

**Case report**

**Dysmorphic megakaryocytes in TAFRO syndrome: A case series from a single institute**

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**Abstract**

TAFRO syndrome is a rare systemic inflammatory disorder of unknown etiology characterized by thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly. The diagnosis of TAFRO syndrome can be challenging; however, prompt diagnosis is vital because TAFRO syndrome is a progressive and life-threatening disease. We have showcased five patients with TAFRO syndrome who had similar bone marrow (BM) findings that could be considered the findings that characterize TAFRO syndrome. All patients were treated with corticosteroids and tocilizumab; three of the five patients (60%) responded positively to the treatment. The unique BM findings observed in this study were megakaryocytes with distinct multinuclei and three-dimensional and indistinct bizarre nuclei (“dysmorphic megakaryocyte”), similar to the megakaryocyte morphology observed in myeloproliferative neoplasms (MPNs). Notably, dysmorphic megakaryocytes were observed in all five cases, whereas only two of the five patients tested positive for reticulin myelofibrosis, and three of the five patients had megakaryocytic hyperplasia, which are considered typical findings of TAFRO syndrome. Thus, the BM findings of dysmorphic megakaryocytes could help in the correct and immediate diagnosis of TAFRO syndrome.

**Key words:** TAFRO syndrome; bone marrow aspirate; dysmorphic megakaryocytes; megakaryocytes with bizarre nuclei; tocilizumab

## Introduction

TAFRO syndrome is a rare systemic inflammatory disorder of unknown etiology characterized by thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly[1]. Clinical features include the abovementioned nonspecific clinical symptoms, which can result from various infectious diseases, malignancies, rheumatologic disorders, and idiopathic multicentric Castleman disease (iMCD). Furthermore, TAFRO syndrome has no specific biomarkers, making its diagnosis quite challenging. However, prompt diagnosis is necessary because TAFRO syndrome is progressive and life threatening.

iMCD is also a rare heterogeneous inflammatory disorder characterized by systemic inflammation, multicentric lymphadenopathy, and organ dysfunction resulting from elevated interleukin-6 (IL-6) levels. iMCD and TAFRO syndrome share some clinical and pathological features; therefore, iMCD patients with TAFRO symptoms (iMCD-TAFRO) are considered subtypes of iMCD[2]. Diagnosis of iMCD based on lymph node histopathology, abnormal clinical features, and laboratory findings is difficult. Furthermore, the complex clinical presentation and abnormal laboratory findings of iMCD, which are similar to those of lymphomas, often make an accurate diagnosis of iMCD more challenging.

There is no doubt regarding the significance of bone marrow (BM) aspirates in the diagnosis of hematological disorders. The BM aspirate of patients with TAFRO syndrome could indicate reticulin myelofibrosis and/or an increased number of megakaryocytes. These findings obtained from BM aspirates of TAFRO patients could be confusing, since they are similar to the findings obtained in some subtypes of myeloproliferative neoplasms (MPNs), and hence are of little consequence; indeed the findings are considered as one minor category of the diagnosis. Thus, further diagnostic criteria using either BM aspirate or other modalities are needed for an accurate diagnosis of TAFRO syndrome.

In this study, we showcased five patients with TAFRO syndrome with similar BM findings that could be considered representative findings of TAFRO syndrome.

## **Patients and Methods**

### **Diagnostic criteria for TAFRO syndrome**

The major features of TAFRO syndrome are as follows [3]: (1) anasarca (pleural effusion, ascites, or systemic edema); (2) thrombocytopenia (platelet count  $\leq 100,000/\mu\text{L}$ ); and (3) systemic inflammation (fever of unknown etiology above  $37.5^{\circ}\text{C}$  and/or a serum C-reactive protein concentration  $\geq 2 \text{ mg/dL}$ ). The minor features are as follows: (1) features resembling those of Castleman disease on lymph node biopsy; (2) reticulin myelofibrosis and/or an increased number of megakaryocytes in the bone marrow; (3) mild organomegaly (hepatosplenomegaly or systemic lymphadenopathy); and (4) progressive renal insufficiency.

All three major categories and at least two of the four minor categories need to be met to diagnose TAFRO syndrome. Furthermore, malignancies, autoimmune disorders, infection, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes) syndrome, IgG4-related disease, liver cirrhosis, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome should be excluded. Notably, patients with lymph node histopathology (consistent with iMCD) are diagnosed with iMCD-TAFRO [4, 5].

### **Evaluation of morphological features**

BM aspirations from patients with malignant lymphoma without BM invasion (as a control), MPN and TAFRO syndrome for evaluation of the BM findings were obtained. Baseline patient characteristics were also obtained from hospital records including clinical diagnosis, general characteristics (age and sex), laboratory data (complete white cell counts, blast counts,

hemoglobin level, platelet counts). We evaluated the morphological features of the 30 megakaryocytes identified on BM aspirate smears. When dysplastic cells in the BM exceed 10%, existence of dysplasia in BM is considered. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees and Declaration of Helsinki. The Institutional Review Board of Hiroshima University reviewed and approved the study protocol (approval number **E2020-2149**, date of decision, **August 21, 2020**). Informed consent was obtained using the opt-out method; no patients objected to the study.

### **Statistical analysis**

Statistically significant differences between three or more groups were determined using the Kruskal-Wallis and the Bonferroni was used as multiple pairwise tests. P values < 0.05 were considered statistically significant. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R.

## **Results**

### **Case Presentation**

#### **Case 1**

A 76-year-old man presented with a 10-day history of leg edema and fever. His medical history included aortic abdominal aneurysm and atrial fibrillation. **He was on aspirin, olmesartan, famotidine, warfarin and tolvaptan.** Physical examination revealed a body temperature of 38.4°C, mild anemia, and pitting edema. There was no evidence of systemic lymphadenopathy or hepatosplenomegaly. Blood tests revealed a slightly elevated white blood cell count (12,670/ $\mu$ L), normal hemoglobin level (13.6 g/dL), and severe thrombocytopenia (17000/ $\mu$ L).

Laboratory tests revealed low serum albumin levels (2.1 g/dL), high C-reactive protein (CRP) levels (20.56 mg/dL), elevated creatinine levels (2.42 mg/dL), and slightly elevated alkaline phosphatase (ALP) levels (520 U/mL). Computed tomography revealed massive pleural effusion, ascites, and hepatomegaly, without systemic lymphadenopathy. BM aspirate revealed slightly hypocellular BM with normal or enlarged multinucleated megakaryocytes with three-dimensional and indistinct bizarre nuclei (dysmorphic megakaryocytes). Megakaryocyte counts were not elevated, and there was no evidence of reticulin myelofibrosis. A diagnosis of TAFRO syndrome was made, and corticosteroids and tocilizumab were initiated on day 3 following admission. However, the general condition of the patient deteriorated, resulting in his death on day 43.

## Case 2

A 64-year-old woman presented to our hospital with a 1-month history of fever, edema, thrombocytopenia, and renal dysfunction. Her medical history included uterine sarcoma, subarachnoid hemorrhage, and chronic subdural hematoma and home medications included suvorexant and trazodone. She had received several antibiotics for her fever, which had been diagnosed and treated for acute cholecystitis for one month before she visited us. Her condition continued to deteriorate with the development of thrombocytopenia, systemic edema, and renal dysfunction. Physical examination revealed a body temperature of 38.5°C, mild anemia, and systemic edema. Systemic lymphadenopathy and hepatosplenomegaly were observed. Complete blood cell counts revealed a slightly elevated white blood cell count (13,600/ $\mu$ L), mild anemia (hemoglobin level of 8.3 g/dL), and severe thrombocytopenia (31,000/ $\mu$ L). She also had low serum albumin levels (1.5 g/dL), high CRP levels (19.47 mg/dL), elevated creatinine levels (1.07 mg/dL), and normal ALP levels (291 U/mL). CT scan indicated massive pleural effusion,

ascites, and hepatomegaly with systemic lymphadenopathy. Histopathological findings of the biopsied lymph node revealed atrophic lymph follicles with vascular proliferation and invasion of plasma cells, suggestive of iMCD-TAFRO syndrome. BM aspirate revealed normocellular bone marrow with normal or enlarged dysmorphic megakaryocytes and normal or enlarged multinucleated megakaryocytes with separate nuclei. The number of megakaryocytes did not increase; however, reticulin myelofibrosis was observed. A diagnosis of TAFRO syndrome (iMCD-TAFRO syndrome) was made. Corticosteroid treatment was initiated on day 6, and tocilizumab was administered from day 10. The general condition of the patient gradually improved.

### Case 3

A 78-year-old man presented with a 1-week history of fever ( $>38^{\circ}\text{C}$ ), edema, thrombocytopenia, and renal dysfunction. His medical history included diabetes mellitus (on sitagliptin), a fatty liver, and reflux esophagitis (on lansoprazole). He received antibiotics and steroids for the fever, which was ruled to be of uncertain etiology. After one month, his general condition deteriorated, and he was transferred to our hospital. On physical examination, the patient's body temperature was  $36.6^{\circ}\text{C}$  (he was prescribed corticosteroids), and systemic edema was observed. Neither systemic lymphadenopathy nor hepatosplenomegaly were observed. Complete blood cell counts revealed an elevated white blood cell count ( $18,370/\mu\text{L}$ ), mild anemia (hemoglobin level of  $11.3\text{ g/dL}$ ), and severe thrombocytopenia ( $19,000/\mu\text{L}$ ). Laboratory tests revealed low serum albumin levels ( $1.9\text{ g/dL}$ ), high CRP levels ( $17.64\text{ mg/dL}$ ), elevated creatinine levels ( $3.32\text{ mg/dL}$ ), and elevated ALP levels ( $580\text{ U/mL}$ ). CT scan demonstrated massive pleural effusion and ascites with systemic lymphadenopathy. BM aspirate revealed slightly hypercellular BM with normal or large-sized dysmorphic megakaryocytes and normal

or large-sized multinucleated megakaryocytes with distinct nuclei. Elevated megakaryocyte counts were observed, but reticulin myelofibrosis was not. The patient was diagnosed with TAFRO syndrome. He was initiated on corticosteroids on day one, and tocilizumab was administered on day two. Unfortunately, the patient's general condition rapidly deteriorated, and he died on day 37 because of a complication of sepsis caused by *Escherichia coli*.

#### Case 4

A 71-year-old woman was admitted to our hospital with a 3-week history of fever, edema, thrombocytopenia, and renal dysfunction. Her medical history included primary biliary cholangitis (on ursodeoxycholic acid), chronic thyroiditis (on levothyroxine), and hypertension (on azelnidipine and olmesartan). Physical examination revealed a body temperature of 36.6°C and the presence of systemic edema. Complete blood cell counts revealed normal white blood cell levels (3640/ $\mu$ L), anemia (hemoglobin level of 8.6 g/dL), and thrombocytopenia (57,000/ $\mu$ L). Laboratory tests indicated low serum albumin levels (2.5 g/dL), high CRP levels (4.82 mg/dL), elevated creatinine levels (0.95 mg/dL), and slightly elevated alkaline phosphatase levels (406 U/mL). CT scan revealed a massive pleural effusion and ascites with systemic lymphadenopathy. There was no evidence of hepatosplenomegaly. BM aspirate revealed slightly hypocellular BM with normal or enlarged dysmorphic megakaryocytes and normal or enlarged multinucleated megakaryocytes with distinct nuclei. A higher number of megakaryocytes was observed in the presence of reticulin myelofibrosis. The patient was diagnosed with TAFRO syndrome. The patient was initiated on corticosteroid treatment on day seven and tocilizumab on day 25. However, the patient's general condition did not improve satisfactorily. Thereafter, cyclosporine was initiated on day 55, following which her condition gradually improved.

**Case 5**

A 73-year-old woman was admitted to our hospital with a 1-month history of fever, edema, thrombocytopenia, and renal dysfunction. Her medical history included acute cholecystitis, benign ovarian tumors, chronic thyroiditis, and leiomyoma uteri. Home medications included levothyroxine, candesartan, amlodipine and esomeprazole. A physical examination revealed a body temperature of 37.8°C along with systemic edema and lymphadenopathy. Complete blood cell counts revealed normal white blood cell levels (5,850/ $\mu$ L), anemia (hemoglobin level of 8.3 g/dL), and thrombocytopenia (35,000/ $\mu$ L). Further laboratory tests also indicated low serum albumin levels (2.2 g/dL), high CRP levels (4.20 mg/dL), elevated creatinine levels (1.71 mg/dL), and normal ALP levels (272 U/mL). CT scan revealed a massive pleural effusion and ascites with systemic lymphadenopathy. Biopsy of the lymph node revealed atrophic lymph follicles with an invasion of plasma cells, which was suggestive of iMCD-TAFRO syndrome. BM aspirate revealed normocellular bone marrow with normal or enlarged dysmorphic megakaryocytes and normal or enlarged multinucleated megakaryocytes with distinct nuclei. Higher megakaryocyte counts were observed; however, there was no evidence of reticulin myelofibrosis. The diagnosis of TAFRO syndrome (iMCD-TAFRO syndrome) was made. Corticosteroid treatment was initiated on day 4, followed by the initiation of tocilizumab on day 17. The general condition of the patient rapidly improved following the initiation of tocilizumab.

**Treatments and clinical outcomes of the TAFRO syndrome**

The median age of the patients was 73 years (range, 64–78 years); including two males and three females; two patients had severe disease, and three patients had slightly severe disease [3].



Two patients met the iMCD-TAFRO diagnostic criteria, and all patients had elevated serum IL-6 levels (median, 36.5 pg/mL); three patients had elevated serum vascular endothelial growth factor (VEGF) levels (median 159.5 pg/mL); all patients were treated with corticosteroids and tocilizumab; two patients who were diagnosed with severe disease died. All patients had splenomegaly, while no patients received valproic acid which may induce megakaryocytic dysplasia. Serum thrombopoietin levels and somatic mutations in the JAK2, MPL, and CALR genes were not assessed. Detailed clinical characteristics are summarized in **Table 1**.

#### Summary of BM findings in the five cases

We evaluated the morphological features of the 30 megakaryocytes identified on BM aspirate smears. All patients had dysmorphic megakaryocytes (median 43.3%), which are defined as normal or large-multinucleated megakaryocytes with three-dimensional and indistinct bizarre nuclei (**Figure 1A–D**), and four of the five cases had normal or large-multinucleated megakaryocytes with distinct nuclei (**Figure 1E–H**). Thus, all patients had at least 10% incidence of megakaryocytic dysplasia. Notably, the dysmorphic megakaryocytes were observed in all five patients. These megakaryocytic dysplasias were similar to the BM findings in essential thrombocythemia (ET, "staghorn-shaped nuclei") and primary myelofibrosis (PMF, "cloud-like nuclei"). Megakaryocytes in abnormal localization such as adjacent to bone were also observed. Myeloid/erythroid ratio was slightly elevated (median 4.9, range 2.8–8.3) and erythroblastic islands were observed in case 1 and 4. These findings were summarized in the **Table 2**. Although only two of the five patients displayed reticulin myelofibrosis (cases 2 and 5), three of the five patients had megakaryocytic hyperplasia, which is considered a typical BM finding of TAFRO syndrome. No obvious dyserythropoiesis or dysmyelopoiesis were observed.

## **Patients with TAFRO syndrome and MPN had similar BM findings, while distinct clinical findings**

We evaluated the BM findings of patients with malignant lymphoma (without BM invasion) as control (n = 43), MPN (n = 7) and TAFRO (n = 5). Patients with TAFRO syndrome had decreased platelet counts (median,  $19 \times 10^9/L$  v.s.  $244 \times 10^9/L$ ,  $p = 0.0015$ ), while MPN had increased (median,  $752 \times 10^9/L$  v.s.  $244 \times 10^9/L$ ,  $p = 0.0268$ ) compared with control (**Figure 2A**). Whereas, the dysmorphic megakaryocytes were increased both in patients with TAFRO syndrome (median, 3 v.s. 17,  $p = 0.0007$ ) and MPN (median, 3 v.s. 14,  $p = 0.0017$ ). These results suggest patients with TAFRO syndrome and MPN had similar BM findings, while distinct clinical findings. Patients with decreased platelet counts and increased the dysmorphic megakaryocytes may be diagnosed with TAFRO syndrome.

## **Discussion**

Herein, we have reported five cases of TAFRO syndrome. Although TAFRO syndrome is classified as a subgroup of iMCD, only two of the five patients fulfilled the diagnostic criteria of iMCD-TAFRO in the present study[2].

Common BM findings of TAFRO syndrome previously described in the literature are increase in megakaryocytes and/or reticulin myelofibrosis[5]. These symptoms are similar to those commonly observed in patients with MPNs [6, 7], indicating that BM findings might not specifically identify TAFRO syndrome. Furthermore, only three of the five patients exhibited increase in megakaryocytes, and two of the five patients in this study displayed reticulin myelofibrosis. Approximately 20%–30% of iMCD-TAFRO patients did not exhibit the typical findings of TAFRO syndrome [8, 9], more characteristic BM findings will be useful in diagnosing patients with TAFRO syndrome.

The unique BM findings that were frequently observed in all five cases included in this study were dysmorphic megakaryocytes, defined as megakaryocytes with normal or large-sized, distinct multinuclei, three-dimensional, and indistinct bizarre nuclei [10], similar to the megakaryocyte morphology observed in some subtypes of classical MPNs, especially in JAK2-mutated ones [11]. Notably, all five cases were characterized by dysmorphic megakaryocytes. The dysmorphic megakaryocytes are quite distinct from the micromegakaryocytes observed in patients with myelodysplastic syndrome (MDS). None of the five cases had micromegakaryocytes.

Similar megakaryocyte morphological findings in TAFRO syndrome have been reported [9]. Megakaryocytic hyperplasia with multiple and widely separated nuclei, hypolobulated nuclei, hyperchromatic nuclei, and clustering were reportedly observed in the TAFRO cases [8]. We mainly investigated BM smear specimens which may be significant for the correct diagnosis of TAFRO syndrome. Although dysmorphic megakaryocytes are also observed in some cases of MPNs, the clinical features of TAFRO syndrome and MPNs are quite different (e.g. platelet counts) [1], suggesting that the dysmorphic megakaryocytes could be the findings that characterize TAFRO syndrome.

Large (not giant) megakaryocytes with severe nuclear atypia, small cytoplasm with hypolobulated nuclei ("cloud-like nuclei"), hyperchromatic nuclei, and tight clustering are observed in PMF (profibrotic stage). Increased number and loose clustering of large or giant megakaryocytes with lobulated nuclei ("staghorn-like") with mature cytoplasm are observed in ET [6]. Increased numbers of megakaryocytes with hypolobulation and tight clustering are observed in immune thrombocytopenia patients who received thrombopoietin receptor agonist therapy [12]. Valproic acid often induces hematological adverse events (thrombocytopenia) and megakaryocyte dysplasia. Megakaryocytes with nuclear hypolobulation, separated nuclear

lobes, and clustering are observed in patients who receive valproic acid [13]. Megakaryocyte dysplasia is commonly observed in patients with MDS. Megakaryocyte morphologic features of typical MDS cases are nuclear with hypolobulation, multiple separate nuclei, and micromegakaryocyte. Whereas, MDS with cohesion gene mutations (e.g. STAG2) has small hypolobated megakaryocytes with separated nuclei [14]. Osteoclasts are large cells with granular cytoplasm which are resembling with megakaryocytes, and are generally multinucleated and separated nuclei, which are different from megakaryocytes. The above BM findings may resemble the BM findings in the present TAFRO syndrome.

Somatic mutations in JAK2, CALR, and MPL genes are important to diagnose MPNs. Unfortunately, we did not assess somatic mutations in the JAK2, MPL, and CALR genes[15], because the clinical manifestation of TAFRO syndrome can be distinguished from those of MPNs, thus somatic mutations in the JAK2, MPL, and CALR genes are not commonly assessed in patients with TAFRO syndrome (patients with thrombocytopenia). In the present study, we found that BM findings in TAFRO syndrome were similar to those in MPNs, thus it would be meaningful to investigate genetic aberrations of TAFRO syndrome and MPNs in future investigation.

Currently, there is no standard treatment for TAFRO syndrome because of its rare incidence and unknown cause. Possible mechanisms responsible for the pathogenesis of TAFRO syndrome, which have been mentioned in previously conducted studies, include excessive inflammatory cytokines derived from IL-6 and/or VEGF[2, 9] ; abnormal immune cells; and bacterial or viral infections (e.g. HHV-8) may be a main pathogenesis of TAFRO syndrome[4, 16]. In the present study, IL-6 levels were elevated in all patients, and VEGF levels were elevated in three of the four patients, which is consistent with previous reports. Corticosteroids, cyclosporine, tocilizumab, and rituximab, are commonly used in the general

clinical setting for treating TAFRO syndrome[17]. Among these, tocilizumab (IL-6 receptor blockade) combined with corticosteroids is the most frequently used and is regarded as a reasonable treatment strategy considering the pathogenesis of TAFRO syndrome (elevated serum IL-6). Approximately 50% of patients achieve a favorable clinical response[18]. Consistent with these previous reports, three of the five patients (60%) in the present study responded positively to tocilizumab combined with corticosteroids (one patient received additional cyclosporine, leading to remission).

Although the severity of TAFRO disease has been defined at five levels (mild, moderate, slightly severe, severe, and very severe), the correlation between severity and prognosis has not been fully elucidated[3]. In the present study, only two patients with severe disease died, whereas the remaining patients with slightly severe disease recovered after receiving the same tocilizumab and corticosteroid treatment. These results suggest that the severity of TAFRO syndrome might predict survival outcomes in patients with TAFRO syndrome more accurately.

To summarize, the presence of dysmorphic megakaryocytes associated with severe thrombocytopenia might be a representative clinical finding of TAFRO syndrome and might help in the timely diagnosis of this intractable disease that requires early therapeutic intervention.

#### **Statement of Ethics**

The study protocol was reviewed and approved by Institutional Review Board of Hiroshima University, approval number (E2020-2149), date of decision (21 August, 2020).

#### **Conflict-of-interest disclosure**

The authors declare no conflict-of-interest relevant to this work.

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### **Author Contributions**

SM, HU, SY and TI made substantial contributions to study conception, design, analysis and data interpretation. SM, HN and KK collected data. MS, HU and TI wrote the paper and critically reviewed the drafts. All authors approved the final version.

### **Data sharing**

All data can be accessed by contacting the corresponding author (HU).

### **References**

1. Kawabata H, Takai K, Kojima M, et al (2013) 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 . J Clin Exp Hematop 53:57–61.
2. Fujimoto S, Sakai T, Kawabata H, et al (2019) Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease? Am J Hematol 94:975–983.
3. Masaki Y, Ueda Y, Yanagisawa H, et al (2023) TAFRO Syndrome: A Disease Requiring Immediate Medical Attention. Intern Med 62:27–32.
4. Dispenzieri A, Fajgenbaum DC (2020) Overview of castleman disease. Blood 135:1353–1364.
5. Nishimura Y, Fajgenbaum DC, Pierson SK, et al (2021) 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.
6. Ng ZY, Fuller KA, Mazza-Parton A, Erber WN (2023) Morphology of myeloproliferative neoplasms. *Int J Lab Hematol* 45:59–70.
  7. Barosi G, Rosti V, Gale RP (2023) Myelofibrosis-type megakaryocyte dysplasia (MTMD) as a distinct category of BCR::ABL-negative myeloproliferative neoplasms. Challenges and perspectives. *Leukemia* 37:725–727.
  8. Belyaeva E, Rubenstein A, Pierson SK, et al (2022) Bone marrow findings of idiopathic Multicentric Castleman disease: A histopathologic analysis and systematic literature review. *Hematol Oncol* 40:191–201.
  9. Iwaki N, Fajgenbaum DC, Nabel CS, et al (2016) Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol* 91:220–226.
  10. Koopmans SM, Bot FJ, Lam KH, et al (2011) Reproducibility of histologic classification in nonfibrotic myeloproliferative neoplasia. *Am J Clin Pathol* 136:618–624.
  11. Rajpal M, Sancheti S, Somal PK, et al (2022) Atypical Megakaryocyte Morphology: an Important Diagnostic Clue for JAK2 Mutation–Associated Disorders. *SN Compr Clin Med* 5:2.
  12. Boiocchi L, Orazi A, Ghanima W, et al (2012) Thrombopoietin receptor agonist therapy in primary immune thrombocytopenia is associated with bone marrow hypercellularity and mild reticulin fibrosis but not other stromal abnormalities. *Mod Pathol* 25:65–74.
  13. Gesundheit B, Kirby M, Lau W, et al (2002) Thrombocytopenia and megakaryocyte dysplasia: an adverse effect of valproic acid treatment. *J Pediatr Hematol Oncol* 24:589–90.
  14. Wong WJ, Zon RL, Ho C, et al (2023) STAG2 Somatic Mutations Are Associated with Specific Dysplastic Megakaryocytic and Myeloid Cell Features in Myelodysplastic Syndrome. *Blood* 142:3233.
  15. Luque Paz D, Kralovics R, Skoda RC (2023) Genetic basis and molecular profiling in myeloproliferative neoplasms. *Blood* 141:1909–1921.
  16. Fajgenbaum DC (2018) Novel insights and therapeutic approaches in idiopathic multicentric Castleman disease. *Blood* 132:2323–2330.
  17. Fujimoto S, Kawabata H, Sakai T, et al (2021) Optimal treatments for TAFRO syndrome: a retrospective surveillance study in Japan. *Int J Hematol* 113:73–80.
  18. Akiyama M, Kaneko Y, Takeuchi T (2020) Tocilizumab for the treatment of TAFRO syndrome: a systematic literature review. *Ann Hematol* 99:2463–2475.

**Figure legends****Figure 1. Representative bone marrow findings**

Normal sized (A, B) and large sized bizarre multinucleated megakaryocytes (C, D). Normal sized (E, F) and large sized multinucleated megakaryocyte with separate nuclei (G, H).

**Figure 2.**

Platelet counts according to the disease (A). The dysmorphic megakaryocyte counts according to the disease (B). The Kruskal-Wallis and the Bonferroni.



**Table 1. Patient characteristics**

Case	Age	Gender	Severity of disease	IL-6 (pg/mL)	VEGF (pg/mL)	Treatment	iMCD-TAFRO	Splenomegaly	Outcomes
1	76	male	severe	36.5	169	corticosteroid + tocilizumab	no	yes	death
2	64	female	slightly severe	38.4	32.5	corticosteroid + tocilizumab	yes	yes	alive
3	78	male	severe	67.8	150	corticosteroid + tocilizumab	no	N.A.	death
4	71	female	slightly severe	10.9	NA	corticosteroid + tocilizumab + CyA	no	yes	alive
5	73	female	slightly severe	13.5	609	corticosteroid + tocilizumab	yes	yes	alive

Abbreviations: VEGF, vascular endothelial growth factor; iMCD, idiopathic multicentric Castleman disease, N.A., not applicable

**Table 2. Bone marrow features of their TAFRO cases**

	Dysmorphic megakaryocyte	Reticulin myelofibrosis	Megakaryocytic hyperplasia	Megakaryocyte clustering	Megakaryocyte localization adjacent to bone	M/E ratio	Presence of other cells
Case 1	yes (43.3%)	no	no	loose	yes	3.7	erythroblastic islands
Case 2	yes (43.3%)	yes	no	loose	yes	4.0	none
Case 3	yes (26.7%)	no	yes	loose	N.A.	6.0	none
Case 4	yes (43.3%)	yes	yes	loose	yes	1.9	erythroblastic islands, plasma cells
Case 5	yes (46.7%)	no	yes	loose	yes	3.3	none

N.A., not applicable (due to biopsy specimen in poor condition); M/E ratio, myeloid erythroid ratio.



Figure 1

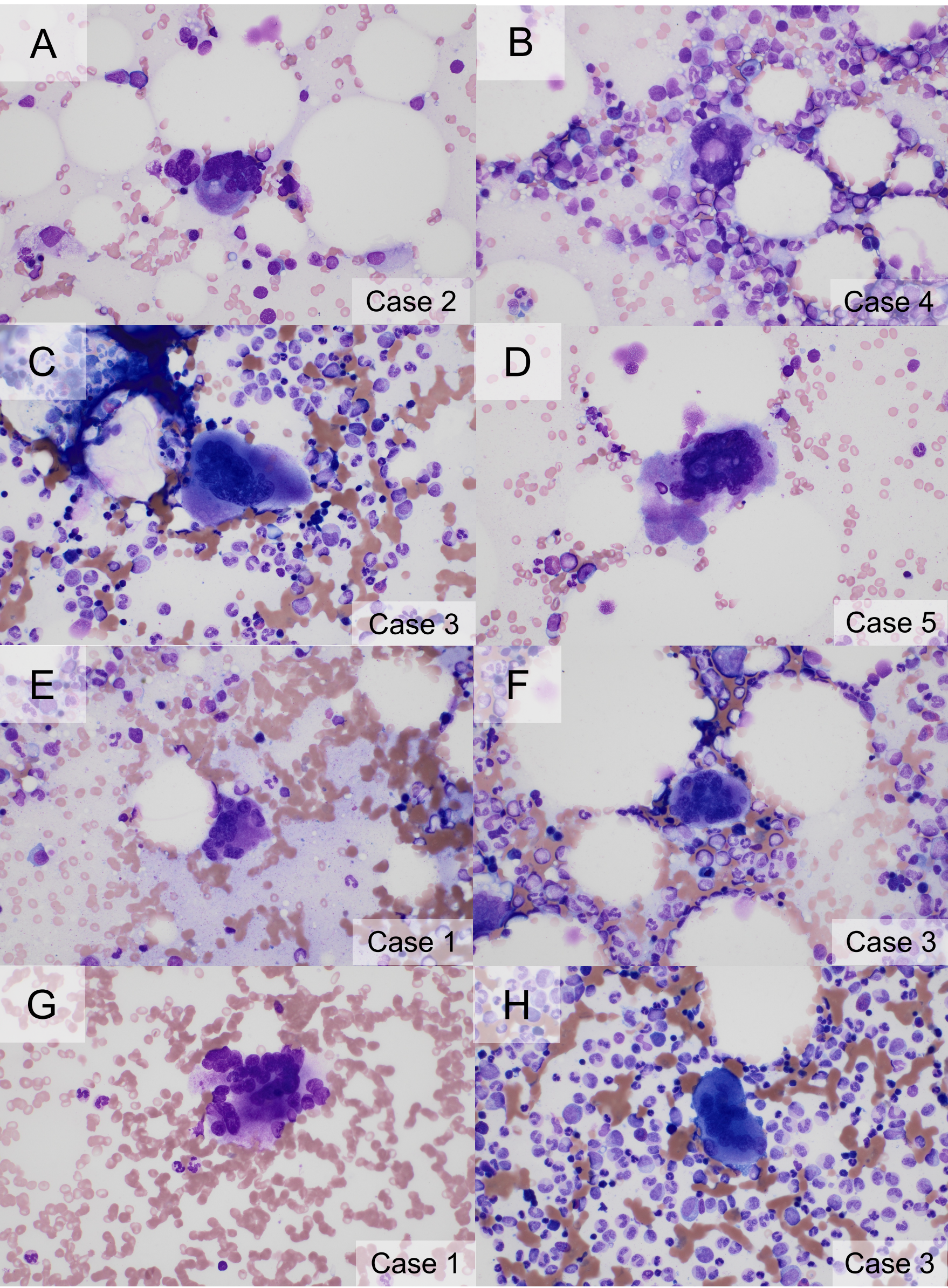




Figure 2

