Characteristics of thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly syndrome: a retrospective study from a large Western cohort

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Characteristics of TAFRO syndrome : a retrospective study from a large western cohort

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Abstract

Idiopathic Multicentric Castleman Disease (iMCD) is a non-clonal inflammatory lymphoproliferative disorder of unknown origin. Recently, TAFRO syndrome (Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis and Organomegaly) emerged as a singular variant of iMCD in Asia and was associated with a severe course and a poor outcome. The present study describes the first large Western cohort of TAFRO syndrome patients (n=25) meeting the All Japan TAFRO Syndrome Research Group diagnostic criteria. Characteristics of TAFRO patients were compared to iMCD-not otherwise specified (iMCD-NOS) patients used as a control group (n=43). Our results show that despite baseline characteristics in accordance with previously reported series, Western TAFRO syndrome patients do not appear to present with a worse outcome than iMCD-NOS patients. There were no significant differences between the two groups regarding treatment choice, response to rituximab (71% vs 67%) or tocilizumab (69% vs 91%) in TAFRO and iMCD-NOS, respectively. The 2-year overall survival was above 95% in both groups. Limits of inclusion and exclusion criteria for TAFRO definition are also discussed. These findings raise the question of the singularity of TAFRO entity in Western countries. These data should promote further research using unsupervised models to identify markers of disease severity in Western cohorts of iMCD patients.

Key words

Western TAFRO syndrome, idiopathic Multicentric Castleman Disease, rituximab, tocilizumab

Word count :

Introduction

Castleman disease (CD) is a rare non-clonal lymphoproliferative disorder first described in 1956 by Benjamin Castleman (1). Since its first description, the CD spectrum has widened to include three different forms : unicentric CD (UCD) corresponding to the original description, HHV-8+ multicentric CD (HHV-8+ MCD) and the so-called "idiopathic" multicentric CD (iMCD) (2). iMCD is a life-threatening condition secondary to a cytokine storm characterized by systemic symptoms and enlarged secondary lymphoid organs. More recently, TAFRO syndrome has emerged as a severe variant of iMCD (TAFRO-iMCD) in Asia, defined by the association of Thrombocytopenia, Anasarca, Fever, Reticulin myelofibrosis and Organomegaly (3). TAFRO syndrome still represents a diagnostic and therapeutic challenge, with several mimickers, and is characterized by a severe clinical presentation and poorer outcome as compared to iMCD-not otherwise specified (iMCD-NOS) in Asia (4,5). Two sets of diagnostic criteria (Iwaki et al. (6) and the more recent All Japan TAFRO Syndrome Research Group in 2015 (7)) are currently used for diagnosing TAFRO syndrome, with substantial differences. In the latter definition, pathological findings of CD are no longer a major and necessary criterion, meaning that TAFRO syndrome might not always be related to CD.

Characteristics of TAFRO syndrome patients have been assessed in Western countries but only through case reports or small series. The aim of the study was to describe the characteristics of TAFRO syndrome patients in a large Western cohort identified through the French National Registry for CD and TAFRO, and to compare these to those of iMCD-NOS patients.

Methods

Patients with biopsy-proven Castleman disease and/or defined TAFRO syndrome referred to the French national reference center for Castleman disease and TAFRO between January 1994 and June 2021 were screened for this study. All patients gave informed consent. This study was reviewed and approved by our local ethics committee. UCD, HHV-8+ MCD, POEMS syndrome and all secondary CD were excluded (Figure 1). Patients were included as TAFRO syndrome if they fulfilled diagnostic criteria as defined by the All Japan TAFRO Syndrome Research Group described by Masaki et al. (Supplemental table 1 (7)). Other patients were included as iMCD-NOS. Every case was reviewed by two CD experts before inclusion in the study. All TAFRO patients were also reviewed according to Iwaki's criteria (Supplemental table 2 (6)). Data concerning baseline clinical characteristics (including ECOG status, need for ICU), laboratory features (including VEGF and IL6 levels), histological features, imaging data, as well as clinical management and outcomes (including number of relapses and treatment lines) were collected and compared in both TAFRO syndrome and iMCD-NOS groups. Lymphadenopathy was defined as a lymph node larger than 1cm. Renal impairment was defined as the development of renal failure (pathological elevation of creatinine levels, or an elevation higher than

26μmol/L from baseline), and/or presence of proteinuria greater than 500mg/g of urinary creatinine. Complete treatment response was defined by a complete remission of clinical and biological symptoms. Partial treatment response was defined by a global improvement without complete remission and not requiring adjunctive therapy. Treatment failure was defined by a lack of response to therapy or a partial improvement requiring adjunctive therapy.

Statistical analysis

Wilcoxon's test was used for the comparison of continuous variables while Fisher's test was applied to that of categorical variables. To compare evolution and follow-up between the two groups, survival curves were performed with Kaplan-Meier's method stratified by group. Two-sided testing was used, with a *P*-value of 0,05 or less considered significant. All analyses were made using R and R studio v. 3.5.1 software.

Results

Clinical characteristics of TAFRO syndrome and iMCD-NOS patients

Case reviewing led to the identification of 25 patients diagnosed with TAFRO syndrome and 43 with iMCD-NOS. Two TAFRO cases were not associated with CD (TAFRO-NOS).

TAFRO syndrome group. Major characteristics and data are summarized in Table 1. The TAFRO syndrome group included 11 males and 14 females. The median age at diagnosis was 32 years (IQR [22-55]). Most patients were Caucasian (n=21, 84%), 3 patients originated from Western Africa and 1 was from Asian descent. All patients satisfied the Masaki criteria for TAFRO syndrome, *i.e.* all 3 major criteria (anasarca, thrombocytopenia, systemic inflammation), Castleman's disease-like features on lymph node biopsy (n=23, 92%), and at least 1 criterion among reticulin myelofibrosis (n=13, 62%), mild organomegaly (lymphadenopathy n=24, 96%, splenomegaly n=16, 64%), or renal impairment (n=23, 92%). At diagnosis, 8 patients (35%) were admitted to an intensive care unit.

Among these TAFRO patients, all meeting the Masaki criteria, 10 patients (40%) however did not satisfy the Iwaki criteria (6 due to hypergammaglobulinemia, 2 due to the absence of a lymph node biopsy with pathological findings compatible with CD, and 2 due to the absence of one minor criterion (hyper/normoplasia of megakaryocytes in bone marrow or high levels of serum alkaline phosphatase without markedly elevated serum transaminase levels)).

iMCD-NOS group. Forty-three patients with iMCD-NOS were used as comparators, including 13 women and 30 men. All of them fulfilled the International Consensus Diagnostic Criteria (7). The median age was 55 years (IQR [27-66]). Thirty-eight patients were Caucasian, 2 originated from Western Africa and 3 patients were from Asian descent. Twenty-five patients had fever at diagnosis (60%). As expected, iMCD-NOS patients exhibited less often anasarca (n=8, 20%), organomegaly (n=12, 29%) and renal impairment (n=6, 17%) than TAFRO syndrome patients. Only one case of reticulin fibrosis was found among the 12 bone marrow biopsies available in this group.

IMCD patients seemed to have a better general condition at diagnosis with lower ECOG scores and less requirement for intensive care (n=2.7%).

Laboratory Features of TAFRO and iMCD-NOS groups

Laboratory features are summarized in Table 2. As expected, TAFRO patients had a lower platelet count than the iMCD-NOS group (median 52 G/L vs 257 G/L, $p<0,01$). Lower gammaglobulin (12,2 g/l vs 21,3g/l, $p<0,01$) and higher alkaline phosphatase levels (151 UI/l vs 85 UI/l , $p<0,01$) were found among TAFRO patients. Only one patient, from the iMCD-NOS group, had an abnormal alanine aminotransferase elevation (data not shown). In addition, TAFRO patients displayed higher leukocyte counts (10,0 G/L vs 8,0 G/L, $p = 0,02$), higher serum CRP levels (204 mg/l vs 90mg/l , $p<0,01$), higher ferritin levels (875 µg/L vs 106 µg/L, $p<0,01$) and lower albumin levels (25g/l vs 31g/l, $p<0,01$). No significant differences were found regarding sVEGF and sIL6 levels. The

proportion of patients with positive anti-nuclear autoantibodies was not different between the two groups (9/24 vs 19/35, p = 0,29). No monoclonal components were found in any group.

Histological Features of TAFRO and iMCD-NOS groups

In TAFRO patients, lymph node biopsies showed plasma-cell type CD in 12 patients, hyaline vascular CD in 4, and mixed-type CD in 5. Detailed pathological characteristics of CD lesions were not available for 2 patients. Two other patients were classified as TAFRO-NOS in the absence of lymphadenopathy.

Among the iMCD-NOS patients, 29 lymph nodes biopsies revealed CD of the plasma-cell type, 5 of the hyaline vascular type, and 9 of the mixed type. There were no significant differences between the two groups.

PET-CT Features of TAFRO and iMCD-NOS groups

The majority of TAFRO patients were classified as stage III on PET-CT (n = 16, 88%) with a median SUV max (Maximum Standardized Uptake Value) of 5,9 (IQR : [4,4-7,6]). In the iMCD-NOS group, results were more heterogeneous with a PET-CT classified as stage II for 39% (n = 13) and stage III for 49% (n = 16) with a median SUV max of 5,4 (IQR : [3,2-8,1]).

Disease Management and follow-up

Data are summarized in Table 3. The median time interval between the first symptoms and diagnosis was 7 weeks (IQR [4-15]) for TAFRO syndrome patients and 22 weeks (IQR [8-183]) for iMCD-NOS patients (p<0,01). The median follow-up duration was 23 months (IQR [10-47]) for the TAFRO group and 75 months (IQR [21-122]) for the iMCD-NOS group (p<0,01).

Three patients in the TAFRO group and 5 in the iMCD-NOS group were treated with corticosteroids alone (12% each, p = 1). Twenty-two TAFRO and 31 iMCD-NOS patients needed another immunosuppressive or immunomodulatory treatment.

In the TAFRO group, tocilizumab was used in 16 patients (as first-line treatment in 3), in whom a complete response was observed in 8 cases (50%), a partial response in 3 (19%) and a treatment failure in 5 (31%). Rituximab was used in 14 patients (as first-line treatment in 1) resulting in a complete response in 9 (64%) and a partial response in 1 (7%). Rituximab failure was observed in 4 patients (29%).

In 3 patients, other treatments including hydroxychloroquine, intravenous immunoglobulins, anakinra, etoposide, eculizumab, dapsone, sirolimus and polychemotherapy were used.

In the iMCD-NOS group, tocilizumab was used in 23 patients (as first-line treatment in 12). A complete or partial response was obtained respectively in 17 (74%) and 4 (17%) cases, while treatment failure occurred in 2 (9%) cases. Rituximab was used in 9 patients (as first-line treatment in

2) resulting in a complete response in 2 (22%) cases, a partial response in 4 (45%) cases, and a lack of efficacy in 3 (33%).

In 9 patients, other treatments were used including hydroxychloroquine, etoposide, anakinra, plasma exchanges and polychemotherapy.

There were no significant differences between the two groups regarding treatment choice and response to rituximab or tocilizumab. Deaths occurred in 2 patients in the TAFRO group and 5 in the iMCD-NOS group. The 2- year estimated Overall Survival (OS) was 96 % in the TAFRO group and 97 % in the iMCD-NOS group.

During follow-up, a complete or partial control of disease activity was observed respectively in 23 (92%) and 2 (8%) patients from the TAFRO group, as compared respectively to 18 (42%) and 10 (23%) patients from the iMCD-NOS group. In this latter group, ten patients (23%) kept an active disease at the last visit.

Discussion

Our study constitutes the first description of a large Western cohort of TAFRO syndrome patients. In our cohort, TAFRO-iMCD is largely predominant over TAFRO-NOS due to the characteristics of our center which is a national referral center for Castleman disease. The median age at diagnosis appeared to be younger in our cohort than in the previously reported Japanese cohorts (5,6,8–10) (supplementary table 3). This difference may explain the better overall survival of our TAFRO syndrome patients compared to that of the Japanese cohorts, since age appears to be the strongest predictor of death in a recent report (11). This difference in age between Western and Eastern cohorts has been already reported in a literature review from Coutier et al. (12).

Because of the criteria used to define TAFRO syndrome by the All Japan TAFRO Syndrome Research Group, the TAFRO group unsurprisingly showed a higher prevalence of reticulin fibrosis and kidney failure, a lower gammaglobulin level and a higher alkaline phosphatase level than the iMCD-NOS group (6,7). Median time from first symptoms to diagnosis was 7 weeks and was significantly inferior to the diagnosis delay observed in iMCD-NOS. This observation might be related to the more aggressive clinical course of TAFRO syndrome, as shown by higher ECOG scores and a higher requirement for intensive care. All these data were in accordance with previous studies (5,6,9). Systemic inflammation was also more pronounced in the TAFRO group but no differences in levels of sIL6 and sVEGF were found between both groups. Limited data availability might explain these observations but these findings are in line with previous reports (supplementary table 3). These elements altogether corroborate the fact that TAFRO syndrome might be a distinct entity.

However, contrasting with previous data, Western TAFRO syndrome did not appear to be associated with treatment failure. Moreover, the 2-year overall survival was 96% in the TAFRO group and 97% in the iMCD group, a finding which differed from previously published series (around 65% in the cohort from Fujimoto's et al. (5) and 67.8% in the Multicenter Collaborative Retrospective Study for Establishing the Concept of TAFRO syndrome registry (11)). Only two deaths were reported and a complete response was obtained in the majority (91%) of TAFRO patients, with a low relapse rate. Median time between initial presentation and initiation of appropriate treatment might have accounted for the increased observed overall survival. Data from Fujimoto et al. (10) published earlier this year seem to argue however against this hypothesis, since the median time period from initial presentation to initiation of appropriate treatment was even shorter than in our study (between 0.5 and 0.8 months). This discrepancy further advocates for a singular behavior of Western TAFRO syndrome.

Tocilizumab and rituximab were shown to be effective treatments of TAFRO, with a response obtained in about two-thirds of the cases. We did not perform statistical comparison on survival curves due to the low number of events in each group and because of a significant difference in the follow-up duration. This difference of follow-up between the two groups was primarily related to a more recent inclusion of patients with TAFRO syndrome in our cohort, probably because of a recent increased awareness of this syndrome and its relationship with iMCD. These data raise the question of the

singularity of TAFRO syndrome in Western countries. It might also indirectly indicate that Western iMCD-NOS might be more aggressive and differ from the chronic and often indolent form of the disease described in Asian cohorts.

This study has several limitations. Despite careful exclusion procedures, patients with disorders mimicking TAFRO syndrome might have been incorporated into this study cohort. The small number of deaths prevented us from performing multivariate analysis for OS assessment between the two groups. Another limitation of the study is related to the choice of response criteria which might appear subjective. Response criteria were separated between CR, PR and treatment failure using local criteria, based on a pragmatic approach aiming at identifying patients who required treatment modifications.

In this study, TAFRO was defined using criteria issued from the All Japan TAFRO Syndrome Research Group (Masaki et al. criteria, listed in Supplementary table 1). In 2016, Iwaki et al proposed other diagnostic criteria (listed in Supplementary table 2). More than one third of our patients (n=10) did not fulfill these criteria and this was mainly due to a serum gammaglobulin level higher than 15g/l. This observation led us to question the use of a gammaglobulin threshold for the diagnosis of TAFRO syndrome, as this parameter may substantially vary between populations.

Before TAFRO syndrome was individualized as a separate entity, Kojima et al. distinguished Idiopathic Plasmacytic Lymphadenopathy (IPL) from non-IPL variants among iMCD. The latter type, which met TAFRO syndrome criteria, appeared to have a strong association with autoimmune diseases and autoantibodies (13). Current definitions of TAFRO syndrome consider the presence of an auto-immune disorder as an exclusion criterion. Five patients with a clinical and biological presentation highly suggestive of TAFRO were excluded from our analysis due to the presence of SLE international criteria. As an increased type-1 interferon response gene signature has been described in both SLE (14,15) and TAFRO-iMCD (16), these interesting observations raise the question of an overlap syndrome between the two diseases, which might benefit from iMCD/TAFRO therapeutic options more than from classical immunosuppressive regimens.

This study highlights the particularities of Western TAFRO syndrome and raises questions that should promote research to further define the nosological framework of TAFRO syndrome.

AUTHORSHIP CONTRIBUTIONS

L.M, R.B and D.B wrote the manuscript. L.M, R.B, D.B, L.Galicier, C.F, M.M, J.F, L. Gérard, L.D, S.G, M.H, B.D., V.D.W, F.V, L.Z, M.G, N.S, M.G and E.O contributed to the patient recruitment and management. L.M, R.B, M.B and D.B extracted and analyzed the data. L.M. performed statistical analysis. B.D performed English editing of the manuscript. D.B, R.B and E.O supervised the project. All the authors reviewed the manuscript.

CONFLICT OF INTEREST DISCLOSURE

E.O. is a consultant for Eusapharma. The other authors have no conflict of interest to disclose.

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Figure 1: Study flow chart

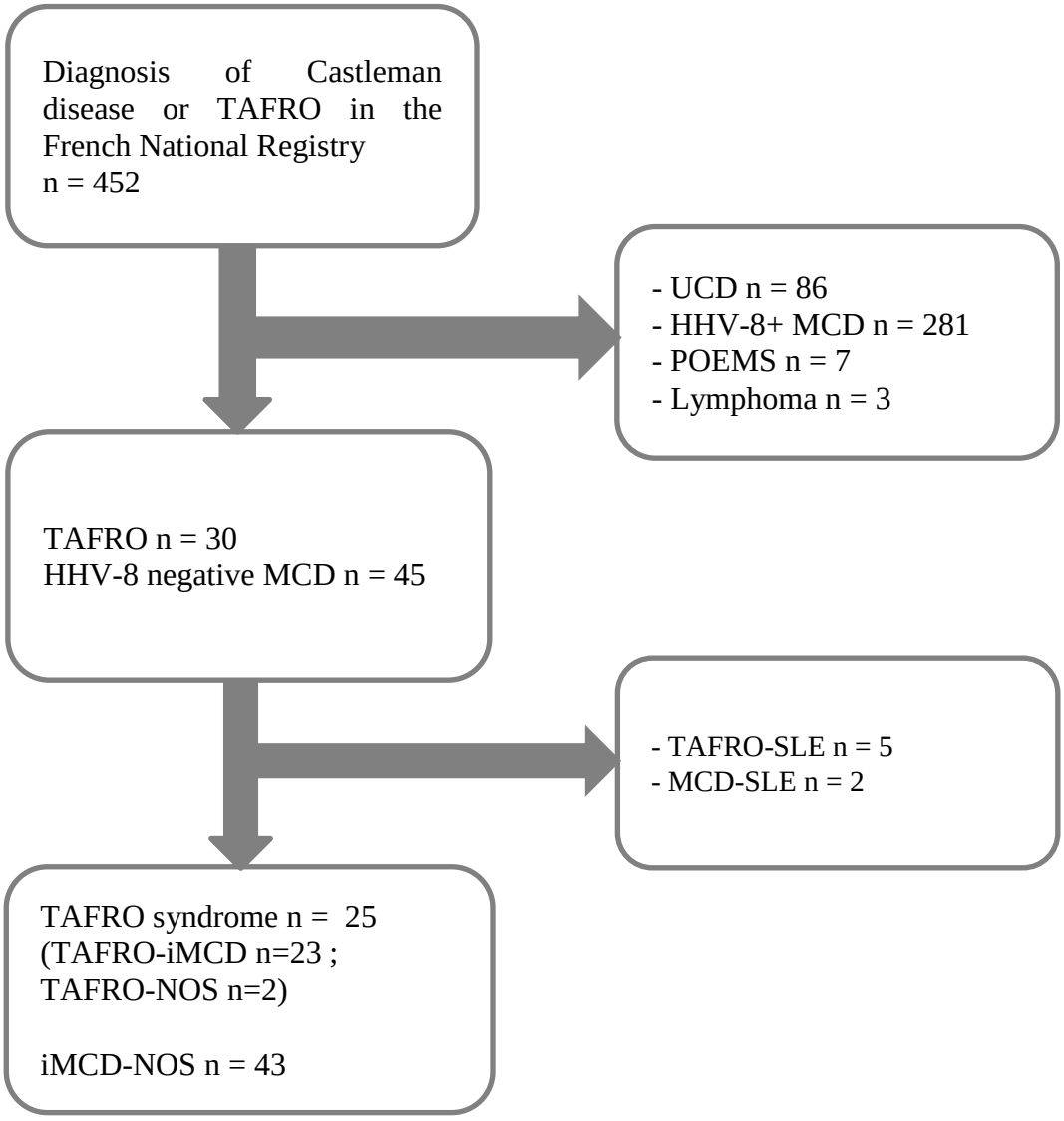


Table 1: Demographic, clinical and radiological characteristics at diagnosis.

	TAFRO n = 25	iMCD n = 43	p
Sex F/M (%)	14/11 (56%)	13/30 (30%)	**0.04**
Origin n/N (%) Caucasian Western Africa Asian	 21/25 (84%) 3/25 (12%) 1/25 (4%)	 38/43 (88%) 2/43 (5%) 3/43 (7%)	0,54
Age at diagnosis years median [IQR]	32 [22-55]	55 [27-66]	0,06
Age at first symptoms years median [IQR]	27 [21-55]	45 [21-64]	0,26
ECOG n/N (%) <=2 >2	 11/24 (46%) 13/24 (54%)	 29/31 (94%) 2/31 (6%)	**<0,01**
ICU at diagnosis n/N (%)	8/23 (35%)	2/29 (7%)	**0,02**
Histopathology n/N (%) Hyaline-Vascular type Plasma-cell type Mixed type	 4/21 (19%) 12/21 (57%) 5/21 (24%)	 5/43 (12%) 29/43 (68%) 9/43 (21%)	0,69
Thrombocytopenia n/N (%)	25/25 (100%)	2/41 (5%)	**<0,01**
Anasarca n/N (%)	25/25 (100%)	8/42 (20%)	**<0,01**
Fever n/N (%)	23/25 (92%)	25/42 (60%)	**<0,01**
Organomegaly n/N (%)	24/25 (96%)	12/42 (29%)	**<0,01**
Renal failure n/N (%)	23/25 (92%)	6/35 (17%)	**<0,01**
Reticulin fibrosis n/N (%)	13/21 (62%)	1/12 (8%)	**<0,01**

PET-stage n/N (%) **I** **II** **III** **IV**	 0/18 (0%) 1/18 (6%) 16/18 (88%) 1/18 (6%)	 1/33 (3%) 13/33 (39%) 16/33 (49%) 3/33 (9%)	 **0,02**
PET-SUV max median [IQR]	5,9 [4,4-7,6] (n = 11)	5,4 [3,2-8,1] (n = 31)	0,70

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICU, Intensive Care Unit; iMCD, idiopathic Multicentric Castleman Disease; IQR, interquartile range; PET, Positron Emission Tomography; SUVmax: Maximum Standardized Uptake Value

Table 2: Detailed biological features at diagnosis.

Laboratory features	TAFRO n = 25	iMCD n = 43	p
Platelets (G/L) median [IQR]	52 [19-78] (n = 25)	257 [194-385] (n = 41)	**<0,01**
Gammaglobulin level (g/L) median [IQR]	12,2 [8,8-18,3] (n = 23)	21,3 [13,5-25,9] (n = 39)	**<0,01**
ALP (UI/L) median [IQR]	151 [111-247] (n = 20)	85 [76-115] (n = 25)	**<0,01**
Leukocytes (G/L) median [IQR]	10,0 [7,8-15,5] (n = 22)	8,0 [6,1-10,5] (n = 41)	**0,02**
Lymphocytes (G/L) median [IQR]	1,5 [1,1-2,1] (n = 22)	1,3 [1,0-1,9] (n = 41)	0,33
Hæmoglobin (G/L) median [IQR]	9,6 [7,4-11,6] (n = 24)	9,8 [8,9-12,4] (n = 41)	0,24
CRP (mg/l) median [IQR]	204 [92-253] (n = 24)	90 [34-123] (n = 40)	**<0,01**
Albumin (g/L) median [IQR]	25 [20-28] (n = 24)	31 [28-36] (n = 41)	**<0,01**
Ferritin (µg/L) median [IQR]	875 [597-1259] (n = 21)	106 [169-469] (n = 32)	**<0,01**
Creatinine (µmol/L) median [IQR]	113 [77-170] (n = 21)	88 [64-99] (n = 40)	**0,01**
IL6 (pg/mL) median [IQR]	25 [13,9-153,4] (n = 11)	45,2 [35,3-55,0] (n = 9)	0,55
Abnormal sVEGF level (>500pg/mL)	12/15 (80%)	12/18 (67%)	0,46
ANA positive	9/24 (38%)	19/35 (54%)	0,29

Abbreviations: ALP, alkaline phosphatase; ANA, antinuclear antibodies; CRP, C-reactive protein; IL6, interleukine-6; iMCD, idiopathic Multicentric Castleman Disease; IQR, interquartile range; sVEGF, serum Vascular Endothelial Growth Factor

Table 3 : Follow-up, disease management and outcomes

	TAFRO n = 25	iMCD n = 43	P
Interval between symptoms & diagnosis (weeks) median [IQR]	7 [4-15]	22 [8-183]	**<0,01**
Follow up (months) median [IQR]	23 [10-47] (n = 25)	75 [21-122] (n = 38)	**<0,01**
Steroids only	3/25 (12%)	5/43 (12%)	1
Wait & watch only	0/25 (0%)	7/43 (16%)	**0,04**
Use of Tocilizumab	16/25 (68%)	23/43 (54%)	0,45
Use of Rituximab	14/25 (56%)	9/43 (21%)	**<0,01**
Use of other	8/25 (32%) *	9/45 (21%) **	0,39
First line :			
Steroids	18/25 (72%)	21/36 (58%)	0,14
Tocilizumab	3/25 (12%)	12/36 (33%)	
Rituximab	1/25 (4%)	2/36 (6%)	
Other	3/25 (12%)$^{+}$	1/36 (3%) $^{++}$	
Tocilizumab use in:			
First-line	3/16 (19%)	12/23 (52%)	0,09
Second-line	8/16 (50%)	5/23 (22%)	
After second line	5/16 (31%)	6/23 (26%)	
Rituximab use in :			
First-line	1/14 (7%)	2/9 (22%)	0,30
Second-line	8/14 (57%)	2/9 (22%)	
After second line	5/14 (36%)	5/9 (56%)	
Response to Tocilizumab			
CR	8/16 (50%)	17/23 (74%)	0,19
PR	3/16 (19%)	4/23 (17%)	
Failure	5/16 (31%)	2/23 (9%)	

Response to Rituximab			
CR	9/14 (64%)	2/9 (22%)	0,06
PR	1/14 (7%)	4/9 (45%)	
Failure	4/14 (29%)	3/9 (33%)	
Deaths	2/25 (8%)	5/43 (12%)	
Disease status at last visit			
CR			
PR	21/23 (91%)	18/38 (49%)	**<0,01**
Active disease	2/23 (9%)	10/38 (24%)	
	0/23 (0%)	10/38 (27%)	
Number of relapses			
0	19/25 (76%)	30/43 (70%)	
1	4/25 (16%)	9/43 (21%)	0,92
>1	2/25 (8%)	4/43 (9%)	

Abbreviations: CR, complete response; iMCD, idiopathic Multicentric Castleman Disease; IQR, interquartile range; PR, partial response

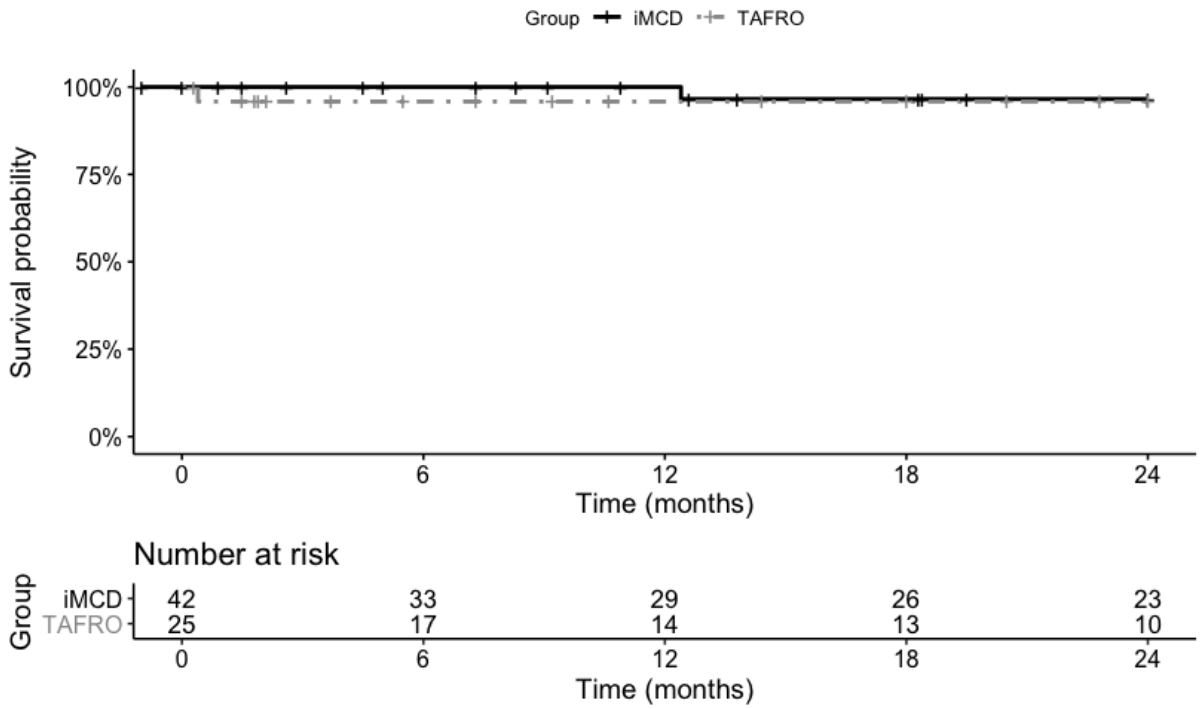
* Among : hydroxychloroquine, IgIV, anakinra, etoposide, eculizumab, dapsone, sirolimus, chemotherapy

** Among : hydroxychloroquine, etoposide, anakinra, plasma exchange, chemotherapy

[+] hydroxychloroquine, IVIg, chemotherapy

[++] etoposide

Figure 2: Stratified Kaplan-Meier survival curves censored at 24 months (TAFRO vs iMCD)



Supplementary table 1: TAFRO diagnostic criteria according to Masaki et al. (7)

1) Major categories
   - Anasarca, including pleural effusion, ascites and general edema
   - Thrombocytopenia, defined as a pre-treatment platelet count < or = 100000/mm3
   - Systemic inflammation, defined as fever of unknown etiology above 37,5°C and / or serum C-reactive protein concentration > or – 2mg/dl

2) Minor categories
   - Castleman's disease-like features on lymph node biopsy
   - Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow
   - Mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy
   - Progressive renal insufficiency

3) Diseases to be excluded
   - Malignancies, including lymphoma, myeloma, mesothelioma, et cetera
   - Autoimmune disorders, including systemic lupus erythematosus, ANCA-associated vasculitis, et cetera
   - Infectious disorders, including acid fast bacterial infection, rickettsia disease, Lyme disease, severe fever with thrombocytopenia syndrome, et cetera
   - POEMS syndrome
   - IgG4-related disease
   - Hepatic cirrhosis
   - Thrombotic thrombocytopenic purpura / hemolytic uremic syndrome

4) Points to consider
   - Marked polyclonal hypergammaglobulinemia is rare in TAFRO patients, with serum IgG concentrations remaining below 3000mg/dl
   - Obvious monoclonal protein should not be present
   - Few patients show elevated serum LDH
   - Most patients show elevated level of serum ALP
   - Hepatosplenomegaly in this disease is usually mild and only confirmed by CT-scan, whereas presence of huge hepatosplenomegaly may indicate lymphoma and other diseases
   - Lymphadenopathy in this disease is usually smaller than 1.5cm in diameter, whereas huge lymphadenopathy may indicate lymphoma and other diseases
   - Exclusion criteria for Castleman's disease and immune thrombocytopenia have not been determined, so these diseases may not be excluded at present.

Requirements: all of the three major categories and at least two of four minor categories

Supplementary table 2: TAFRO diagnostic criteria according to Iwaki et al.(6)

1) Histopathological Criteria :

- Compatible with pathological findings of lymph nodes as TAFRO-iMCD
- Negative LANA-1 for HHV-8

2) Major criteria :

- Presents 3 of 5 TAFRO symptoms :

- Thrombocytopenia
- Anasarca
- Fever
- Reticulin fibrosis
- Organomegaly

- Absence of hypergammaglobulinemia
- Small volume lymphadenopathy

3) Minor criteria need 1 or more :

- Hyper/normoplasia of megakaryocytes in bone marrow
- High levels of serum alkaline phosphatase without markedly elevated serum transaminase

Requirements: fulfill histopathological criteria, all major criteria, and 1 or more of minor criteria.

Diseases that should be excluded include rheumatologic diseases such as SLE, infectious diseases such as acute Epstein-Barr Virus, and neoplastic diseases such as lymphoma, POEMS syndrome, and other cancers.

Supplementary table 3: clinical and laboratory features from previous TAFRO cohorts

	Maisonobe et al. (n = 25)	Masaki et al. (7) (n = 18)	Iwaki et al. (6) (n = 25)	Fujimoto et al. (5)		Nishimura et al. (9) (n = 8)
				TAFRO-IMCD (n = 63)	TAFRO-NOS (n = 19)	
Sex F/M	14/11	10/18	11/14	27/36	12/7	3/5
Age at diagnosis years Median [IQR]	32 [22-55]	54	50 [23-72]	49 [44-63]	55 [44-67]	43.5 [19-81]
Thrombocytopenia n/N (%)	25/25 (100)	18/18 (100)	21/25 (84)	63/63 (100)	19/19 (100)	8/8 (100)
Anasarca n/N (%)	25/25 (100)	18/18 (100)	24/25 (96)	63/63 (100)	19/19 (100)	7/8 (88)
Fever n/N (%)	23/25 (92)	11/18 (61)	21/25 (84)	61/63 (97)	19/19 (100)	7/8 (88)
Organomegaly n/N (%)	24/25 (96)	16/18 (89)	25/25 (100)	45/63 (71)	7/19 (37)	8/8 (100)
Renal failure n/N (%)	23/25 (94)	10/18 (56)	-	-	-	1/8 (13)
Reticulin fibrosis n/N (%)	13/21 (62)	9/12 (75)	13/16 (81)	-	-	-
Platelets (G/L) median [IQR]	52 [19-78]	-	43 [14-171]	33 [17-56]	44 [18-74]	39 [8-91]
Immunoglobulin G level (g/L) median [IQR]	12 [9-18]	-	15 [9-28]	14 [11-18]	12 [9-14]	10 [9-22]
ALP (UI/L) median [IQR]	151 [111-247]	-	469 [102-2388]	537 [375-1108]	502 [397-782]	550 [195-1357]
Leukocytes (G/L) median [IQR]	10.0 [7.8-15.5]	-	-	9.3 [7.1-13.0]	7.4 [5.0-12.8]	13.4 [4.6-18.3]
Hæmoglobin (g/dL) median [IQR]	9.6 [7.4-11.6]	-	9.1 [6.2-16.3]	9.6 [7.4-11.6]	9.8 [7.2-11.3]	11.7 [8.2-13.8]
CRP (mg/L) median [IQR]	204 [92-253]	-	149 [8-302]	161 [63-217]	127 [63-267]	178 [72-282]
Albumin (g/L) median [IQR]	25 [20-28]	-	23 [11-35]	23 [19-27]	21 [19-25]	19 [11-23]
Ferritin (µg/L) median [IQR]	875 [597-1259]	-	-	-	-	578 [386-994]
Creatinin (µmol/l) median [IQR]	113 [77-170]	-	84 [46-535]	132 [97-211]	143 [77-176]	133 [40-219]
IL6 (pg/mL) median [IQR]	25 [14-153]	-	16 [6-67]	26 [15-40]	23 [13-40]	28 [17-141]
sVEGF(pg/mL) median [IQR]	*	-	305 [<20-1410]	188 [112-362]	172 [31-310]	684 [215-1710]

Abbreviations: F, female; M, male; ALP, alkaline phosphatase; CRP, IL6, interleukine-6, sVEGF, serum Vascular Endothelial Growth Factor
*only qualitative values (normal vs increased levels) were available for some patients