedimentation rate (median: 43.0 mm/h vs. 48.5 mm/h, p=0.631), interleukin (IL)-6 (median: 25.70 pg/mL vs. 12.70 pg/mL, p=0.120), and vascular endothelial growth factor (VEGF) (median: 1654 pg/mL vs. 1895 pg/mL, p=0.590). Both groups also had elevated serum alkaline phosphatase levels (median: 171.0 U/L vs. 156.0 U/L, p=0.170) and the absence of polyclonal hypergammaglobulinemia (median: 10.84 g/L vs. 12.93 g/L, p=0.393). Bone marrow biopsy findings were similar between the groups, with no significant differences in the rates of increased megakaryocytes (42.6% vs. 60.0%, p=0.512) or myelofibrosis (36.2% vs. 40.0%, p=1.000), highlighting the overlapping of pathological features. In terms of renal involvement, 2 TAFRO-w/o-iMCD patients underwent renal biopsy revealing endothelial cell disease, consistent with common renal biopsy findings in iMCD-TAFRO patients [15].

Treatment and Outcomes

The treatment decisions for these patients were made collaboratively by a team of experienced clinicians, considering factors such as disease severity, comorbidities, and the patients' general conditions. For both the iMCD-TAFRO and TAFRO-w/o-iMCD patients, a similar iMCD-targeted strategy addressing cytokine storms was utilized (Table 2). First-line treatments included siltuximab with the bortezomib, cyclophosphamide, and dexamethasone regimen, bortezomib-based treatment, tocilizumab-based therapy, R-CHOP, sirolimus-based therapy, and high-dose steroids. Among the 50 patients with iMCD-TAFRO and the 11 patients with TAFRO-w/o-iMCD, one patient in each group achieved spontaneous remission without treatment.

The remaining 59 patients received therapy targeting cytokine storms. There was no significant difference in the composition of the first-line treatment between the two groups (p=1.000).

There was no significant difference in follow-up duration between the iMCD-TAFRO (median follow-up: 22.0 [range: 1.0-107.0] months) and TAFRO-w/o-iMCD (median follow-up: 20.0 [range: 0.5-105.0] months) groups (p=0.564). For the entire patient cohort, during the median follow-up period of 21.4 (range: 0.5-107.0) months, 16 iMCD-TAFRO patients experienced disease progression and 9 died. In the TAFRO-w/o-iMCD group, 1 patient experienced disease progression and no deaths occurred. Notably, 3 of the 9 patients who died in the iMCD-TAFRO group initially had inconclusive lymph node biopsies, experiencing a delay of 2 to 4 months in starting treatment until CD was confirmed. The 3-month mortality rate was 12% for the iMCD-TAFRO patients compared to 0% for the TAFRO-w/o-iMCD group (p=0.515). At 6 months, the mortality rate for the iMCD-TAFRO patients increased to 14%, while no deaths were observed in the TAFRO-w/o-iMCD group (p=0.426).

For 3-month and 6-month treatment efficacy, there were no significant differences in symptomatic, biochemical, and overall responses between the two groups. The best overall response rate was 77.6% for iMCD-TAFRO and 90.0% for TAFRO-w/o-iMCD (p=0.645), also showing no statistical difference. Long-term outcomes, as reflected by the 3-year estimated PFS and OS rates, showed a trend favoring TAFRO-w/o-iMCD patients, though the differences were not statistically significant (Figure 1). Upon comparing iMCD-TAFRO patients to TAFRO-w/o-iMCD patients, the 3-month mortality rates (12.0% vs. 0%, p=0.515), estimated 3-year PFS rates (65.8% vs. 90.0%, log-rank p=0.163), and estimated 3-year OS rates (77.0% vs. 100%, log-rank p=0.145) were also not significantly different.

Prognostic Findings

As there were no differences in clinical manifestations and outcomes between the groups, prognostic analysis was carried out after consolidating the two patient cohorts into one larger group. Univariate Cox regression analysis revealed that sex, age, and pathological consistency with CD (iMCD-TAFRO vs. TAFRO-w/o-iMCD) were not significantly associated with disease progression (Table 3). However, eGFR was significantly associated with disease progression. Decreased eGFR level (<60 mL/min/1.73 m^2) was associated with an increased risk of disease progression (hazard ratio: 4.133, 95% confidence interval: 1.561-10.940, p=0.004) among all patients.

Discussion

The classification of TAFRO syndrome as a severe variant of iMCD remains a subject of debate, posing significant diagnostic and therapeutic challenges [16]. Traditionally, a definitive diagnosis of iMCD-TAFRO required a lymph node biopsy consistent with CD, but obtaining lymph node biopsies for these patients was difficult. Even when biopsies are obtained with great effort, they may not yield conclusive pathological findings supporting CD. As a result, many patients have experienced delays in treatment initiation due to inconclusive biopsy results or the inability to obtain a biopsy sample at all. This delay was particularly detrimental given the rapid disease progression and high mortality associated with TAFRO syndrome [12], a disease accompanied by cytokine storms [6]. These diagnostic and therapeutic challenges highlight the broader uncertainties about the classification of TAFRO syndrome within the iMCD spectrum. Whether TAFRO syndrome represents a distinct clinical entity or a subtype of iMCD remains contentious. Some researchers advocated for its distinction from iMCD due to its unique clinical features and aggressive course, while others emphasize the overlapping characteristics between iMCD-TAFRO and TAFRO without CD-like histopathology [6,7]. A previous study demonstrated that TAFRO-w/op-iMCD patients showed no significant differences in

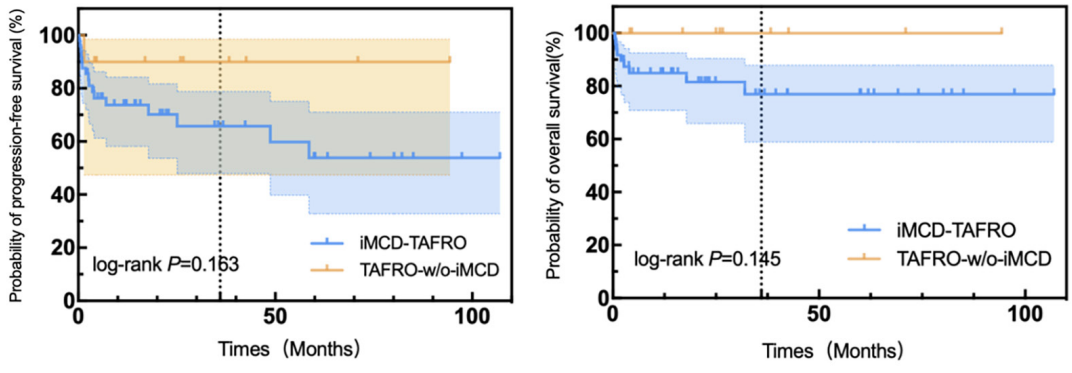

Figure 1. Kaplan-Meier plots of progression-free survival and overall survival in patients with iMCD-TAFRO (n=49) and TAFRO-w/o-iMCD (n=10).

iMCD: Idiopathic multicentric Castleman disease; TAFRO-w/o-iMCD: TAFRO syndrome with lymph node histopathology inconsistent with iMCD or other comorbidities.

Table 2. First-line treatment options and outcomes in patients with iMCD-TAFRO and TAFRO-w/o-iMCD.

	iMCD-TAFRO (n=49)	TAFRO-w/o-iMCD (n=10)	p
First-line treatment			1.000
Siltuximab + BCD	15/49 (30.6%)	3/10 (30%)	
Bortezomib based	16/49 (32.7%)	1/10 (10%)	
Thalidomide based	12/49 (24.5%)	2/10 (20%)	
R-CHOP	1/49 (2.0%)	0/10 (0)	
Sirolimus based	1/49 (2.0%)	1/10 (10%)	
Steroids	4/49 (8.2%)	3/10 (30%)	
3-month symptomatic response			0.717
Remission	33/43 (76.7%)	8/9 (88.9%)	
Failure	10/43 (23.3%)	1/9 (11.1%)	
3-month biochemical response			0.593
Remission	31/42 (73.81%)	8/9 (88.9%)	
Failure	11/42 (26.19%)	1/9 (11.1%)	
3-month overall response			0.525
Remission	31/43 (72.1%)	8/9 (88.9%)	
Failure	12/43 (27.9%)	1/9 (11.1%)	
6-month symptomatic response			0.948
Remission	29/40 (72.5%)	5/6 (83.3%)	
Failure	11/40 (27.5%)	1/6 (16.7%)	
6-month biochemical response			0.921
Remission	28/39 (71.8%)	5/6 (83.3%)	
Failure	11/39 (28.2%)	1/6 (16.7%)	
6-month overall response			0.849
Remission	28/40 (70.0%)	5/6 (83.3%)	
Failure	12/40 (30.0%)	1/6 (16.7%)	
Best symptomatic response			0.322
Remission	40/49 (81.6%)	10/10 (100%)	
Failure	9/49 (18.4%)	0/10 (0%)	
Best biochemical response			0.645
Remission	38/49 (77.6%)	9/10 (90%)	
Failure	11/49 (22.4%)	1/10 (10%)	
Best overall response			0.645
Remission	38/49 (77.6%)	9/10 (90%)	
Failure	11/49 (22.4%)	1/10 (10%)	
3-month mortality	6/50 (12%)	0/10 (0%)	0.515
6-month mortality	7/50 (14%)	0/10 (0%)	0.426
3-year estimated PFS rate	65.8%	90.0%	0.163
3-year estimated OS rate	77.0%	100.0%	0.145

"Remission" was defined as patients who achieved at least partial response.

iMCD: Idiopathic multicentric Castleman disease; TAFRO-w/o-iMCD, TAFRO syndrome with lymph node histopathology not consistent with iMCD or other comorbidities; BCD: bortezomib-cyclophosphamide-dexamethasone; R-CHOP: rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone; PFS: progression-free survival; OS: overall survival.

clinical presentation, laboratory findings, and treatment efficacy compared to iMCD-TAFRO patients and that TAFRO-w/op-iMCD could thus be regarded as the same entity, requiring prompt diagnosis [12]. However, whether TAFRO-w/o-iMCD could be treated similarly to iMCD-TAFRO remains unclear.

With the largest single-center cohort of TAFRO syndrome patients to date, we systematically analyzed the clinical, laboratory, and prognostic features of 50 iMCD-TAFRO patients and 11 TAFRO-w/o-iMCD patients. These groups experienced a similar spectrum of life-threatening cytokine-storm-related symptoms including fatigue, fever, fluid accumulation, and organomegaly, consistent with findings from previous studies [9]. Laboratory data from both groups revealed thrombocytopenia, renal dysfunction, and a hyperinflammatory status, including prominent elevations in IL-6 and VEGF. These symptoms and laboratory abnormalities may be directly due to cytokine-induced tissue damage or acute-phase

Table 3. Univariate Cox regression analysis of progression-free survival of 49 iMCD-TAFRO and 10 TAFRO-w/o-iMCD patients.

Risk factors	Univariate analysis	
	HR (95% CIs)	p
Sex, male (n)	0.862 (0.303-2.453)	0.781
Age at CD diagnosis (years)	1.013 (0.978-1.049)	0.474
Hemoglobin (g/L)	1.001 (0.979-1.023)	0.961
Platelet ($\times 10^9$/L)	0.985 (0.968-1.002)	0.089
Albumin (g/L)	1.037 (0.941-1.143)	0.465
eGFR <60 mL/min/1.73 m^2	4.133 (1.561-10.940)	0.004
ALP (U/L)	1.001 (0.997-1.004)	0.707
IgG (g/L)	1.026 (0.947-1.112)	0.523
hsCRP (mg/L)	1.000 (0.993-1.006)	0.887
IL-6 (pg/mL)	1.013 (0.997-1.029)	0.112

iMCD: Idiopathic multicentric Castleman disease; TAFRO-w/o-iMCD, TAFRO syndrome with lymph node histopathology not consistent with iMCD or other comorbidities; OR: odds ratios; HR: hazard ratios; eGFR: estimated glomerular filtration rate; ALP: alkaline phosphatase; IgG: immunoglobin G; hsCRP: hypersensitive C-reactive protein; IL: interleukin.

physiological changes or may result from immune-cell mediated responses [8]. Although previous studies of pediatric iMCD cases have reported co-occurrence with HLH [14,17], our study included only adult patients and no cases of HLH were observed in this cohort.

The two groups in our study received similar therapy options targeting elevated serum cytokines and cellular signaling pathways, such as siltuximab neutralizing IL-6 directly, thalidomide suppressing angiogenesis and inhibiting the production of IL-6 and VEGF, bortezomib blocking the NF-κB-dependent production of cytokines, and sirolimus inhibiting the mTOR pathway, all of which have been reported to have successfully treated iMCD cases [18,19,20,21]. Undergoing similar treatment regimens, the two patient groups in our study showed no significant differences in symptomatic, biochemical, and overall response rates at various time points, including 3 months, 6 months, and the time for the best overall response rate during the treatment period. In the evaluation of long-term prognosis, Kaplan-Meier analyses showed no statistically significant differences in the estimated 3-year PFS and OS rates. Despite differences in lymph node pathological features, our findings suggest that iMCD-TAFRO and TAFRO-w/o-iMCD share overlapping clinical, laboratory, and prognostic characteristics. These similarities may indicate that the two conditions constitute related clinical entities, supporting the potential utility of the classification criteria proposed by Nishimura et al. [11] for TAFRO syndrome. However, further studies with larger multicenter cohorts are necessary to validate these findings and clarify the precise relationship between these entities.

Treatment delays due to inconclusive biopsy results were notable in our cohort. Among the 9 patients who died in the iMCD-TAFRO group, 3 initially had inconclusive lymph node biopsies and could have been diagnosed with TAFRO-w/o-iMCD. Their treatments were not initiated until the biopsies confirmed CD. To improve the poor prognosis caused by treatment delays due to the necessity of lymph node biopsy for confirming CD, and based on the results of this study, we suggest that for TAFRO patients who are unable to undergo a lymph node biopsy, this procedure should not be mandatory or impede the initiation of treatment targeting life-threatening cytokine storms. For patients who are eligible for biopsy, it is also crucial to initiate treatment promptly in the event of clinical deterioration.

The urgency of timely treatment is particularly evident given the central role of cytokine storms in the pathophysiology of TAFRO syndrome [8]. Fajgenbaum and June [8] proposed three criteria for identifying cytokine storms, one of which included secondary organ dysfunction, often manifesting as renal, hepatic, or pulmonary damage. Our findings revealed that decreased eGFR was a significant risk factor for disease progression. Due to the limited sample size and the small number of progression events, we opted to use univariate logistic regression instead of Cox proportional hazards regression for the prognostic analysis. Renal dysfunction reflects the systemic impact of elevated circulating cytokines, such as IL-6 and VEGF, which are known to induce microvascular injury, immune cell infiltration, and tubular damage [22,23]. The decline in renal function may not only signify direct organ damage but may also contribute to acute systemic inflammatory effects. Therefore, close monitoring of renal function and early intervention, particularly in cases of accelerated renal dysfunction, are essential.

Study Limitations

There are several limitations of this study. First, due to the rare nature of the disease, the inherently limited number of available cases may have impacted the statistical power. The results from this single-center study would benefit from external validation based on larger multicenter cohorts. Furthermore, the follow-up duration may not have been sufficient to capture long-term outcomes. Extended follow-up periods would provide a better understanding of the disease's prognosis.

Conclusion

In conclusion, iMCD-TAFRO and TAFRO-w/o-iMCD could be considered as overlapping disease entities and these patients should be treated promptly, targeting cytokine storms using similar treatment strategies.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and received prior approval from the Institutional Review Board and the Ethics

Committee of Peking Union Medical College Hospital (Beijing, China; approval no: I-23PJ1862, date: 2023-11-07).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: L.Z., J.L.; Concept: L.Z., J.L.; Design: L.Z., J.L.; Data Collection or Processing: S.Y-L., Y.D., J.L., Z.L.; Analysis or Interpretation: S.Y-L.; Y.H-G.; Literature Search: S.Y-L., Y.H-G., Y.D.; Writing: S.Y-L., Y.H-G., L.Z., J.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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