Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9622-22
Intern Med 62: 27-32, 2023
http://internmed.jp

【 REVIEW ARTICLE 】

TAFRO Syndrome: A Disease Requiring Immediate Medical Attention

Yasufumi Masaki[1], Yusuke Ueda[1], Hiroto Yanagisawa[1], Kotaro Arita[1], Tomoyuki Sakai[1], Kazunori Yamada[1], Shuichi Mizuta[1], Toshihiro Fukushima[1], Kazue Takai[2], Sadao Aoki[3] and Hiroshi Kawabata[4]

Abstract:
TAFRO syndrome was first described in 2010, standing for thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly. Because the lymph node histopathology of TAFRO syndrome mimics idiopathic multicentric Castleman disease (iMCD), some researchers consider TAFRO syndrome to be a subtype of iMCD. However, the clinical features of TAFRO syndrome considerably differ from those of iMCD without TAFRO. The clinical features of patients with TAFRO syndrome with or without iMCD-histopathology are similar, and these patients require an accurate diagnosis and urgent treatment. Although a histological diagnosis, including a differential diagnosis, is important, lymph node involvement in patients with TAFRO syndrome is usually modest or sometimes absent. Furthermore, a bleeding tendency due to thrombocytopenia and severe anasarca hampers performing a biopsy. Nonetheless, patients with various other disorders may manifest TAFRO syndrome-like symptoms, making the differential diagnosis in borderline cases difficult. Therefore, the establishment of precise and specific biomarkers is important.

Key words: idiopathic multicentric Castleman disease, POEMS syndrome, interleukin-6, tocilizumab, rituximab, cyclosporin A

(Intern Med 62: 27-32, 2023)
(DOI: 10.2169/internalmedicine.9622-22)

1. TAFRO Syndrome

TAFRO syndrome was first described by Takai et al. in 2010 (1). They reported three cases of thrombocytopenia associated with a fever, anasarca, hepatosplenomegaly and reticulin myelofibrosis in the bone marrow and proposed a new disease concept. TAFRO is an acronym of the disease symptoms thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly. Since its initial description, a number of similar cases have been reported, prompting a meeting by researchers and clinicians (2).

The onset of TAFRO syndrome in most cases is acute, and its progression is rapid and fatal without urgent treatment. However, the number of cured cases has been increasing recently due to prompt, early treatment. The histopathological diagnoses of lymph node in TAFRO cases are mixed-type, plasma cell (PC)-type or hypervascular-type Castleman disease (CD) (3).

In an epidemiological analysis of TAFRO syndrome, we investigated the prevalence and incidence rates of TAFRO syndrome in Japan using a fixed-point observation method based on the incidence in Ishikawa Prefecture, a relatively rural area with a stable population where few of the 1,140,000 residents have transferred into or out of the area (4). Annual incidences of TAFRO syndrome in Japan were estimated to be between 110 and 502 new cases, yielding national annual incidence rates per million individuals of 0.9 to 4.9 and nationwide prevalences of 860 to 7,240. The Research Group on Castleman Disease, sponsored by the

[1]Department of Hematology and Immunology, Medicine, Kanazawa Medical University, Japan, [2]Department of Hematology, Niigata City General Hospital, Japan, [3]Department of Pathophysiology, Faculty of Pharmaceutical Sciences, Niigata University of Pharmacy and Applied Life Sciences, Japan and [4]Department of Hematology, National Hospital Organization Kyoto Medical Center, Japan
Received: February 18, 2022; Accepted: April 3, 2022; Advance Publication by J-STAGE: May 21, 2022
Correspondence to Dr. Yasufumi Masaki, yasum@kanazawa-med.ac.jp

Ministry of Health, Labor and Welfare of Japan, had previously estimated that the prevalence was 150 patients based on data from a multicenter collaborative retrospective study establishing the concept of TAFRO syndrome (UMIN 000011809); TAFRO syndrome was thus suspected not to be as rare as previously assumed. Because TAFRO syndrome is a relatively new concept, its diagnosis was difficult or impossible before 2010, but the situation is gradually changing.

In 2015, the Ministry of Health, Labour and Welfare of Japan organized and funded (through Health and Labour Sciences Research Grants for Research on Rare and Intractable Diseases) a nationwide research team for TAFRO syndrome [H27-Nanchi, etc. (Nan)-General-008]. Since then, research on this disorder has progressed. Members of the TAFRO research group, including hematologists, rheumatologists, pulmonologists, pathologists, radiologists, and basic researchers, have attended meetings to discuss and devise diagnostic criteria, disease severity classifications, and disease treatment strategies for TAFRO syndrome, based on reported cases, including patients with the disease and those registered in retrospective studies (5, 6).

According to the 2019 diagnostic criteria (6), there are three major symptom categories, including 1) anasarca, including pleural effusion, ascites and general edema; 2) thrombocytopenia, defined as pretreatment platelet count ≤100,000/μL; and 3) systemic inflammation, defined as a fever of unknown etiology >37.5°C and/or serum C-reactive protein concentration ≥2 mg/dL; and 4 minor symptom categories, including 1) CD-like features on a lymph node biopsy; 2) reticulin myelofibrosis and/or an increased number of megakaryocytes in bone marrow; 3) mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy; and 4) progressive renal insufficiency (Table). A diagnosis of TAFRO syndrome requires patients fulfill all three major categories and at least two of the four minor categories. Furthermore, as it is essential to exclude malignancies, including lymphoma, a lymph node biopsy, if applicable, is strongly recommended.

However, Iwaki et al. proposed another criterion for idiopathic multicentric CD (iMCD)-TAFRO, which essentially requires histopathological findings from the lymph nodes (7), and their group consequently updated the criteria (8). Like many diseases, it is impossible to completely exclude mimickers by clinical findings alone. However, in patients with TAFRO syndrome, lymph node involvement is usually modest or sometimes absent, and a bleeding tendency due to thrombocytopenia and severe anasarca can make biopsies difficult. Furthermore, most cases are severe, requiring urgent initiation of appropriate treatment. Since we must start treatment early for such cases, the lymph node histology is considered a minor category in our diagnostic criteria (5, 6). In addition, whether or not very small lymph nodes reliably indicate pathophysiology in this condition is dubious at present.

To assess the disease severity, up to three points are assigned to each of four items: anasarca (including pleural effusion and ascites), thrombocytopenia, fever/inflammation, and renal insufficiency. Disease severity is classified based on the total score as mild (grade 1) for 0 to 4, moderate (grade 2) for 5 or 6, slightly severe (grade 3) for 7 or 8, severe (grade 4) for 9 or 10, and very severe (grade 5) for 11 or 12 (Table) (6). According to a retrospective analysis, cases classified as very severe (grade 5) have a significantly worse prognosis than those with other classifications (grades 1 to 4), so starting appropriate treatment in patients to prevent progression to grade 5 severity is important. Furthermore, based on our experience, this disease severity classification can also be used as a disease activity score.

We determined appropriate treatment strategies based on a retrospective analysis, case reports, and our own experience, so the evidence level is not high at present, and the further collection and assessment of data from retrospective and prospective studies is necessary. Most TAFRO syndrome cases show severe illness at the disease onset and at an early phase, so high-dose steroids or pulse therapy is administered; however, only a small proportion of cases can be cured by steroid therapy alone. Thus, most cases require second-line treatment, such as tocilizumab, rituximab, and cyclosporin A. In addition, various immunosuppressive therapies or anticancer chemotherapies have been attempted, with sporadic reports published. However, no medicine has yet been approved by the healthcare insurance system in Japan. Further evidence should thus be collected to achieve accreditation of such medicines for their use in treating TAFRO syndrome.

2. iMCD

CD came to be known due to a report by Benjamin Castleman, a famous pathologist, who described cases of mediastinal tumor with particular pathological findings in 1956 (9). His report described lymphoid follicle hyperplasia with hyalinized vessels penetrating to the germinal center. These findings were termed hyaline-vascular (HV)-type or giant lymph node hyperplasia. The PC type was identified next, involving plasma cell expansion of an intrafollicular area of the lymph node, followed by the mixed type, which involves characteristics of both the HV and PC types. These types were recognized as subgroups of the disease entity by Frizzera et al. (10). Furthermore, the hypervascular type and plasmablastic type were recently added to the histopathological classification of CD (11). In clinical practice, CD is classified as having either a single lesion [unicentric CD (UCD)] or multiple lesions [multicentric CD (MCD)]. Most cases of UCD have HV histopathology (HV-UCD) with no systemic symptoms and are curable by resection, making HV-UCD a distinct clinical entity. In contrast, MCD cases show PC or mixed histopathology and demonstrate various clinical symptoms and courses.

Most MCD cases in Western countries are human immunodeficiency virus (HIV) infection [acquired immunodefi-

Table. The Diagnostic Criteria and Disease Severity Classification for TAFRO Syndrome.

1. The 2019 updated diagnostic criteria for TAFRO syndrome, as determined by All Japan TAFRO Syndrome Research Group in the Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan. Revised from Ref.6, Table 1.

Diagnostic criteria of TAFRO syndrome

・A diagnosis of TAFRO syndrome requires all three major categories and at least two of four minor categories.

A. Major categories

1) Anasarca, including pleural effusion, ascites and general edema

2) Thrombocytopenia; platelet count ≤100,000/μL, without myelosuppressive treatment.

3) Systemic inflammation, defined as fever of unknown etiology above 37.5℃ and/or serum C-reactive protein concentration ≥2 mg/dL.

B. Minor categories

1) Castleman disease-like features on lymph node biopsy

2) Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow

3) Mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy

4) Progressive renal insufficiency

C. Diseases to be excluded

1) Malignancies, including lymphoma, myeloma, mesothelioma, *et cetera*.

2) Autoimmune disorders, including systemic lupus erythematosus (SLE), Sjögren's syndrome, ANCA-associated vasculitis, *et cetera*.

3) Infectious disorders, including acid fast bacterial infection, rickettsial disease, Lyme disease, severe fever with thrombocytopenia syndrome (SFTS), *et cetera*.

4) POEMS syndrome

5) Hepatic cirrhosis

6) Thrombotic thrombocytopenic purpura (TTP)/ hemolytic uremic syndrome (HUS).

2. The 2019 updated disease severity classification for TAFRO syndrome.

Total points are calculated by summing up the points of present symptoms.

1) Anasarca: three points maximum

One point for pleural effusion on imaging

One point for ascites on imaging

One point for pitting edema on physical examination

2) Thrombocytopenia: three points maximum

One point for lowest platelet counts <100,000/μL

Two points for lowest platelet counts <50,000/μL

Three points for lowest platelet counts <10,000/μL

3) Fever and/or inflammation: three points maximum

One point for fever ≥37.5℃ but <38.0℃ or for CRP ≥2 mg/dL but <10 mg/dL

Two points for fever ≥38.0℃ but <39.0℃ or for CRP ≥10 mg/dL but <20 mg/dL

Three points for fever ≥39.0℃ or for CRP ≥20 mg/dL

4) Renal insufficiency: three points maximum

One point for GFR <60 mL/min/1.73 m^2

Two point for GFR <30 mL/min/1.73 m^2

Three points for GFR <15 mL/min/1.73 m^2 or in need of hemodialysis

Relationship between score and disease severity

0-4 points:	mild	(grade 1)
5-6 points:	moderate	(grade 2)
7-8 points:	slightly severe	(grade 3)
9-10 points:	severe	(grade 4)
11-12 points:	very severe	(grade 5)

ciency syndrome (AIDS)]-related. Most HIV-positive MCD cases are also human herpes virus (HHV)-8 positive, wherein viral interleukin-6 (IL-6) expression causes various symptoms. Hyper-IL-6-nemia causes plasma cell expansion and polyclonal hypergammaglobulinemia by B-cell differentiation, vasculogenesis by vascular endothelial growth factor (VEGF) production, and thrombocytosis by acceleration of megakaryocyte differentiation in the bone marrow. Furthermore, in the liver, the production of acute inflammation proteins, such as C-reactive protein (CRP), fibrinogen, serum amyloid A, and hepcidin, are increased, causing microcytic anemia via the inhibition of iron absorption in the gastroin-

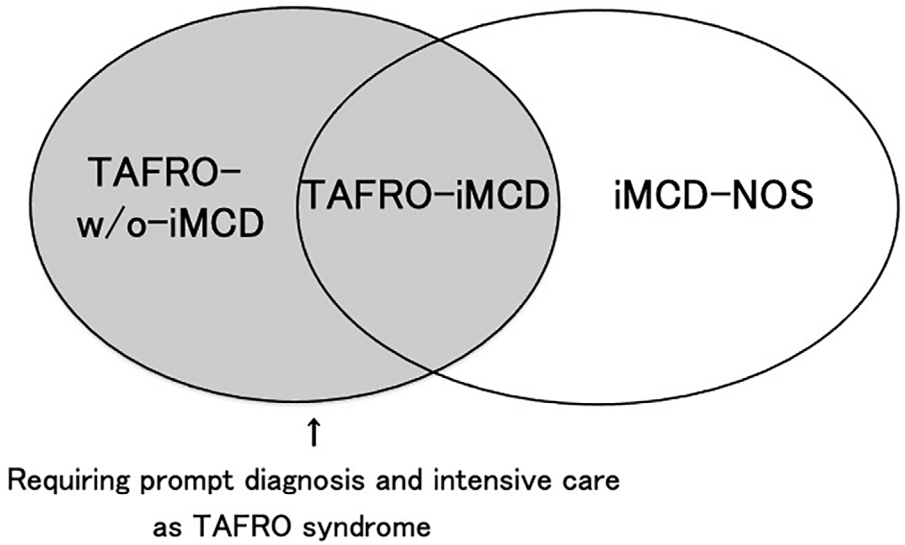

Figure. **Correlation between TAFRO syndrome and iMCD. In clinical practice, TAFRO-w/o-iMCD and TAFRO-iMCD are the same entity, requiring an early diagnosis and early treatment. iMCD-NOS differs in that it shows a slow chronic progress, requiring less-urgent treatment. TAFRO: thrombocytopenia (T), anasarca (A), fevers (F), reticulin myelofibrosis (R), organomegaly (O), w/o: without, NOS: not otherwise specified, iMCD: idiopathic multicentric Castleman disease**

testinal tract and reduction of iron recycling in reticuloendothelial systems. In contrast, most Japanese MCD cases have neither HIV nor HHV-8 (12, 13). Despite differences in positivity for HIV and HHV-8, both Western and Japanese MCD cases commonly have systemic symptoms of polyclonal hypergammaglobulinemia, marked inflammation, a fever, anemia, and thrombocytosis due to hyper-IL-6-nemia. Western MCD patients are often complicated with various infections, or neoplasms, such as Kaposi's sarcoma and lymphoma, and have acute, lethal clinical courses. Japanese MCD patients generally have indolent clinical courses and rarely develop Kaposi's sarcoma or lymphoma (14). Kojima et al. reported that Japanese MCD cases had significantly better prognoses than Western cases (13, 14). In 2014, Fajgenbaum et al. collected clinical reported data of MCD cases from the US, over half of which were HHV-8-negative, and assigned the name idiopathic MCD (iMCD) to HHV-8-negative cases (15, 16). Therefore, most Japanese MCD cases are iMCD.

The diagnostic criteria were independently proposed by both Japan and the US. In Japan, the group sponsored by the Ministry of Health, Labour and Welfare of Japan, through Health and Labour Sciences Research Grants for Research on Rare and Intractable Diseases, proposed a reference guideline for medical care of CD patients (17), including tentative diagnostic criteria and a disease severity classification scale [CRP, hemoglobin, albumin, and performance status (CHAP) score] (18). In the US, international diagnostic criteria for HHV-8-negative/iMCD were proposed by the Castleman Disease Collaborative Network (CDCN) (10). The requirements of lymphadenopathy and pathological findings are common to the Japanese and US criteria. As laboratory findings in minor items required by USA criteria seem lax, further international discussion is required.

3. Differences between TAFRO Syndrome and iMCD

Because the histopathology of TAFRO syndrome mimics iMCD, some researchers consider TAFRO syndrome to be a unique subtype of iMCD. However, the clinical features of TAFRO syndrome differ from those of iMCD. Patients with iMCD typically demonstrate polyclonal hypergammopathy, multiple lymphadenopathy, severe inflammation, microcytic anemia, and thrombocytosis, and most Japanese iMCD cases have chromic and indolent clinical courses. In contrast, patients with TAFRO syndrome demonstrate normo- or hypogammaglobulinemia, small or unclear lymphadenopathy, thrombocytopenia, and severe pleural effusion and ascites, and their disease onset is acute followed by a rapid clinical course.

We retrospectively analyzed the clinical data of patients with clinical TAFRO syndrome without iMCD-histopathology (TAFRO-w/o-iMCD), patients with clinical TAFRO symptoms and iMCD-histopathology (TAFRO-iMCD) and patients with iMCD not otherwise specified, without clinical TAFRO symptoms (iMCD-NOS). The clinical features of TAFRO-iMCD cases and TAFRO-w/o-iMCD cases were similar in both groups requiring urgent treatment but differed from those of iMCD-NOS cases with relatively chronic and indolent clinical courses (Figure) (19).

Patients with various states of chronic inflammation may show MCD-like clinical features, such as a fever, anemia, thrombocytosis, and polyclonal hypergammopathy associated with hypercytokinemia. In such cases, lymph node histology may demonstrate non-monoclonality (exclude lymphoma),

particular lymphoid follicles, and plasmacytosis, and have often been diagnosed as "undeniable iMCD." These cases might include patients with TAFRO syndrome, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities) syndrome, IgG4-related disease, or various other infections, including tuberculosis and other mycobacterium infections, autoimmune disease/vasculitis syndrome, and satellite lymph nodes of malignant neoplasms. Even in cases with a pathological diagnosis of iMCD, we must consider differential diagnoses in those with uncommon clinical symptoms.

Our Japanese research teams for TAFRO syndrome and MCD combined in 2017. We are continuing to conduct research and hold discussions in our quest to optimize the diagnosis and treatment strategies for not only TAFRO syndrome and iMCD but other similar conditions, such as IgG4-related disease and POEMS syndrome.

4. Other Related Disorders

Patients with other disorders may demonstrate TAFRO syndrome-like symptoms and iMCD-like lymph node histopathology, so a differential diagnosis is essential (20). POEMS syndrome [Crow-Fukase syndrome, Takatsuki disease, PEP (plasma cell dyscrasia, endocrinopathy, polyneuropathy)] is a polyneuropathy associated with elevated VEGF and dysgammaglobulinemia. Patients with POEMS syndrome may have a high fever and various symptoms as well as iMCD-like histopathology of the lymph nodes. In cases with severe neuropathic symptoms, POEMS syndrome is particularly strongly suspected. Furthermore, patients with some lymphomas (T-cell lymphoma and intravascular large B-cell lymphoma), other cancers, sarcoidosis, various infections (e.g. tuberculosis), and collagen-vascular disorders (systemic lupus erythematosus, vasculitis syndrome, Sjogren's syndrome) may have hyper-IL-6 syndrome and demonstrate TAFRO syndrome-like symptoms. In such cases, we sometimes encounter an iMCD-like histopathology if the satellite lymph node is excised via a biopsy. A diagnosis of TAFRO syndrome should be made after careful differentiation. However, the differential diagnosis is sometimes very difficult in such borderline cases, so the establishment of precise and specific biomarkers is important.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This study was supported in part by grants from Ministry of Health, Labor and Welfare, Japan (H29 Nanchi, etc. (Nan)-General-019, H27-28 Nanchi, etc. (Nan)-General-002 and -008), and Japanese Ministry of Education, Culture, Sports, Science and Technology (Grant Nos. 17591060 and 15K09510), Kanazawa Medical University Research Foundation (Grant Nos. S2004-16 and S2007-5), Grant for Assist KAKEN from Kanazawa Medical University (Grant No. K2011-7), Grant for Project Research from High-Tech Research Center of Kanazawa Medical University (Grant No. H2011-11) and Grant for Alumni Research (A) from Kanazawa Medical University (AR2012-06).

Acknowledgments

We thank all participants from the Japan, Ministry of Health, Labor, and Welfare (MHLW) TAFRO syndrome Team and Castleman Disease Team for their help and critical discussion. We would also like to thank David Price for the English language editing.

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 **51**: 320-325, 2010 (in Japanese).
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 **53**: 57-61, 2013.
3. Kurose N, Futatsuya C, Mizutani KI, et al. The clinicopathological comparison among nodal cases of idiopathic multicentric Castleman disease with and without TAFRO syndrome. Hum Pathol **77**: 130-138, 2018.
4. Masaki Y, Kawabata H, Fujimoto S, et al. Epidemiological analysis of multicentric and unicentric Castleman disease and TAFRO syndrome in Japan. J Clin Exp Hematopathol **59**: 175-178, 2019.
5. 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 **103**: 686-692, 2016.
6. Masaki Y, Kawabata H, Takai K, et al. 2019 updated diagnostic criteria and disease severity classification for TAFRO syndrome. Int J Hematol **111**: 155-158, 2020.
7. 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 **91**: 220-226, 2016.
8. 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 **96**: 1241-1252, 2021.
9. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling lymphoma. Cancer **9**: 822-830, 1956.
10. Frizzera G. Castleman's disease and related disorders. Semin Diagn Pathol **5**: 346-364, 1988.
11. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood **129**: 1646-1657, 2017.
12. Suda T, Katano H, Delsol G, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castlman's disease. Pathol Int **51**: 671-679, 2001.
13. Kojima M, Nakamura N, Tsukamoto N, et al. Clinical implications of idiopathic multicentric Castleman disease among Japanese. A report of 28 cases. Int J Surg Pathol **16**: 391-398, 2008.
14. Kojima M, Nakamura S, Shimizu K, et al. Clinical implication of idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia. A report of 16 cases. Int J Surg Pathol **12**: 25-30, 2004.

15. Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. Blood **123**: 2924-2933, 2014.
16. Yu L, Tu M, Cortes J, et al. Clinical and pathological characteristics of HIV- and HHV8-negative Castleman disease. Blood **129**: 1658-1668, 2017.
17. Yoshizaki K. A reference guide for management of Castleman disease. Rinsho Ketsueki **58**: 97-107, 2017 (in Japanese).
18. Fujimoto S, Koga T, Kawakami A, et al. Tentative diagnostic criteria and disease severity classification for Castleman disease: a report of the research group on Castleman disease in Japan. Mod Rheumatol **28**: 161-167, 2018.
19. Fujimoto S, Sakai T, Kawabata H, et al. Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease? Am J Hematol **94**: 975-983, 2019.
20. Masaki Y, Arita K, Sakai T, Takai K, Aoki S, Kawabata H. Castleman disease and TAFRO syndrome. Ann Hematol **101**: 485-490, 2022.