

Case report

Fatal case of TAFRO syndrome with unilateral adrenal hemorrhage in early-stage disease

Tomoya Okamoto,¹⁾ Shinichi Ochi,¹⁾ Yuki Motokawa,²⁾ Hidekazu Azumi,¹⁾ Shinya Kobayashi,¹⁾ Fumihiko Nakamura,³⁾ Toshiya Nakatani,²⁾ Hideo Yagi¹⁾

Thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly comprise TAFRO syndrome, which was proposed as a distinct clinical entity from iMCD without TAFRO syndrome (iMCD-NOS) due to its aggressive clinical course, refractoriness to corticosteroids, presence of thrombocytopenia, increased level of alkaline phosphatase, and normal level of gammaglobulin. However, diagnosing TAFRO syndrome in its early stages is challenging because it is rare and its diagnostic criteria are complicated. We describe a patient with TAFRO syndrome and adrenal hemorrhage who demonstrated a rapid decline in her clinical condition and did not respond to steroid pulse therapy, resulting in a fatal outcome. In the early stage of her clinical course, she developed unilateral adrenal hemorrhage with mild thrombocytopenia and normal clotting times, suggesting adrenal hemorrhage as a unique manifestation of TAFRO syndrome. In general, patients with TAFRO syndrome exhibit a more aggressive clinical course and poorer outcome than those with iMCD-NOS. To ameliorate this poor prognosis, it is important to diagnose the disease early and immediately start powerful immunosuppressive agents such as tocilizumab. Based on this case, adrenal hemorrhage may suggest TAFRO syndrome, and facilitate the rapid diagnosis of this complicated and rare disease.

Keywords: TAFRO, iMCD, adrenal hemorrhage

INTRODUCTION

Castleman's disease (CD), first described by Castleman *et al.* in 1954, is a rare lymphoproliferative disorder characterized by systemic inflammation and multiple lymphadenopathy.¹ CD comprises three different variants with several common histopathological features. Unicentric CD is localized to a single region of lymph nodes. Multicentric CD (MCD) manifests with systemic inflammatory symptoms, such as multiple regions of lymphadenopathy and organ insufficiency, caused by the overexpression of cytokines, mainly interleukin-6 (IL-6).² Human herpesvirus 8 (HHV8) was identified as a major cause of MCD in immunocompromised patients infected with human immunodeficiency virus (HIV). However, the majority of patients with MCD are HIV- and HHV-8-negative, and are defined as having idiopathic MCD (iMCD). The etiology of iMCD is thought to be proinflammatory hypercytokinemia with several potential causes, including viruses (other than HHV8), inflammation,


and neoplastic disease.³ In 2010, Takai *et al.*⁴ proposed a new variant of iMCD characterized by thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly, and termed this condition TAFRO syndrome. After this publication, many similar patients with TAFRO syndrome were reported, and Masaki *et al.* newly proposed diagnostic criteria based on the clinical manifestations and laboratory findings in 2016.⁵ Simultaneously, Iwaki *et al.* proposed diagnostic criteria for TAFRO syndrome with iMCD histology and divided iMCD into two categories, iMCD, not otherwise specified (iMCD-NOS) and TAFRO syndrome with iMCD (TAFRO-iMCD) because of its heterogeneous clinical features.⁶ It was recently reported that patients with TAFRO syndrome exhibit a more aggressive clinical course and greater refractoriness to corticosteroids than those with iMCD-NOS.^{7,8} Furthermore, they have thrombocytopenia, increased levels of alkaline phosphatase (ALP), and normal levels of gammaglobulin. These clinical manifestations suggested that TAFRO-iMCD and iMCD-NOS should be con-

Received: December 24, 2020. Revised: March 13, 2021. Accepted: March 21, 2021. Online Published: June 5, 2021
DOI: 10.3960/jslrt.20065

¹⁾Department of Oncology and Hematology, Nara Prefecture General Medical Center, Nara, Japan, ²⁾Department of Gastroenterology, Nara Prefecture General Medical Center, Nara, Japan, ³⁾Department of Clinical Laboratory, Nara Prefecture General Medical Center, Nara, Japan

Corresponding author: Hideo Yagi, M.D., Department of Oncology and Hematology, Nara Prefecture General Medical Center, 2-897-5 Nanajyo-nishimachi, Nara City, Nara, 630-8581, Japan. E-mail: hyagi@nike.eonet.ne.jp

Copyright © 2021 The Japanese Society for Lymphoreticular Tissue Research

 This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

sidered as distinct clinical entities.

We describe a patient with TAFRO syndrome and adrenal hemorrhage who demonstrated rapid deterioration of her clinical condition and failed to respond to steroid pulse therapy, resulting in a fatal outcome. This case suggested that adrenal hemorrhage is a unique manifestation of TAFRO syndrome and that early initiation of powerful immunosuppressive drugs, such as tocilizumab, a humanized monoclonal antibody that inhibits the binding of IL-6 to its receptors, is required for better outcomes.

CASE REPORT

A 70-year-old Japanese woman with no significant medical history was referred to our hospital with a 1-week history of fever, right quadrant abdominal pain, general malaise, and facial edema. At the time of presentation, her body temperature was 38.5°C and her arterial blood pressure was normal. Physical examination elicited right quadrant abdominal pain and facial edema was observed. Laboratory data were as follows: white blood cell count, 7,000/ μ L; hemoglobin (Hb), 12.3 g/dL; platelet count, 147×10^9 /L; prothrombin time, 14.2 s (10.5–12.9 s); partial thromboplastin time, 37.9 s (24–39 s); fibrin degradation products, 29 mg/ml; serum total protein, 5.3 g/dL; albumin, 2.3 g/dL; BUN, 11.4 mg/dL; creatinine, 0.77 mg/dL; aspartate aminotransferase, 20 U/L; alanine aminotransferase, 21 U/L; lactate dehydrogenase, 187 U/L; ALP, 726 U/L; γ -glutamyl transpeptidase (GTP), 118 U/L; total bilirubin, 0.85 mg/dL; Na, 140 mEq/L; K, 3.4 mEq/L; and Cl, 104 mEq/L. The level of serum C-reactive protein (CRP) was 21.33 mg/dL. Blood cultures were negative. Computed tomography (CT) revealed bilateral pleural effusion, a gallstone, and edematous thickening of the gallbladder wall. As these findings suggested cholecystitis, we started treatment with cefoperazone/sulbactam, but there was no improvement after 1 week. Additional examination revealed the following: anti-nuclear antibody, 80; anti-DNA antibodies, < 2.0; anti-RNP antibodies, negative; anti-Sm antibodies, negative; anti-SS-A antibodies, negative; anti-SS-B antibodies, negative; anti-Jo-1 antibodies, negative; anti-centromere antibodies, < 5.0; anti-aminoacyl tRNA synthetase antibodies, < 5.0; IgG, 1248 mg/dl; IgA, 117 mg/dl; IgM, 47 mg/dl;

C3, 75 mg/dl; C4, 12 mg/dl; CH50, 17.6 U/ml; PR3-ANCA and MPO-ANCA, negative; soluble IL-2 receptor, 2180 U/ml; and IL-6, 28.9 pg/ml. There was no evidence of infection caused by hepatitis B virus, hepatitis C virus, cytomegalovirus, Epstein-Barr virus, or HIV. No monoclonal paraproteins were found on serum or urinary protein electrophoresis.

The patient's right quadrant abdominal pain worsened on day 11 after admission. Contrast CT revealed slightly enlarged deep lymph nodes, bilateral pleural effusion, and right adrenal hemorrhage (Fig. 1). All laboratory parameters deteriorated since admission, and the patient demonstrated leukocytosis (19,400/ μ L), anemia (Hb 10 g/dl), thrombocytopenia (105×10^9 /L), and high levels of γ -GTP (94 U/L), ALP (690 U/L), and CRP (21.26 mg/dl). On day 16 after admission, we performed bone marrow aspiration and biopsy, and excluded the possibility of myelodysplastic syndrome by the absence of dysplasia, and blood cell maturation and differentiation. Furthermore, G-banding analysis demonstrated a normal karyotype. Pathological examination revealed bone marrow fibrosis classified as MF-1, and increased numbers of megakaryocytes with slight dysplasia and plasma cells (Fig. 2). Based on these clinical findings, biochemical laboratory data, and histopathological results, the patient was diagnosed with TAFRO syndrome according to the 2019 updated diagnostic criteria.⁹ In accordance with the therapeutic guidelines for this syndrome, we immediately started steroid pulse therapy, but the bilateral pleural effusion rapidly exacerbated, resulting in respiratory failure. Subsequently, her renal function quickly deteriorated and she died on day 26 after admission. (Fig. 3)

DISCUSSION

TAFRO syndrome is currently categorized as a variant of iMCD because lymph nodes in the two conditions share similar pathological features, such as interfollicular vascular proliferation with slight regression and atrophy of the lymphoid follicles. Although their histopathology is similar, TAFRO syndrome is distinguished from iMCD by several clinical findings. Thrombocytopenia, mild lymphadenopathy, high ALP level, normal immunoglobulin level, and anasarca are

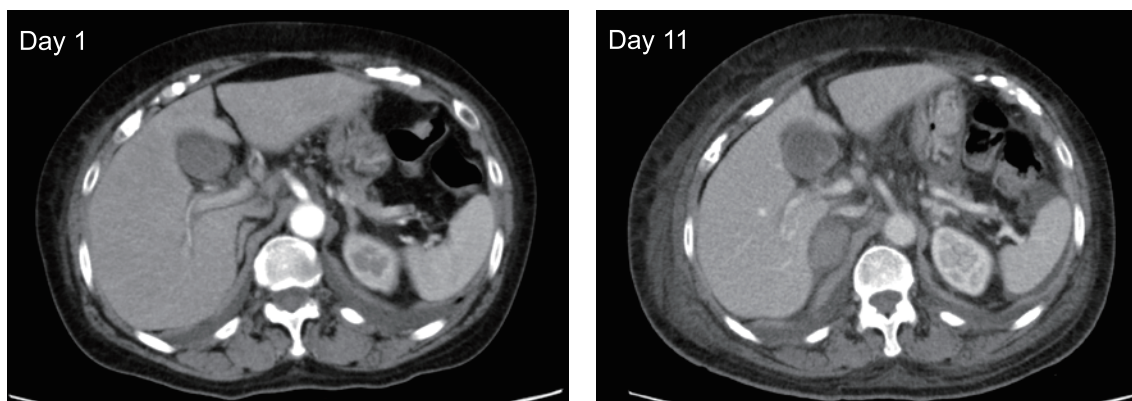


Fig. 1. Abdominal contrast-enhanced computed tomography (CT). Unilateral adrenal hemorrhage was detected in the right adrenal gland on day 11.

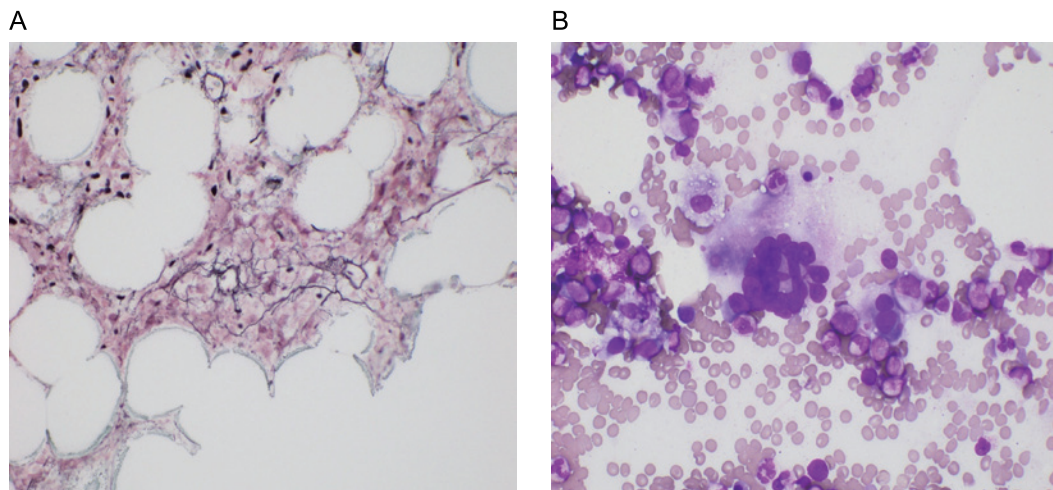


Fig. 2. Bone marrow biopsy on day 16. (A) Gomori ($\times 200$) staining of the bone marrow biopsy specimen. Bone marrow fibrosis was classified as MF-1. (B) Wright ($\times 200$) staining of a bone marrow smear. Increasing numbers of megakaryocytes with slight dysplasia and plasma cells were observed. These are characteristic findings of TAFRO syndrome.

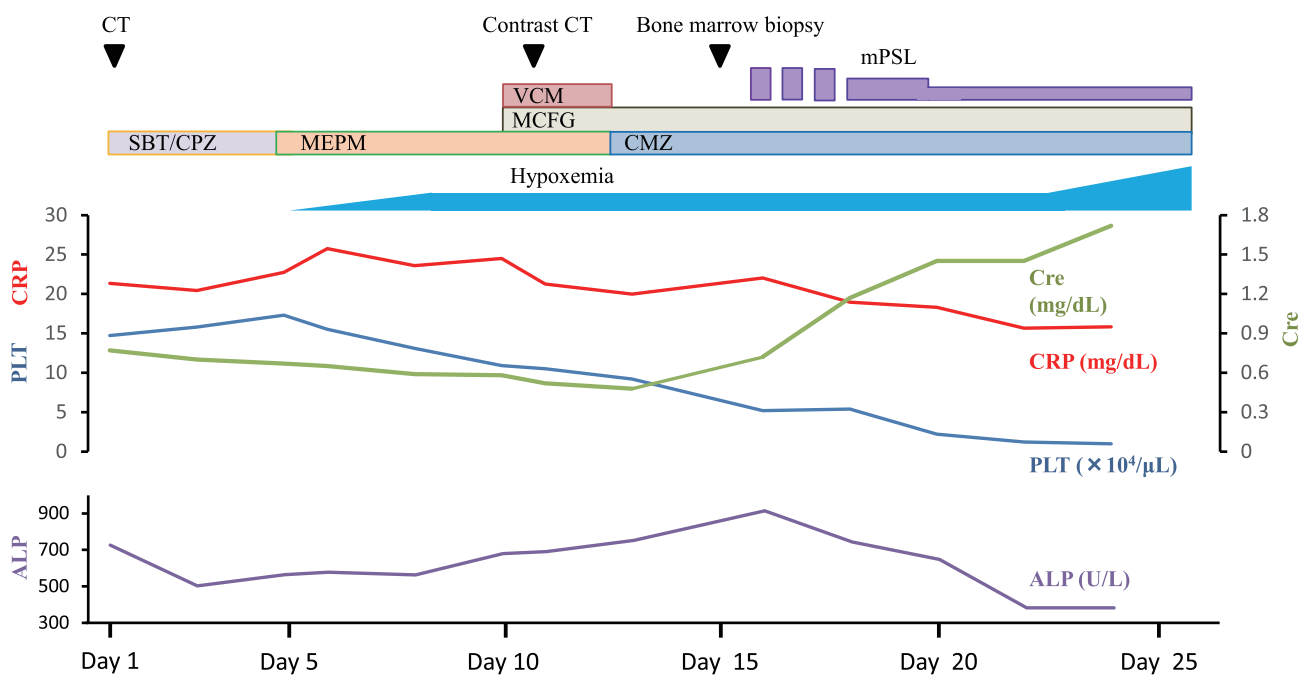


Fig. 3. Clinical course

Several antibiotic therapies were sequentially performed. After making a definitive diagnosis of TAFRO syndrome by bone marrow biopsy on day 16, steroid pulse therapy was initiated. However, hypoxemia and high values of CRP and ALP did not improve. Thrombocytopenia and renal dysfunction were exacerbated, and the patient died on day 26.

CT, computed tomography; SBT/CPZ, sulbactam/cefoperazone; MEPM, meropenem; VCM, vancomycin; MCFG, micafungin; CMZ, cefmetazole; mPSL, methylprednisolone

more common in TAFRO syndrome, whereas thrombocytosis, polyclonal hypergammaglobulinemia, and significant lymphadenopathy are typical of iMCD. Furthermore, patients with TAFRO syndrome frequently have rapidly deteriorating clinical courses and are refractory to corticosteroids. Indeed, several case reports suggested that the additional administration of cyclosporine A, tocilizumab (an anti-IL-6 receptor antibody), and rituximab (an anti-CD20 antibody) is required for better outcomes.^{10,11}

In 2015, Masaki *et al.*⁵ proposed diagnostic criteria, a disease severity classification, and treatment strategies for TAFRO syndrome based on a nationwide survey in Japan. For its diagnosis, they defined anasarca, thrombocytopenia, and systemic inflammation, including fever and/or increased serum CRP level, as major categories, and CD-like histological features on lymph node biopsy, reticulin myelofibrosis, and/or an increased number of megakaryocytes on bone marrow biopsy, mild organomegaly, and progressive renal

insufficiency as minor categories. Recently, they updated these criteria and the disease severity classification for TAFRO syndrome.⁹ Our patient presented with bilateral pleural effusion, thrombocytopenia ($52 \times 10^9/L$ on day 16 as the worst), fever, and a high serum CRP level. She also had reticulin myelofibrosis, lymphadenopathy, and progressive renal insufficiency. Lymph node biopsy is important for not only the exclusion of malignancy, including lymphoma, but also for confirming the diagnosis of TAFRO syndrome because of the lack of specific symptoms and biomarkers, and unclear etiology. In our case, however, lymph node biopsy was unable to be performed because the patient did not consent due to its physical and mental burden during the rapid deterioration of her general condition. She met all three major categories and three minor categories; therefore, we diagnosed her with TAFRO syndrome. In 2016, Iwaki proposed diagnostic criteria for TAFRO syndrome as follows: histopathological criteria; compatible with pathological findings of lymph nodes as TAFRO-iMCD, and negative LANA-1 for HHV-8, major criteria; presents 3 of 5 TAFRO symptoms, absence of hypergammaglobulinemia and small volume lymphadenopathy, and minor criteria; hyper/normoplasia of megakaryocytes in bone marrow, and high levels of serum ALP without marked increase in serum transaminase. Histopathological criteria, all major criteria, and 1 or more minor criteria must be met. In our case, the patient met all major criteria and minor criteria except the histopathological criteria.

In addition, she developed right abdominal pain after admission and we identified right adrenal hemorrhage without adrenal insufficiency. In general, adrenal hemorrhage does not cause specific signs or symptoms, and the majority of cases are diagnosed on autopsy.¹² The condition can be caused by several factors, such as infection, congestive heart failure, anticoagulants, trauma, and coagulopathy, although some patients with no causative factors have been reported. Among patients with TAFRO syndrome, six with adrenal hemorrhage were previously reported.¹³⁻¹⁷ Of these, four were Japanese and two were Caucasian. Five were male and one was female, and the median age was 48 years (range 19-62). Adrenal hemorrhage was bilateral in five patients and unilateral in one. According to the 2015 disease severity

classification for TAFRO syndrome, the condition was slightly severe in three patients, moderate in one, mild in one, and not evaluated in one. The patient in the present study was an older female and exhibited unilateral adrenal hemorrhage without adrenal insufficiency. TAFRO syndrome was initially graded as mild, but rapidly became severe and did not respond to corticosteroids. (Table 1)

On the other hand, in CD, adrenal involvement has been reported without hemorrhage.¹⁸ It usually presents as an adrenal mass without adrenal insufficiency. To our best knowledge, there are no reports of adrenal hemorrhage in patients with other subtypes of CD, suggesting that it is a specific manifestation of TAFRO syndrome. The mechanism of adrenal hemorrhage in TAFRO syndrome has not been elucidated. Several case reports suggested that thrombocytopenia and coagulopathy are predisposing factors for adrenal hemorrhage in TAFRO syndrome. Indeed, the majority of patients with adrenal hemorrhage exhibit marked thrombocytopenia and/or prolongation of clotting times. Our patient, however, demonstrated unilateral adrenal hemorrhage in the early stage of her clinical course, with mild thrombocytopenia and normal clotting times.

In a study of CT results in TAFRO syndrome, Kiguchi *et al.*¹⁹ reported that 75% of patients had post-peritoneal edema or adrenal swelling. This suggests that adrenal hemorrhage in TAFRO syndrome is caused by destruction of the adrenal gland vasculature induced by post-peritoneal inflammation. Kurokawa *et al.*²⁰ noted adrenomegaly and adrenal ischemia in 46.2% and 30.8% of patients, respectively, in the early stage of TAFRO syndrome. This suggests that adrenal hemorrhage occurs before the exacerbation of thrombocytopenia and/or coagulopathy due to inflammatory changes in the early stage of the disease.

In conclusion, TAFRO syndrome is a systemic inflammatory disease whose etiology is not yet well explained. As patients with this condition exhibit a more aggressive clinical course and poorer outcomes than those with iMCD-NOS, it is important to establish an early diagnosis and start powerful immunosuppressive agents such as tocilizumab. Adrenal hemorrhage may suggest the presence of TAFRO syndrome, and facilitate the early diagnosis of this complicated and rare disease.

Table 1. Summary of cases of TAFRO syndrome with adrenal hemorrhage.

Publication year, Reference	Race	Age, Sex	Adrenal hemorrhage	Thrombocytopenia	Coagulopathy	Disease status	Outcome
2016, Iбата <i>et al.</i> ¹³	Japanese	62, Male	Bilateral	Yes	Yes	Moderate	N.D.
2017, Nara <i>et al.</i> ¹⁴	Japanese	48, Male	Unilateral (right)	Yes	No	Slightly severe	Alive
2017, Nara <i>et al.</i> ¹⁴	Japanese	48, Male	Bilateral	Yes	No	Slightly severe	Alive
2018, Tsutsumi <i>et al.</i> ¹⁶	Japanese	49, Male	Bilateral	N.D.	Yes	N.D.	Alive
2020, Ducoux <i>et al.</i> ¹⁷	Caucasian	19, Male	Bilateral	Yes	No	Slightly severe	Alive
2020, Ducoux <i>et al.</i> ¹⁷	Caucasian	31, Female	Bilateral	Yes	No	Mild	Dead
Present case	Japanese	70, Female	Unilateral (right)	No	No	Severe	Dead

Thrombocytopenia, platelet count $< 100 \times 10^9/L$; coagulopathy, prolongation of PT and/or APTT, high FDP and/or D-dimer; N.D., not described

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

- 1 Castleman B. CASE records of the Massachusetts General Hospital Weekly Clinicopathological Exercises: Case 40011. *N Engl J Med.* 1954; 250 : 26-30.
- 2 Cronin DMP, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. *Adv Anat Pathol.* 2009; 16 : 236-246.
- 3 Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. *Blood.* 2014; 123 : 2924-2933.
- 4 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 [in Japanese, Abstract in English].
- 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.* 2016; 103 : 686-692.
- 6 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.
- 7 Fujimoto S, Sakai T, Kawabata H, *et al.* Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease? *Am J Hematol.* 2019; 94 : 975-983.
- 8 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.
- 9 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.
- 10 Sakai K, Maeda T, Kuriyama A, *et al.* TAFRO syndrome successfully treated with tocilizumab: A case report and systematic review. *Mod Rheumatol.* 2018; 28 : 564-569.
- 11 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.
- 12 Karwacka IM, Obolończyk L, Sworczak K. Adrenal hemorrhage: A single center experience and literature review. *Adv Clin Exp Med.* 2018; 27 : 681-687.
- 13 Iyata T, Sawatari Y, Yonesaki K, *et al.* A case report of bilateral adrenal hemorrhage in the course of TAFRO syndrome. *Nippon Naibunpitsu Gakkai Zasshi.* 2016; 92 : 319 [in Japanese].
- 14 Nara M, Komatsuda A, Itoh F, *et al.* Two cases of thrombocytopenia, anasarca, fever, reticulosis/fibrosis/renal failure, and organomegaly (TAFRO) syndrome with high serum procalcitonin levels, including the first case complicated with adrenal hemorrhage. *Intern Med.* 2017; 56 : 1247-1252.
- 15 Ito F, Kameoka Y, Nara M, *et al.* [TAFRO syndrome with bilateral adrenal hemorrhage]. *Nihon Naika Gakkai Zasshi.* 2017; 106 : 288-294 [in Japanese].
- 16 Tsutsumi T, Ichikawa R, Takano K, *et al.* A case of TAFRO syndrome with bilateral adrenal hemorrhage with difficulty in diagnosis and treatment. *Nippon Naibunpitsu Gakkai Zasshi.* 2018; 94 : 428 [in Japanese].
- 17 Ducoux G, Guerber A, Durel CA, *et al.* Thrombocytopenia, Anasarca, fever, reticulosis/fibrosis/renal failure, and organomegaly (TAFRO) syndrome with bilateral adrenal hemorrhage in two Caucasian patients. *Am J Case Rep.* 2020; 21 : e919536-1-e919536-7.
- 18 Müssig K, Horger M, Wehrmann M. Adrenal Castleman's disease. *Ann Hematol.* 2007; 86 : 63-65.
- 19 Kiguchi T, Sato C, Takai K, *et al.* CT findings in 11 patients with TAFRO syndrome: a variant of multicentric Castleman's disease. *Clin Radiol.* 2017; 72 : 905.e1-905.e5.
- 20 Kurokawa R, Gono W, Yokota H, *et al.* Computed tomography findings of early-stage TAFRO syndrome and associated adrenal abnormalities. *Eur Radiol.* 2020; 30 : 5588-5598.