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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.

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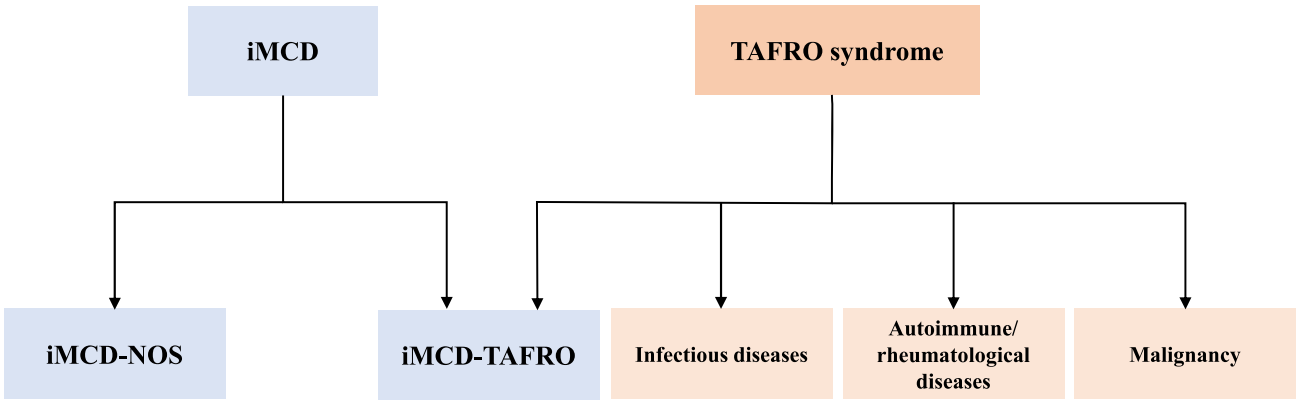

Fig. 1. Concepts of TAFRO syndrome and iMCD-TAFRO
TAFRO syndrome is a constellation of symptoms comprising thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis or renal insufficiency (R), and organomegaly (O), which is a consequence of either iMCD-TAFRO, infectious diseases, autoimmune diseases, or malignancy. The figure conceptualizes the classification of iMCD and causes of TAFRO syndrome. Attention needs to be paid not to confuse TAFRO syndrome and iMCD-TAFRO. Adapted from Nishimura *et al*.[46]
Abbreviations: iMCD-TAFRO, TAFRO clinical subtype of idiopathic multicentric Castleman disease; iMCD-NOS, idiopathic multicentric Castleman disease not otherwise specified.

THE INCEPTION OF TAFRO SYNDROME

As noted above, the initial report of TAFRO syndrome was made in 2010 by Takai *et al*.[1] 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.[3] 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.[4] 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.[27,47-49]

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.[6] 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.[43,50] 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.[44]

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.[42] 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

evidence at the time.

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).[46]

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 m^2 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 10^4/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[42]
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 m^2, 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 hypergammaglobulinemia (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*.[46]
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),[51] 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.[52-55] 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	Required Clinical Criteria	Other Criteria	
Masaki *et al*. for TAFRO syndrome (2020)[4]	Not specified (noted in minor criteria)	(Mandatory) Anasarca, including pleural effusion, ascites, and general edema Thrombocytopenia (≤ 10 x 10^4/μL) Systemic inflammation[42]	(Need 2 or more) Castleman disease-like features on LN Reticulin myelofibrosis and/or hyperplasia of megakaryocytes in BM Mild organomegaly Progressive renal insufficiency	Malignancies Autoimmune disorders Infectious disorders POEMS syndrome Cirrhosis TTP/HUS
Nishimura *et al*. for iMCD-TAFRO (2021)[46]	(Mandatory for definite diagnosis) LN that is consistent with the histopathological features of the International iMCD Diagnostic Criteria[42]	(Mandatory) Thrombocytopenia: Minimum pre-treatment platelet ≤ 10 x 10^4/μL Anasarca (Pleural effusion, ascites, or subcutaneous edema) Fever or hyperinflammatory status: Fever ≥ 37.5°C of unknown etiology or CRP ≥ 2.0 mg/dL Organomegaly: Small volume lymphadenopathy (≤ 2.0 cm) in more than two regions, hepatomegaly, or splenomegaly on CT	(Not required, but contributory) Renal insufficiency: Pre-treatment eGFR ≤ 60 mL/min/1.73 m^2, creatinine > 1.1 mg/dL (female)/ > 1.3 mg/dL (male), or renal failure necessitating hemodialysis. Absence of polyclonal hypergammaglobulinemia (immunoglobulin G ≤ 1.2x upper limit of normal by nephelometry High ALP with mild to no increase in bilirubin and transaminases Hyperplasia of megakaryocytes or reticulin fibrosis in BM	Infectious diseases - HHV-8, EBV, HIV, TB, COVID-19-CSS Autoimmune/rheumatologic diseases - SLE, SjS, RA, AOSD, JIA, IgG ≥ 3,400 mg/dL, HLH Malignancy - ML, MM, metastatic cancer, POEMS syndrome

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; SjS, 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.[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.[57-59]

In conclusion, the review and our validated international definition, highlighting 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.

REFERENCES

1 Takai K, Nikkuni K, Shibuya H, Hashidate H. [Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly]. Rinsho Ketsueki. 2010; 51: 320-325.

2 Kawabata H, Takai K, Kojima M, *et al*. Castleman-Kojima disease (TAFRO syndrome): a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly: a status report and summary of Fukushima (6 June, 2012) and Nagoya meetings (22 September, 2012). J Clin Exp Hematop. 2013; 53: 57-61.

3 Masaki Y, Kawabata H, Takai K, *et al*. Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. Int J Hematol. 2016; 103: 686-692.

4 Masaki Y, Kawabata H, Takai K, *et al*. 2019 Updated diagnostic criteria and disease severity classification for TAFRO syndrome. Int J Hematol. 2020; 111: 155-158.

5 Inoue M, Ankou M, Hua J, *et al*. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after immunosuppressive therapies using corticosteroids and cyclosporin A: a case report. J Clin Exp Hematop. 2013; 53: 95-99.

6 Iwaki N, Sato Y, Takata K, *et al*. Atypical hyaline vascular-type castleman's disease with thrombocytopenia, anasarca, fever, and systemic lymphadenopathy. J Clin Exp Hematop. 2013; 53: 87-93.

7 Masaki Y, Nakajima A, Iwao H, *et al*. Japanese variant of multicentric castleman's disease associated with serositis and thrombocytopenia--a report of two cases: is TAFRO syndrome (Castleman- Kojima disease) a distinct clinicopathological entity? J Clin Exp Hematop. 2013; 53: 79-85.

8 Kubokawa I, Yachie A, Hayakawa A, *et al*. The first report of adolescent TAFRO syndrome, a unique clinicopathologic variant of multicentric Castleman's disease. BMC Pediatr. 2014; 14: 139.

9 Ozawa T, Kosugi S, Kito M, *et al*. [Efficacy of rituximab for TAFRO syndrome, a variant type of multicentric Castleman's disease]. Rinsho Ketsueki. 2014; 55: 350-355.

10 Edahiro Y, Ichikawa K, Sunami Y, Koike M, Komatsu N. [Autoimmune hemolytic anemia in a patient with TAFRO syndrome]. Rinsho Ketsueki. 2015; 56: 2346-2350.

11 Konishi Y, Takahashi S, Nishi K, *et al*. Successful Treatment of TAFRO syndrome, a variant of multicentric Castleman's disease, with cyclosporine A: Possible pathogenetic contribution of interleukin-2. Tohoku J Exp Med. 2015; 236: 289-295.

12 Tatekawa S, Umemura K, Fukuyama R, *et al*. Thalidomide for tocilizumab-resistant ascites with TAFRO syndrome. Clin Case Rep. 2015; 3: 472-478.

13 Fujiwara S, Mochinaga H, Nakata H, *et al*. Successful treatment of TAFRO syndrome, a variant type of multicentric Castleman disease with thrombotic microangiopathy, with anti-IL-6 receptor antibody and steroids. Int J Hematol. 2016; 103: 718-723.

14 Hiramatsu S, Ohmura K, Tsuji H, *et al*. Successful treatment by rituximab in a patient with TAFRO syndrome with cardiomyopathy. Nihon Rinsho Meneki Gakkai Kaishi. 2016; 39: 64-71.

15 Iwanaga N, Harada K, Tsuji Y, *et al*. [TAFRO syndrome with primary Sjogren's syndrome]. Nihon Rinsho Meneki Gakkai Kaishi. 2016; 39: 478-484.

16 Morisawa N, Satoh H, Matsuyama M, *et al*. [Usefulness of the treatment with corticosteroids and ciclosporin A for TAFRO syndrome]. Nihon Naika Gakkai Zasshi. 2016; 105: 2432-2439.

17 Nagai Y, Ando S, Honda N, *et al*. [TAFRO syndrome showing cholangitis on liver biopsy]. Rinsho Ketsueki. 2016; 57: 2490-2495.

18 Nagano M, Matsumoto J. A case of TAFRO syndrome with a large mediastinal mass treated with debulking surgery. Surg Case Rep. 2016; 2: 61.

19 Ohya E, Mizutani M, Sakaguchi H, Sekine T. Diffuse large B-cell lymphoma during corticosteroid therapy for TAFRO syndrome. Intern Med. 2016; 55: 2861-2867.

20 Sakashita K, Murata K, Inagaki Y, Oota S, Takamori M. An anterior mediastinal lesion in TAFRO syndrome showing complete remission after glucocorticoid and tocilizumab therapy. Respirol Case Rep. 2016; 4: e00173.

21 Suzuki K, Nakamura K, Kasuya T, *et al*. [A case of TAFRO syndrome successfully treated with intravenous cyclophosphamide therapy]. Nihon Naika Gakkai Zasshi. 2016; 105: 2417-2425.

22 Tadokoro A, Kanaji N, Hara T, *et al*. An Uncharted Constellation: TAFRO Syndrome. Am J Med. 2016; 129: 938-941.

23 Yamaga Y, Tokuyama K, Kato T, *et al*. Successful treatment with cyclosporin A in tocilizumab-resistant TAFRO syndrome. Intern Med. 2016; 55: 185-190.

24 Yasuda S, Tanaka K, Ichikawa A, *et al*. Aggressive TAFRO syndrome with reversible cardiomyopathy successfully treated with combination chemotherapy. Int J Hematol. 2016; 104: 512-518.

25 Aoki T, Wada M, Kawashima A, *et al*. Tocilizumab-resistant TAFRO syndrome complicated by type II respiratory failure.

Intern Med. 2017; 56: 3249-3254.
26 Fujiki T, Hirasawa S, Watanabe S, Iwamoto S, Ando R. Successful treatment by tocilizumab without steroid in a very severe case of TAFRO syndrome. CEN Case Rep. 2017; 6: 105-110.
27 Fujimoto S, Kawabata H, Kurose N, *et al*. Sjögren's syndrome manifesting as clinicopathological features of TAFRO syndrome. Medicine (Baltimore). 2017; 96: e9220.
28 Ito F, Kameoka Y, Nara M, *et al*. [TAFRO Syndrome with Bilateral Adrenal Hemorrhage]. Nihon Naika Gakkai Zasshi. 2017; 106: 288-294.
29 Kawashima M, Usui T, Okada H, *et al*. TAFRO syndrome: 2 cases and review of the literature. Mod Rheumatol. 2017; 27: 1093-1097.
30 Kikuchi T, Shimizu T, Toyama T, Abe R, Okamoto S. Successful treatment of TAFRO syndrome with tocilizumab, prednisone, and cyclophosphamide. Intern Med. 2017; 56: 2205-2211.
31 Allegra A, Rotondo F, Russo S, *et al*. Castleman–Kojima disease (TAFRO syndrome) in a Caucasian patient: A rare case report and review of the literature. Blood Cells Mol Dis. 2015; 55: 206-207.
32 Hawkins JM, Pillai V. TAFRO syndrome or Castleman-Kojima syndrome: a variant of multicentric Castleman disease. Blood. 2015; 126: 2163.
33 Jain P, Verstovsek S, Loghavi S, *et al*. Durable remission with rituximab in a patient with an unusual variant of Castleman's disease with myelofibrosis-TAFRO syndrome. Am J Hematol. 2015; 90: 1091-1092.
34 Simons M, Apor E, Butera JN, Treaba DO. TAFRO syndrome associated with EBV and successful triple therapy treatment: Case report and review of the literature. Case Rep Hematol. 2016; 2016: 4703608.
35 Alhoulaiby S, Ahmad B, Alrstom A, Kudsi M. Castleman's disease with TAFRO syndrome: a case report from Syria. Oxf Med Case Reports. 2017; 2017: omx021.
36 Behnia F, Elojeimy S, Matesan M, Fajgenbaum DC. Potential value of FDG PET-CT in diagnosis and follow-up of TAFRO syndrome. Ann Hematol. 2017; 96: 497-500.
37 José FF, Kerbauy LN, Perini GF, *et al*. A life-threatening case of TAFRO syndrome with dramatic response to tocilizumab, rituximab, and pulse steroids: The first case report in Latin America. Medicine (Baltimore). 2017; 96: e6271.
38 Louis C, Vijgen S, Samii K, *et al*. TAFRO Syndrome in caucasians: A case report and review of the literature. Front Med (Lausanne). 2017; 4: 149.
39 Morel G, Mootien J, Guiot P, Kuteifan K. Anasarca, fever, thrombocytopenia, organomegaly, and multiorgan failure in a 24-year-old pregnant woman. Case Rep Crit Care. 2017; 2017: 3871593.
40 Islamoğlu Z, Duman AE, Sirin G, *et al*. TAFRO syndrome: A case report from Turkey and review of the literature. Int J Hematol Oncol Stem Cell Res. 2018; 12: 253-259.
41 Owattanapanich W, Pholmoo W, Pongpruttipan T, Siritanaratkul N. High proportion of TAFRO syndrome in Thai adult Castleman's disease patients: a 10-year experience. Ann Hematol. 2018; 97: 1019-1026.
42 Fajgenbaum DC, Uldrick TS, Bagg A, *et al*. International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease. Blood. 2017; 129: 1646-1657.
43 Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. Blood. 2020; 135: 1353-1364.
44 Iwaki N, Fajgenbaum DC, Nabel CS, *et al*. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. Am J Hematol. 2016; 91: 220-226.
45 Sakashita K, Murata K, Takamori M. TAFRO syndrome: current perspectives. J Blood Med. 2018; 9: 15-23.
46 Nishimura Y, Fajgenbaum DC, Pierson SK, *et al*. Validated international definition of the thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease. Am J Hematol. 2021; 96: 1241-1252.
47 Tokunaga M, Yamada M, Yoshikawa S, *et al*. [Systemic lupus erythematosus with marked eosinophilia and clinical features mimicking TAFRO syndrome]. Rinsho Ketsueki. 2018; 59: 688-694.
48 Oka K, Yamane M, Yokota Y, *et al*. Disseminated Mycobacterium genavense infection mimicking TAFRO syndrome. J Infect Chemother. 2020; 26: 1095-1099.
49 Hasegawa E, Sato H, Wada Y, *et al*. Characterization of patients with systemic lupus erythematosus who meet the diagnostic criteria for TAFRO syndrome. Lupus. 2018; 27: 417-427.
50 Wang HW, Pittaluga S, Jaffe ES. Multicentric Castleman disease: Where are we now? Semin Diagn Pathol. 2016; 33: 294-306.
51 Pierson SK, Khor JS, Ziglar J, *et al*. ACCELERATE: A patient-powered natural history study design enabling clinical and therapeutic discoveries in a rare disorder. Cell Rep Med. 2020; 1: 100158.
52 Fujimoto S, Kawabata H, Sakai T, *et al*. Optimal treatments for TAFRO syndrome: a retrospective surveillance study in Japan. Int J Hematol. 2021; 113: 73-80.
53 Nishimura Y, Hanayama Y, Fujii N, Kondo E, Otsuka F. Comparison of the clinical characteristics of TAFRO syndrome and idiopathic multicentric Castleman disease in general internal medicine: a 6-year retrospective study. Intern Med J. 2020; 50: 184-191.
54 Akiyama M, Kaneko Y, Takeuchi T. Tocilizumab for the treatment of TAFRO syndrome: a systematic literature review. Ann Hematol. 2020; 99: 2463-2475.
55 Carbone A, Borok M, Damania B, *et al*. Castleman disease. Nat Rev Dis Primers. 2021; 7: 84.
56 Fajgenbaum DC, Wu D, Goodman A, *et al*. Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease. Am J Hematol. 2020; 95: 1553-1561.
57 Yoshimi A, Trippett TM, Zhang N, *et al*. Genetic basis for iMCD-TAFRO. Oncogene. 2020; 39: 3218-3225.
58 Arenas DJ, Floess K, Kobrin D, *et al*. Increased mTOR activation in idiopathic multicentric Castleman disease. Blood. 2020; 135: 1673-1684.
59 Butzmann A, Kumar J, Sridhar K, Gollapudi S, Ohgami RS. A review of genetic abnormalities in unicentric and multicentric Castleman disease. Biology (Basel). 2021; 10: 251.