Review Article

International definition of iMCD-TAFRO: future perspectives

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Since thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly (TAFRO) syndrome was first proposed in 2010, there has been considerable progress in this area, particularly regarding its association with idiopathic multicentric Castleman disease (iMCD). TAFRO syndrome is a heterogeneous category with a constellation of symptoms that can develop in the setting of infection, rheumatologic disorder, malignancy, and iMCD. Now, iMCD with TAFRO symptoms is subtyped as iMCD-TAFRO. However, confusion between TAFRO syndrome and iMCD-TAFRO remains. In this article, we discuss the current understanding and future research agenda of TAFRO syndrome and iMCD-TAFRO from the perspective of its new validated international definition.

Keywords: idiopathic multicentric Castleman disease, TAFRO syndrome, iMCD-TAFRO

INTRODUCTION

It has been more than a decade since Takai, et al. first reported a series of cases of thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis or renal insufficiency (R), and organomegaly (O), which later was named TAFRO syndrome in 2010.1 TAFRO syndrome is a heterogeneous category with a constellation of the above symptoms, including infectious diseases, malignancies, and rheumatologic disorders.2-4 In the early 2010s, the majority of TAFRO syndrome cases were from Japan.5-30 However, since the late 2010s, there has been an increasing number of case reports of TAFRO syndrome worldwide.31-41 Idiopathic multicentric Castleman disease (iMCD) is one of the primary causes of TAFRO syndrome. MCD is a rare disorder with systemic inflammation, diffuse lymphadenopathy with characteristic lymph node histopathology, and multi-organ dysfunction.42 Of the types of MCD, iMCD is defined as human immunodeficiency virus (HIV)-negative and human herpesvirus 8 (HHV-8)-negative type, which accounts for approximately 50% of MCD cases.43

To date, several diagnostic criteria have been proposed for TAFRO syndrome and iMCD-TAFRO. The first diagnostic criteria for TAFRO syndrome were published in 2015 by Masaki et al. based on an investigation of 28 cases with and without TAFRO symptoms, which consist of three major and four minor categories (all of the three major and at least two minor criteria need to be met).3 The criteria were updated in 2019 with revisions to the disease description, but no changes to the major and minor categories for diagnosis were made.4 In 2016, Iwaki et al. released the diagnostic criteria for iMCD-TAFRO based on an analysis of 25 cases of iMCD-TAFRO and 19 cases of iMCD without TAFRO symptoms (iMCD-NOS; those with iMCD that do not meet the criteria for iMCD-TAFRO), which defined lymph node histopathology as necessary for the diagnosis of iMCD-TAFRO.44 These criteria facilitated the understanding of TAFRO syndrome and iMCD among physicians and researchers. However, confusion remained surrounding TAFRO syndrome and iMCD-TAFRO, although differentiation of iMCD-TAFRO from TAFRO syndrome is essential due to differences in the therapeutic approach and its high mortality (2-year survival rate of 85%).45 A common misunderstanding is “TAFRO syndrome is a subtype of iMCD.” To resolve the confusion, we performed a systematic review of existing articles on TAFRO syndrome and iMCD-TAFRO to make updated criteria with validation using a natural history registry, with the results published as the validated international definition of iMCD-TAFRO in 2021.46 The concepts of TAFRO syndrome and iMCD-TAFRO are described in Figure 1. In this review, we delve further into TAFRO syndrome and iMCD-TAFRO from the perspective of the new definition above.
THE INCEPTION OF TAFRO SYNDROME

As noted above, the initial report of TAFRO syndrome was made in 2010 by Takai et al. The report included three cases of severe thrombocytopenia, fever, pleural effusion and ascites, hepatosplenomegaly, lymphadenopathy, mild myelofibrosis, and increased megakaryocytes in the bone marrow. No apparent primary diseases were identified at the time and one of the three patients died despite aggressive medical treatment. Considering its aggressive disease courses in a potentially new clinical category, the report received considerable attention and prompted the organization of a Japanese nationwide research team on TAFRO syndrome. The diagnostic and severity criteria of TAFRO syndrome in 2015 by Masaki et al. were proposed among the need to establish a consensus on whether to diagnose TAFRO syndrome. The criteria require anasarca, thrombocytopenia defined as ≤ 100,000/µL, systemic inflammation with fever > 37.5°C, or serum C-reactive protein ≥ 2 mg/dL, with lymph node histopathology consistent with Castleman disease, reticulin myelofibrosis, organomegaly, and renal insufficiency as minor categories. The criteria helped frontline physicians to decide to treat TAFRO syndrome patients without obvious primary diseases. However, it was made based on 28 patients without a clear diagnosis, rendering significant selection bias.

In 2019, the research group updated the diagnostic criteria with minor revisions. Throughout, lymph node histopathology was not considered necessary for TAFRO syndrome, which is understandable from a standpoint of frontline physicians dealing with critical patients requiring immediate treatment with guidance. At the same time, lymph node biopsy being a minor criterion, and confusion between TAFRO syndrome and iMCD-TAFRO caused misconceptions such as “TAFRO syndrome is a subtype of iMCD and lymph node histopathology is unnecessary for its diagnosis.” The criteria have great sensitivity with low thresholds for fever, inflammation, and thrombocytopenia, with multiple points on its minor categories. However, the exclusion of related diseases needs to be exhaustive. Infectious diseases, malignancies, and rheumatologic disorders are the most common causes of TAFRO syndrome. In particular, atypical causes, such as disseminated cytomegalovirus or nontuberculous mycobacterial infections, uncommon types of lymphoma, autoimmune disorders, such as systemic lupus erythematosus, Sjögren’s syndrome, or vasculitis, must always be considered.

iMCD-TAFRO

After the concept of TAFRO syndrome was proposed in 2010, cases of TAFRO syndrome in patients with iMCD were reported in 2013, which are now considered iMCD-TAFRO. These patients had an aggressive clinical course with TAFRO symptoms, which made researchers think of classifying iMCD into two subtypes – namely iMCD-TAFRO and iMCD-NOS. Moreover, around the time these cases were initially reported, there was considerable confusion regarding the terminology surrounding TAFRO syndrome as discussed above. To address these issues, Iwaki et al. proposed diagnostic criteria for iMCD-TAFRO in 2016, which required lymph node histopathology with three major criteria and at least one minor clinical criterion.

It must be noted that Masaki et al. and Iwaki et al. proposed criteria for different entities – the former for TAFRO syndrome and the latter for iMCD-TAFRO, which is a part of TAFRO syndrome and a subtype of iMCD. Although there was a consensus among pathologists about Castleman-like lymph node features, there was significant inter-observer variability. To address this, Fajgenbaum et al. proposed the international consensus diagnostic criteria for iMCD in 2017, including a definition of the histopathological lymph node features. Fajgenbaum et al. mentioned TAFRO syndrome and its association with iMCD in their consensus diagnostic criteria, but did not further sub-categorize it due to the lack of
Since then, cases of iMCD-TAFRO have been reported worldwide and more definitive evidence has become available. To update the concept of iMCD-TAFRO, we proposed a new international definition in 2021 based on the context of previous studies and literature review (Table 1).

**VALIDATED INTERNATIONAL DEFINITION OF iMCD-TAFRO**

To establish a new definition, we performed a systematic literature review of iMCD-TAFRO and TAFRO syndrome using PubMed and Japan Medical Abstracts Society databases from its inception to May 2019, and identified 54 cases. We classified these cases into three categories: iMCD-TAFRO (TAFRO syndrome with lymph node histopathology consistent with iMCD), possible iMCD-TAFRO (TAFRO syndrome with no lymph node biopsy performed and no other comorbidities identified), and TAFRO syndrome, not iMCD-TAFRO (TAFRO syndrome with lymph node histopathology not consistent with iMCD or meeting exclusion criteria).

All included cases had thrombocytopenia (T of TAFRO), defined as a platelet level of less than 100,000/µL upon the pre-treatment nadir, anasarca (A), fever > 37.5°C or CRP ≥ 2 mg/dL (F), in addition to organomegaly defined as hepatomegaly, splenomegaly, and/or small volume lymphadenopathy (O). However, renal dysfunction and reticulin fibrosis (R) were only present in approximately 80% of cases. Of these, the majority (77.1%) of patients in cases categorized as iMCD-TAFRO had eGFR < 60 mL/min/1.73 m² and 26.9% underwent hemodialysis therapy during their clinical courses.

### Table 1. International Definition of iMCD-TAFRO in 2021

| 1. Definite iMCD-TAFRO Criteria |
|----------------------------------|
| 1.1 Clinical Criteria (all 4 required) |
| Thrombocytopenia (T): Pre-treatment nadir platelet level ≤ 10 x 10⁴/µL |
| Anasarca (A): Pleural effusion, ascites, or subcutaneous edema on CT |
| Fever or hyperinflammatory status (F): Fever ≥ 37.5°C of unknown etiology or CRP ≥ 2.0 mg/dL |
| Organomegaly (O): Small volume lymphadenopathy in two or more regions, hepatomegaly, or splenomegaly on CT |
| 1.2 Pathological Criteria (required) |
| Lymph node consistent with iMCD: Must be consistent with histopathological features of the International iMCD Diagnostic Criteria |
| In brief, atrophic germinal centers, concentric rings of mantle zone cells, and interfollicular hypervascularization or plasmacytosis. Negative for light chain restriction and HHV-8. |
| 1.3 Exclusion Criteria (required): see below |
| 1.4 Additional Clinical and Pathological Criteria (not required but strongly supportive) |
| Renal insufficiency (R): Pre-treatment eGFR ≤ 60 mL/min/1.73 m², creatinine > 1.1 mg/dL (female)/ > 1.3 mg/dL (male), or renal failure necessitating hemodialysis. |
| TAFRO-consistent bone marrow: Reticulin fibrosis (R) or megakaryocytic hyperplasia, without evidence of an alternative diagnosis |
| Absence of polyclonal hypergamaglobulinemia (immunoglobulin G ≤ 1.2x upper limit of normal by nephelometry) |
| High alkaline phosphatase with mild to no increase in bilirubin and transaminases |

2. Probable iMCD-TAFRO Criteria: All 4 clinical criteria met, but pathological criteria not able to be assessed because no lymph node biopsy was performed or an insufficient specimen was obtained

3. TAFRO syndrome, not iMCD-TAFRO: All 4 clinical criteria met, but lymph node biopsy was not consistent with iMCD OR an exclusion criteria diagnosis was made

### Exclusion Criteria - Must exclude the following diseases

Infectious diseases - including the below but not limited to:
1. HHV-8
2. EBV-associated lymphoproliferative disorders
3. Acute HIV infection
4. Tuberculosis
5. COVID-19 cytokine storm syndrome

Autoimmune/rheumatologic diseases:
1. Systemic lupus erythematosus
2. Sjögren syndrome
3. Rheumatoid arthritis
4. Adult-onset Still disease
5. Juvenile idiopathic arthritis
6. IgG ≥ 3,400 mg/dL (suggestive of autoimmune diseases or plasma cell dyscrasias)
7. Primary hemophagocytic lymphohistiocytosis

Malignancy - including the below but not limited to:
1. Malignant lymphoma
2. Multiple myeloma
3. Metastatic cancer
4. POEMS syndrome

Adapted from Nishimura et al. Abbreviations: CRP, C-reactive protein; CT, computed tomography; eGFR, estimated glomerular filtration rate; HHV-8, human herpesvirus-8.
Reticulin fibrosis and megakaryocyte hyperplasia were found on bone marrow biopsy in 86.5% and 87.5% of cases, respectively. None of the chief laboratory findings, including alkaline phosphatase (ALP), immunoglobulins, lactate dehydrogenase, interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF), were significantly different between the groups. Of note, 44.8% of iMCD-TAFRO patients had a positive antinuclear antibody (ANA) titer of 1:40, and 5 were positive for anti-Sjögren-syndrome-related antigen A (SS-A) antibody without meeting any classification criteria for autoimmune disorders. There were insufficient data to evaluate the usefulness of biopsy from organs other than lymph nodes, but 11 patients who underwent kidney biopsy were included, demonstrating a pattern observed in thrombotic microangiopathy (TMA).

Based on the findings, we determined that the new definition requires at least 4 clinical criteria (T, A, F, O) and pathological criteria (iMCD histopathological features in lymph node), and exclusion criteria. As approximately 20% of patients did not have renal dysfunction or characteristic bone marrow findings (R), we employed an additional clinical criterion, requirement of at least one of these. We further assessed the definition using the ACCELERATE natural history registry cohort established by the Castleman Disease Collaborative Network (CDCN), which included 68 pathology-reviewed, expert-confirmed cases of iMCD to guarantee external validity.

Although our criteria were made rigorous, we also aimed to provide flexibility to some extent for the diagnosis of suspected iMCD-TAFRO or TAFRO syndrome. Thus, our criteria also defined probable iMCD-TAFRO (meets TAFO + one of R and exclusion criteria, but no lymph node biopsy available) and TAFRO syndrome, not iMCD-TAFRO (meets TAFRO, but has one exclusion diagnosis or lymph node is not compatible with iMCD). The current definition and diagnostic criteria for TAFRO syndrome and iMCD-TAFRO are summarized and compared in Table 2.

**CONCLUSION AND FUTURE PERSPECTIVES**

The review went through the up-to-date ideas about the diagnosis of iMCD-TAFRO. Over the past decade, considerable progress has been made in establishing the diagnosis of iMCD-TAFRO in relation to TAFRO syndrome. However, there are still issues to be addressed. First, the identification of appropriate treatment strategies needs to be pursued. Currently, aggressive immunosuppressive or cytotoxic agents and monoclonal antibodies, including rituximab, siltuximab, and tocilizumab, have been used for iMCD-TAFRO. Although advances have been made in thera-

### Table 2. Comparison of iMCD-TAFRO and TAFRO Syndrome Criteria/Definition

| Inclusion Criteria | Exclusion Criteria |
|--------------------|--------------------|
| **Required Histopathological Criteria** | Malignancies | Autoimmune disorders |
| Not specified (noted in minor criteria) | Infectious disorders | Infectious diseases |
| (Mandatory) | POEMS syndrome | - HHV-8, EBV, HIV, TB, COVID-19-CSS |
| Anasarca, including pleural effusion, ascites, and general edema | Cirrhosis | Autoimmune/reumatologic diseases |
| Thrombocytopenia (≤ 10 x 10⁹/µL) | TTP/HUS | - SLE, SJ, RA, AOSD, JIA, IgG ≥ 3,400 mg/dL |
| Systemic inflammation | Progressive renal insufficiency | - ML, MM, metastatic cancer, POEMS syndrome |
| (Need 2 or more) | Renal insufficiency: Pre-treatment eGFR ≤ 60 mL/min/1.73 m², creatinine > 1.1 mg/dL (female)/ > 1.3 mg/dL (male), or renal failure necessitating hemodialysis. | |
| Castleman disease-like features on LN | Absence of polyclonal hypergammaglobulinemia | |
| Reticulin myelofibrosis and/or hyperplasia of megakaryocytes in BM | High ALP with mild to no increase in bilirubin and transaminases | |
| Mild organomegaly | Hyperplasia of megakaryocytes or reticulin fibrosis in BM | |
| Progressive renal insufficiency | | |

Adapted from Nishimura et al.46

Abbreviations: ALP, alkaline phosphatase; AOSD, adult-onset Still disease; BM, bone marrow; COVID-19-CSS, COVID-19 cytokine storm syndrome; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HHV-8, human herpesvirus-8; HIV, human immunodeficiency virus; IgG, immunoglobulin G; JIA, juvenile idiopathic arthritis; LN, lymph node; ML, malignant lymphoma; MM, multiple myeloma; RA, rheumatoid arthritis; SJ, Sjögren syndrome; SLE, systemic lupus erythematosus; TB, tuberculosis; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
peutic choices, there are still patients with a poor response to these therapies and there is no clear difference in the extent of treatment response in iMCD patients with different histopathologies.\textsuperscript{56} Clarification of factors related to treatment response is warranted. Second, significant heterogeneity remains among cases categorized as probable iMCD-TAFRO and TAFRO syndrome. In particular, identifying autoimmune diseases with atypical presentations is clinically challenging but essential to determine long-term follow-up and treatment plans. Advanced biological techniques, such as genomics analysis, need to be further incorporated in iMCD-TAFRO research, as previously applied to iMCD in general.\textsuperscript{57,59}

In conclusion, the review and our validated international definition, the necessity of histopathological analysis, should help resolve the confusion surrounding TAFRO syndrome and iMCD-TAFRO. However, further clarification of therapeutic approaches and classification is needed.

CONFLICT OF INTEREST
None.

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