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RESEARCH ARTICLE

Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease?

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Abstract

Castleman disease (CD) is a rare lymphoproliferative disorder that can be unicentric or multicentric. Multicentric CD (MCD) is further subdivided into human herpesvirus type-8-associated, POEMS syndrome-associated, and idiopathic (iMCD). TAFRO syndrome is a newly identified disorder of unknown etiology characterized by **t**hrombocytopenia, **a**nasarca, **f**ever, **r**eticulin myelofibrosis, renal dysfunction, and **o**rganomegaly. The TAFRO syndrome is sometimes regarded as a subtype of iMCD (TAFRO-iMCD), whereas iMCD without TAFRO syndrome is considered "not otherwise specified" (iMCD-NOS). However, a proportion of patients with TAFRO syndrome have been diagnosed without lymph node biopsies (TAFRO syndrome without proven iMCD; TAFRO-w/op-iMCD). To clarify the clinical features of iMCD-NOS, TAFRO-iMCD, and TAFRO-w/op-iMCD, we retrospectively analyzed 220 patients extracted from the database of the Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO Syndrome. The patients included 87 with iMCD-NOS, 63 with TAFRO-iMCD, and 19 with TAFRO-w/op-iMCD. Patients in all three groups exhibited anemia, hypoalbuminemia, and elevated serum C-reactive protein and interleukin-6 levels. No significant differences in clinical, laboratory, and prognostic features were noted between the TAFRO-iMCD, and TAFRO-w/op-iMCD groups. However, the iMCD-NOS group exhibited polyclonal hyper-γ-globulinemia. The five-year survival rates of patients in the iMCD-NOS and TAFRO-involved groups were 100% and 66.5%, respectively (dropping markedly during the first few months in the latter). The iMCD-NOS and the TAFRO-iMCD samples typically showed plasma cell and mixed-type histologies, respectively. Thus, iMCD can be classified into two distinct subtypes, iMCD-NOS and TAFRO-iMCD. As such, TAFRO-iMCD and TAFRO-w/op-iMCD may be considered the same entity, requiring prompt diagnosis and intensive care.

1 | INTRODUCTION

Castleman disease (CD) is a rare lymphoproliferative disorder that was originally described by Benjamin Castleman in the 1950s as "giant follicular lymph node hyperplasia".[1,2] The originally described features were asymptomatic lymph node hyperplasia with hyaline-vascular type histologies localized in the mediastinum.[2] Subsequently, however, patients with enlarged lymph nodes who exhibited plasma cell-type histology accompanied by systemic inflammatory symptoms were reported.[3] In 1980, Mori et al reported 10 Japanese patients manifesting with generalized lymphadenopathy, plasma cell type histology, and features that indicated inflammation. They named this condition "idiopathic plasmacytic lymphadenopathy with polyclonal hyper-immunoglobulinemia (IPL)".[4] Moreover, Mori et al posited that IPL may be a subtype of CD. After their report was published, a number of CD patients with generalized lymphadenopathy were described,[5-16] based on which Frizzera et al classified CD into two categories, according to the distribution of regions of enlarged lymph nodes; the localized form (unicentric CD [UCD]), and CD with multiple lesions (multicentric CD [MCD]).[17,18] Subsequently, a number of patients with MCD coexisting with Kaposi's sarcoma or AIDS were reported.[19,20] In 1995, Soulier et al reported that Kaposi's sarcoma-associated herpesvirus (human herpesvirus type 8, HHV-8) was detected in the lymph nodes of all their HIV-positive MCD patients, as well as in a proportion of HIV-negative counterparts.[21] Since HHV-8 produces viral interleukin-6 (vIL-6), and IL-6 has been identified as the key inducer of the various symptoms of most cases of CD,[22] HHV-8 infection was ascribed as the etiology of MCD in HHV-8-positive patients.[23] Though no research had been done into the relative frequencies of HHV-8-positive MCD vs HHV-8-negative MCD, HHV-8-associated MCD has been recognized as a representative type of MCD in Western countries.

Another distinct MCD category is the POEMS (so-called Takatsuki's or Crow-Fukase's) syndrome-associated MCD.[24] The POEMS syndrome is a rare paraneoplastic condition manifesting as **p**olyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal plasma cell proliferation, and **s**kin changes[25]; moreover, a proportion of patients with POEMS syndrome develop lymphadenopathy with CD histology.[26] Thus, the current categorization of CD includes UCD and MCD, with the latter subdivided into HHV-8-associated MCD, POEMS syndrome-associated MCD, and idiopathic MCD (iMCD), which is negative for both HHV-8 and POEMS syndrome (Figure 1).

The TAFRO syndrome is a newly proposed inflammatory disorder of unknown etiology characterized by **t**hrombocytopenia, **a**nasarca, **f**ever, **r**eticulin myelofibrosis, renal dysfunction, and **o**rganomegaly.[27] This syndrome was originally reported in three Japanese patients with such symptoms by Takai et al in 2010.[28] Two of their patients had lymphadenopathy, one of whom had an enlarged lymph node showing CD-like histology. Prior to this report's publication, patients with iMCD demonstrating all the features of TAFRO had been observed for years without receiving much attention.[29] However, after it was published, a number of similar patients with TAFRO syndrome, together with CD-like lymph node histologies were reported. Some were successfully treated with corticosteroids and tocilizumab; the latter is an anti-IL-6 receptor antibody that is approved for iMCD treatment in Japan.[30-36] Therefore, some researchers consider TAFRO syndrome a subtype of iMCD (Figure S1).[37,38] Based on this viewpoint, Iwaki et al proposed diagnostic criteria for this syndrome, in which lymph node histology consistent with CD is strictly required (Table S1).[38] Applying their diagnostic criteria, they divided iMCD into two categories; iMCD, not otherwise specified (iMCD-NOS) and TAFRO syndrome with iMCD (TAFRO-iMCD), and showed that the clinical manifestations of these two entities were notably distinct.[38]

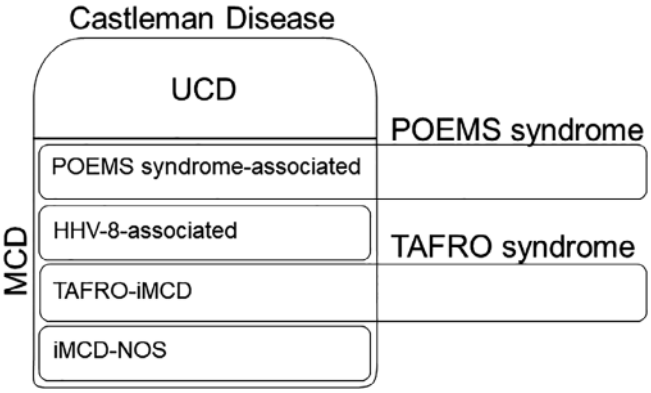

FIGURE 1 Conceptual view of the classification of Castleman disease and related diseases based on our diagnostic criteria for TAFRO syndrome. HHV-8, human herpesvirus type 8; iMCD, idiopathic MCD; MCD, multicentric Castleman disease; NOS, not otherwise specified; TAFRO-iMCD, TAFRO syndrome with iMCD; UCD, unicentric Castleman disease

However, at least three caveats should be considered when applying these criteria. First, a proportion of patients with TAFRO syndrome, including one of the original patients described by Takai et al[28] do not show apparent lymphadenopathy, and would therefore be missed. Second, even if swollen lymph nodes are detected, anasarca and severe hemorrhagic tendencies due to thrombocytopenia and the accompanying disseminated intravascular coagulation often make biopsy difficult to perform. Third, pathological results take time to retrieve, even though they are necessary for the clinical diagnosis of TAFRO syndrome. In contrast to iMCD-NOS, which usually has a chronic clinical course, TAFRO syndrome develops sub-acutely, progresses rapidly, and can often prove fatal. Therefore, prompt diagnosis and intensive treatment with the appropriate intervention are critical for saving these patients.

To achieve a prompt diagnosis, while not excluding patients who have no apparent lymphadenopathy, we proposed another set of diagnostic criteria for TAFRO syndrome. In our criteria, lymphnode biopsy is not required, even though it remains desirable to exclude other diseases (Table S1).[39] Based on our diagnostic criteria,[39] a proportion of patients were diagnosed with TAFRO syndrome without undergoing lymph node biopsy (TAFRO syndrome without proven iMCD [TAFRO-w/op-iMCD]). As a result, iMCD could be sub-divided into iMCD-NOS and TAFRO-iMCD, and TAFRO syndrome could be sub-divided into TAFRO-iMCD and TAFRO-w/op-iMCD. However,

additional research is needed to determine whether TAFRO-iMCD and TAFRO-w/op-iMCD should be considered the same disease entity. To clarify the clinical features of iMCD-NOS, TAFRO-iMCD, and TAFRO-w/op-iMCD, and to verify the validity of our diagnostic criteria, we conducted a retrospective analysis. It used the database of the Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO Syndrome (UMIN000011809), to compare the clinical features of these three categories.

2 | METHODS

2.1 | Patient database

The Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO Syndrome registry (UMIN000011809) includes patients with suspected MCD and TAFRO syndrome. They were documented since October 2013 at 77 collaborating centers in Japan (Table S2).[40] The database includes the clinical data obtained at onset or diagnosis, histopathological reports, treatments, and outcomes of these patients. We extracted three clinical patient groups from this registry by applying the international diagnostic criteria for iMCD[26] with Iwaki et al's criteria for TAFRO-iMCD (which require lymph node biopsy)[38] and our (Masaki et al's) diagnostic criteria for TAFRO syndrome (which do not require lymph node biopsy).[39] The groups comprised patients with iMCD-NOS, those with TAFRO-iMCD, and those with TAFRO-w/op-iMCD. We compared the clinical features and outcomes of these groups; most of the patients with iMCD-NOS and those with TAFRO-iMCD in the current cohort were also included in our previous study as the "iMCD" group.[40] The study protocol was approved by the institutional review board of Kanazawa Medical University and each collaborating facility.

2.2 | Statistical analysis

Two of the three aforementioned subgroups belonged to iMCD, and two belonged to TAFRO syndrome; as such, they were not independent. Therefore, we performed two sets of comparison analyses. Among patients with iMCD, we compared those with TAFRO features to those without. Among patients with TAFRO syndrome, we compared those with proven iMCD to those without; we also compared those with iMCD-NOS to those with whole TAFRO-syndrome. The Fisher's exact test was used to compare binary variables, while Student's *t*-test was used to compare continuous data between the two groups. The Kaplan-Meier method was used for survival analysis, and comparison between groups was performed using the log-rank test. All *P*-values less than .05 were considered statistically significant. All the analyses were conducted using EZR (version 1.30).[41]

3 | RESULTS

3.1 | Clinical features

In total, 220 patients were included in this retrospective registry of those recorded between October 2013 and December 2017. Common collagen diseases, such as systemic lupus erythematosus and Sjögren's syndrome, and IgG4-related diseases were excluded by rheumatologists in each institution, and by rheumatologists (S.F. and Y.M.) at Kanazawa Medical University. This was done by carefully reviewing the provided data, including autoantibody tests and IgG4 values. To make a diagnosis of TAFRO syndrome, a minimum of whole body computed tomography (CT) scan, bone marrow biopsy, and cytological confirmation of pleural effusion/ascites were required. This was necessary to exclude leukemia, lymphoma, infectious diseases, and hemophagocytic lymphohistiocytosis. After these exclusion processes, we extracted 87 patients with iMCD-NOS, 63 with TAFRO-iMCD, and 19 with TAFRO-w/op-iMCD (Figure S2). Lymph node biopsy was not performed in patients with TAFRO-w/op-iMCD; 5 of 19 patients in this group showed no apparent lymphadenopathy on physical examinations or CT scans. All patients with iMCD-NOS fulfilled the international diagnostic criteria for iMCD,[26] but not Iwaki et al's diagnostic criteria for TAFRO-iMCD[38] or Masaki et al's criteria for TAFRO syndrome.[39] All patients with TAFRO-iMCD fulfilled the international diagnostic criteria for iMCD and both Iwaki et al's diagnostic criteria for TAFRO-iMCD, and Masaki et al's criteria for TAFRO syndrome. Moreover, all patients with TAFRO-w/op-iMCD fulfilled Masaki et al's diagnostic criteria for TAFRO syndrome only. Clinical profiles and laboratory data at the time of diagnosis of patients in these three groups are shown in Table 1. Fever (temperatures above 37.5°) was observed in almost all patients with TAFRO syndrome, while only one-third of patients with iMCD-NOS presented with fever at the time of diagnosis. Interstitial lung lesions were observed in a quarter of patients with iMCD-NOS, while it was seldom documented in patients with TAFRO syndrome. Anasarca (pleural effusion, ascites, and/or systemic edema) was observed in all patients with TAFRO syndrome by definition, while only 11% of those with iMCD-NOS presented with the same. One-third of patients with TAFRO syndrome required hemodialysis, while only 5% of those with iMCD-NOS did. In contrast, no significant differences in these clinical features were observed between patients with TAFRO-iMCD, and those with TAFRO-w/op-iMCD.

3.2 | Laboratory features

We collected the patients' laboratory data at the time of diagnosis and compared them between groups (Table 1). There were no significant differences in these characteristics between the TAFRO-iMCD and TAFRO-w/op-iMCD groups. In contrast, the mean values of a number of laboratory parameters differed significantly between the iMCD-NOS group and the TAFRO-iMCD group, and between the iMCD-NOS and all TAFRO syndrome (TAFRO-iMCD plus TAFRO-w/op-iMCD) groups. Patients with all three groups commonly showed anemia, hypoalbuminemia, and elevated serum C-reactive protein (CRP), IL-6, soluble IL-2 receptor, and plasma vascular endothelial growth factor levels. Splenomegaly was frequently observed in patients in all groups. However, the leukocyte counts and CRP levels were significantly higher and the albumin levels significantly lower in the TAFRO groups than in the iMCD-NOS group. Patients in the

TABLE 1 Laboratory findings of patients with iMCD and TAFRO syndrome

		TAFRO syndrome (n = 82) (Groups B + C)		*P*-values		
	iMCD-NOS (n = 87)(Group A)	TAFRO-iMCD (n = 63)(Group B)	TAFRO-w/op-iMCD (n = 19)(Group C)	A vs B	B vs C	A vs B + C
Age (years)	50 (39-59)	49 (44-63)	55 (44-67)	>.1	>.1	.077
Male: female ratio	48:39	36:27	7:12	>.1	>.1	>.1
Fever (temperature > 37.5°C)	31%	97%	100%	<.001	>.1.	<.001
Splenomegaly	67%	71%	74%	>.1	>.1	>.1
Interstitial lung lesions	23%	2%	0%	<.001	>.1	<.001
Anasarca	11%	100%	100%	<.001	>.1	<.001
Hemodialysis required	5%	32%	32%	<.001	>.1	<.001
WBC (×1000/μL)	7.7 (6.0-9.1) (n = 85)	9.3 (7.1-13.0) (n = 63)	7.4 (5.0-12.8) (n = 19)	.001	>.1	.005
Hb (g/dL)	9.8 (8.3-11) (n = 85)	9.6 (7.4-11.6) (n = 63)	9.8 (7.2-11.3) (n = 19)	>.1	>.1	>.1
PLT (×1000/μL)	337 (264-413) (n = 85)	33 (17-56) (n = 63)	44 (18-74) (n = 19)	<.001	>.1	<.001
BUN (mg/dL)	12 (10-16) (n = 71)	31 (20-60) (n = 62)	38 (15-56) (n = 19)	<.001	>.1	<.001
Creatinine (mg/dL)	0.7 (0.6-0.91) (n = 85)	1.5 (1.1-2.4) (n = 63)	1.62 (0.87-2) (n = 19)	<.001	>.1	<.001
Total protein (g/dL)	9.9 (8.8-10.6) (n = 71)	5.7 (5.1-6.3) (n = 62)	5.4 (4.9-6) (n = 19)	<.001	>.1	<.001
ALB (g/dL)	2.8 (2.4-3.2) (n = 85)	2.3 (1.9-2.7) (n = 63)	2.1 (1.89-2.5) (n = 19)	<.001	>.1	<.001
CRP (mg/dL)	7.7 (4.5-11.5) (n = 82)	16.1 (6.3-21.7) (n = 63)	12.7 (6.3-26.7) (n = 19)	<.001	>.1	<.001
LDH (IU/L)	120 (97-158) (n = 84)	207 (176-280) (n = 62)	222 (185-274) (n = 19)	<.001	>.1	>.1
ALP (IU/L)	279 (219-393) (n = 84)	537 (375-1108) (n = 62)	502 (397-782) (n = 19)	<.001	>.1	<.001
γ-GTP (IU/L)	27.5 (16-59) (n = 62)	84 (40-156) (n = 60)	58 (39.5-118.2) (n = 18)	<.001	>.1	<.001
AST (IU/L)	17 (12-22) (n = 72)	23 (17-36) (n = 62)	25 (217-30) (n = 19)	<.001	>.1	<.001
ALT (IU/L)	12 (7.2-18) (n = 72)	15 (10-28) (n = 62)	14 (8-21) (n = 19)	<.001	>.1	.02
IgG (mg/dL)	4905 (3510-6113) (n = 83)	1345 (1091-1778) (n = 58)	1210 (913-1433) (n = 18)	.018	>.1	<.001
IgA (mg/dL)	632 (349-842) (n = 71)	210 (156-264) (n = 57)	214 (167-299) (n = 18)	<.001	>.1	<.001
IgM (mg/dL)	237 (169-366) (n = 71)	77 (58-99) (n = 58)	72 (40-108) (n = 18)	<.001	>.1	<.001
IL-6 (pg/mL)	21 (10-42) (n = 76)	26 (15-40) (n = 52)	23 (13-40) (n = 12)	>.1	>.1	>.1
sIL2R (U/mL)	1450 (1084-2232) (n = 80)	1669 (1070-2490) (n = 59)	1810 (1330-2455) (n = 17)	>.1	>.1	>.1
plasma VEGF (pg/mL)	435 (107-835) (n = 4)	188 (112-362) (n = 20)	172 (31-310) (n = 7)	>.1	>.1	>.1
D-dimer (μg/mL)	1 (0.7-1.2) (n = 35)	10.2 (5.2-18.5) (n = 47)	9.6 (5-16.9) (n = 15)	<.001	>.1	<.001
FDP (μg/mL)	4 (2.4-7.1) (n = 33)	23.9 (13.9-45.8) (n = 45)	21.9 (14.3-34.3) (n = 13)	<.001	>.1	<.001

Notes: For age and laboratory data, median values (25-75th percentile) were shown. For clinical manifestations, percentages of their frequencies were shown. Anasarca indicates pleural effusion, ascites, and/or generalized edema. Reference ranges: WBC, 2.97-9.13 × 1000/μL; Hb, 12.9-9.13 g/dL; PLT, 143-333 × 1000/μL; BUN, 8-22 mg/dL; Creatinine, 0.6-1.1 mg/dL; Total protein, 6.7-8.3 g/dL; ALB, 4.0-5.0 g/dL; CRP, 0-0.3 mg/dL; LDH, 119-229 IU/L; ALP, 115-359 IU/L; γ-GTP, 10-47 IU/L; AST, 13-33 IU/L; ALT, 8-42 IU/L; IgG, 870-1700 mg/dL; IgA, 110-410 mg/dL; IgM 86-160 mg/dL; IL-6 ≤ 4 pg/mL; sIL2R 145-519 U/mL; plasma VEGF ≤38.3 pg/mL; D-dimer ≤1 μg/mL; FDP ≤5 μg/mL.

Abbreviations: iMCD, idiopathic multicentric Castleman disease; NOS, not otherwise specified; TAFRO-w/op-iMCD, TAFRO syndrome without proven iMCD; WBC, white blood cell counts; Hb, hemoglobin; PLT, platelets; BUN, blood urea nitrogen; ALB, albumin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine transaminase; Ig, immunoglobulin; IL-6, interleukin 6; sIL2R, soluble interleukin 2 receptor; VEGF, vascular endothelial growth factor; FDP, fibrin/fibrinogen degenerative products.

TAFRO groups exhibited thrombocytopenia by definition, whereas those with iMCD-NOS did not have thrombocytopenia ($P < .001$). The median serum lactate dehydrogenase (LDH) levels were not elevated in any of the 3 groups, but their levels in iMCD-NOS-group patients were significantly lower than those in the patients of the TAFRO groups. The levels of blood urea nitrogen, creatinine, alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (γ-GTP) were significantly higher in TAFRO-group patients than in those of the iMCD-NOS group (in whom these values were within the reference ranges). In contrast, polyclonal hyper-γ-globulinemia with significantly elevated serum IgA, IgG, and IgM levels was observed in the iMCD-NOS group, but not in the TAFRO groups. The median values of fibrin/fibrinogen degenerative product (FDP) and D-dimer were significantly higher in the TAFRO groups than in the iMCD-NOS group. Among patients with TAFRO-w/op-iMCD, no significant differences in any of these laboratory parameters were observed between those

with detectable lymphadenopathy (n = 14) and those without (n = 5) (Table S3).

3.3 | Histological features

The lymph node histology of CD was classified into three types: hyaline-vascular, plasma cell, and mixed types. Detailed information regarding lymph node histology was available for 66 of the 87 patients with iMCD-NOS, including 4 (6%) with hyaline-vascular type, 51 (77%) with plasma cell type, and 11 (17%) with mixed-type. Moreover, detailed information regarding lymph node histology was available for 49 of the 63 patients with iMCD-TAFRO, including 6 (12%) with hyaline-vascular type, 7 (14%) with plasma cell type, and 36 (73%) with mixed-type. Lymph node biopsy was not performed in patients with TAFRO-w/o-iMCD.

3.4 | Prognostic features

Sixty-nine, 58, and 15 patients with iMCD-NOS, TAFRO-iMCD, and TAFRO-w/op-iMCD, respectively, had available follow-up data. The median follow-up period of the survivors was 63.5 months (iMCD-NOS, 117 months [range, 5-315 months]; TAFRO-iMCD, 42 months [5-161 months]; TAFRO-w/op-iMCD, 27 months [9-231 months]; and combined TAFRO syndrome, 41.5 months [5-231 months]). Among the 69 patients with iMCD-NOS, nine were observed without specific treatments, 50 received corticosteroids, 29 were treated with tocilizumab, two were treated with cyclosporine, and eight received rituximab (some patients received multiple or combination treatments). All patients with TAFRO-iMCD and TAFRO-w/op-iMCD received corticosteroids. Moreover, 24 of the 58 patients with TAFRO-iMCD received tocilizumab, 18 received cyclosporine, and 11 received rituximab. Among 19 patients with TAFRO-w/op-iMCD, three received tocilizumab, nine received cyclosporine, and one received rituximab. Kaplan-Meier analyses revealed that the overall survival (OS) curves of the TAFRO syndrome groups rapidly dropped within 24 months of diagnosis, by which time a third of the patients had died. No significant differences in OS were observed between the TAFRO-iMCD and TAFRO-w/op-iMCD groups. In contrast, more than 90% of patients with iMCD-NOS were alive 10 years after diagnosis. Thus, the OS of patients with iMCD-NOS was markedly and significantly superior to that of patients with TAFRO syndrome groups (Figure 2). The five-year survival rate of patients with iMCD-NOS was 100%, while the two-year survival rates of patients with TAFRO-iMCD and TAFRO-w/op-iMCD were 67.4% and 61.7%, respectively (the survival rate was 66.5% when the TAFRO syndrome-involved groups were combined).

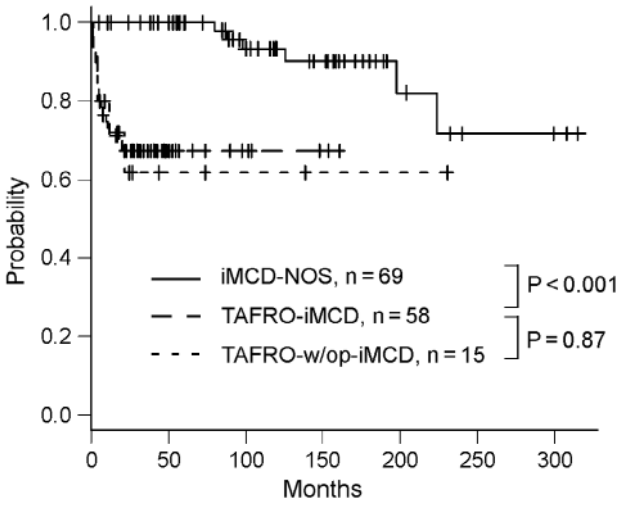

FIGURE 2 Overall survival. Statistic comparisons between iMCD-NOS and TAFRO-iMCD, and between TAFRO-iMCD and TAFRO-w/op-iMCD, were performed using the log-rank test. iMCD-NOS, idiopathic multicentric Castleman disease-not otherwise specified; TAFRO-iMCD, TAFRO syndrome with iMCD; TAFRO-w/op-iMCD, TAFRO syndrome without proven iMCD

4 | DISCUSSION

Iwaki et al analyzed the clinical and histological features of 25 patients with TAFRO-iMCD, and compared them to 19 patients with iMCD-NOS.[38] They reported that the TAFRO-iMCD patients frequently demonstrated abdominal pain, elevated serum ALP levels, and acute kidney failure. Twenty-eight percent of these patients required temporary hemodialysis (a proportion similar to the 32% in our cohort) without showing hyper-γ-globulinemia, which is commonly observed in iMCD-NOS. All patients with iMCD-NOS showed plasma cell-type lymph node histology, while those with TAFRO-iMCD revealed completely different histologies. They included atrophic germinal centers, expansion of the interfollicular zone, proliferation of highly dense endothelial venules, and relatively few mature plasma cells[38] (which is now classified as hypervascular pathology[26]). Similar findings were reported in 2008 by Kojima et al, who classified 28 iMCD patients into two subtypes: IPL and non-IPL.[29] They described the latter as frequently presenting with pleural effusions, thrombocytopenia, and various autoimmune features without marked hyper-γ-globulinemia. Histologically, their lymph nodes exhibited small epithelioid-type follicles, and moderate-to-prominent vascularity with high endothelial venules, and various degrees of plasma cell proliferation in the interfollicular area.[29] This was consistent with hypervascular pathology.[26] We postulate that most patients with this non-IPL type of iMCD fulfilled the diagnostic criteria for TAFRO syndrome.

With our much larger cohort of TAFRO syndrome patients (n = 82), we strove to validate previous findings and obtained essentially consistent results. Anemia, hypoalbuminemia, elevation of serum CRP levels, and organomegaly were commonly observed in both the iMCD-NOS and TAFRO-iMCD groups, and unlike patients with aggressive lymphomas, serum LDH levels were normal. Patients in the iMCD-NOS group typically showed normal or slightly elevated platelet counts, marked hyper-γ-globulinemia, and lymph node histology indicative of plasma cell type. These features are consistent with those of IPL, as previously proposed by Mori et al.[4] In contrast, patients in the TAFRO groups (TAFRO-iMCD and TAFRO-w/op-iMCD) manifested with leukocytosis, thrombocytopenia, normal

γ-globulin levels, elevation of serum ALP and γ-GTP levels, and anasarca. Elevations of serum FDP and D-dimer levels, which were indicative of disseminated intravascular coagulation, were observed in the TAFRO syndrome groups but not in the iMCD-NOS group. Lymph node histology in the majority of patients with TAFRO-iMCD was classified as mixed-type by institutional diagnosis; a proportion of these cases could be reclassified as hypervascular pathology under a recent guideline.[26] In our recent central review of lymph nodes, plasma cell type, mixed-type, and hypervascular type histologies were observed in 67%, 33%, and 0% of iMCD-NOS patients (n = 24), and 6%, 78%, and 16% of TAFRO-iMCD patients (n = 32), respectively.[42] On Kaplan-Meier analyses, the five-year OS in the iMCD-NOS group was 100%; this may have been attributable to the wide use of tocilizumab in Japan after 2005. In contrast, the OS curve for the TAFRO syndrome group dropped rapidly over two years; one-third of patients with TAFRO syndrome died during this period. Very similar survival curves were reported by Yu et al, who analyzed 34 patients with iMCD-NOS, and nine with TAFRO-iMCD in the United States.[43] Because our cohort included the largest number of patients with TAFRO syndrome analyzed to date, the survival curve shown in Figure 2 may reflect real-time rates in Japan. Taken together, iMCD can be classified into at least two types; iMCD-NOS (or IPL type), and TAFRO-iMCD (or non-IPL type); these should be considered as clearly distinct clinical entities.

In addition to iMCD-NOS and TAFRO-iMCD, we analyzed the clinical features of patients with TAFRO-w/op-iMCD as diagnosed using Masaki et al's criteria.[39] The clinical manifestations and laboratory data of patients in this group were similar to those of the TAFRO-iMCD group. Furthermore, the survival rates of these two groups were almost identical, and were significantly inferior to that of patients with iMCD-NOS. Notably, a majority of patients with TAFRO-w/op-iMCD had enlarged lymph nodes. Biopsy of these lymph nodes could have clearly excluded the possibilities of lymphoma and other etiologies, so we strongly recommend performing lymph node biopsy if possible.[39] However, it is also noteworthy that five out of 19 patients presented with no lymphadenopathy on physical examinations or imaging tests were similar to those of patients with detectable lymphadenopathy. Additional research is required to identify the TAFRO-specific clinical features among patients with TAFRO-w/op-iMCD, and overlapping disorders. We still posit that TAFRO-iMCD and TAFRO-w/op-iMCD, including those without lymphadenopathy, ought to be considered a single clinical entity, and that it is appropriate to use Masaki et al's criteria to diagnose TAFRO syndrome promptly.[39] When applying these criteria, we emphasize that specific diseases that are known to manifest TAFRO-like clinical features, should be carefully excluded before making a final diagnosis of TAFRO syndrome, especially of TAFRO-w/op-iMCD.

Based on data from previous studies as well as our own, it is evident that the clinicopathological features of TAFRO syndrome are different from those of iMCD-NOS, although the relationship between TAFRO syndrome and MCD remains controversial. Some researchers regard TAFRO syndrome as an aggressive subtype of iMCD, some consider it serositis with thrombocytopenia driven by autoimmune mechanisms and sometimes accompanied by lymph node histopathology that is coincidentally similar to iMCD, and others regard it as a clinical entity overlapping with iMCD (Figure S1). Based on the data from the current study, we tentatively regard iMCD-NOS and TAFRO syndrome as distinct entities, and consider that TAFRO-iMCD might represent the overlapping entity of iMCD and TAFRO syndrome.

Several limitations should be noted in our study. Because it was conducted retrospectively, patient-selection bias may exist. For example, surviving patients may be more likely to be registered than deceased patients. The periods of diagnosis varied widely (from 1990s to 2016), which may have affected the accuracy of diagnosis, and the outcomes of prognostic analyses. The pathological diagnoses and classifications were largely determined at the individual centers, which might influence their consistencies. Furthermore, not all data were available owing to the multicenter nature of the study, particularly histopathological reports and follow-up data. Nevertheless, our findings confirmed the results of previous studies that characterized the clinical features of TAFRO syndrome, and provided real-world survival rates of patients with this syndrome using the largest cohort investigated to date. We also verified the appropriateness of Masaki et al's diagnostic criteria for TAFRO syndrome.

The etiologies of iMCD-NOS and TAFRO syndrome remain completely unknown. Specific biomarkers for TAFRO syndrome are still lacking, although Iwaki et al recently reported that serum interferon γ-induced protein 10 kDa was elevated in patients with TAFRO-iMCD but not in those with iMCD-NOS, implicating this molecule in the pathogenesis of TAFRO-iMCD.[44] Recently, Pierson et al published an interesting study that revealed distinct proteomic profiles in patients with TAFRO-iMCD, and those with iMCD-NOS, though the number of patients was small.[45]

In a study from China, only half of the patients with MCD, including those who had HHV-8 associated disease, survived beyond five years.[46] According to a retrospective study on CD from the Mayo Clinic and University of Nebraska, the five-year OS of patients with MCD was 65%.[47] Treatments with tocilizumab and siltuximab greatly improved the quality of life, and might also have improved the survival of patients with iMCD-NOS. In contrast, and despite intensive treatments with corticosteroids, tocilizumab, cyclosporine, and/or rituximab,[31,34,35,48,49] the rate of early death in patients with TAFRO syndrome is high, signifying the importance of prompt diagnosis, and intensive treatment without delay, though the development of new therapeutic strategies remains an unmet need. We previously proposed tentative treatment strategies for TAFRO syndrome that included glucocorticoids, calcineurin inhibitors, rituximab, and tocilizumab.[39] Recently, the international guidelines developed for iMCD treatment cited the high response rates achieved with cyclophosphamide-based chemotherapy, rituximab, tocilizumab, and cyclosporine A, and recommended anti-IL-6 monoclonal antibody therapy with or without corticosteroids as the initial therapy.[50] However, these recommendations are essentially based on published case reports and authors' own experiences. In order to establish high-quality evidence for the characteristics of iMCD and TAFRO syndrome, delineate the relationship between them, and establish

standard treatment strategies (especially for the latter), a prospective registration system that incorporates a pathological central review mechanism is warranted.

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AUTHOR CONTRIBUTIONS

S.F. and H.K. analyzed the data, reviewed literature, and co-wrote the manuscript. T.S., K.T., S.A., J.K., M.I., K.S., N.T., H.I.-K., T.K., S.M. and T.F. participated in the clinical enrollment/work-up of the patients and edited the manuscript. N.K. and S.Y. reviewed literature on histopathology and edited the manuscript. Y.M. designed the research and reviewed the study results.

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SUPPORTING INFORMATION

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