To the Editor: Castleman’s disease (CD) describes a group of lymphoproliferative disorders with heterogeneous clinical manifestations. CD comprises at least two distinct diseases (unicentric CD [UCD] and multicentric CD [MCD]) with respective clinical features and prognoses. UCD often involves one lymph node area with favorable outcome; MCD is a systemic disease with relatively poor prognosis which involves multiple lymph node areas with constitutional symptoms (e.g., fever, night sweats, and weakness) and organ dysfunction. According to pathogenesis, MCD can be further divided into different subtypes based on the status of human herpes virus-8 (HHV-8) infection. Of the HHV-8 negative MCD (also named as idiopathic MCD [iMCD]), there is a peculiar subtype named TAFRO syndrome which constitutes a constellation of unique clinical manifestations (T: Thrombocytopenia, A: Anasarca, F: Myelofibrosis, R: Renal dysfunction, and O: Organomegaly). This syndrome, first reported in Japan,[12] has been reported mostly in the Japanese population and occasionally in Caucasians. There is no such case reported in China. We herein report the first patient with TAFRO syndrome in China with confirmed myelofibrosis.

In July 2016, a 39-year-old woman was referred to our center with a 3-year history of hepatosplenomegaly and multiple lymphadenopathy. Five months ago, she complained of fatigue, palpitation, and shortness of breath after minor exercise. Her body temperature ranged over 38°C for the recent 2 months, which was diurnal, with an afebrile period early in the morning and a gradual rise through day time, reaching the peak (38–38.5°C) in the late afternoon or evening. Other complaints included night sweats, malaise, lower extremity edema, enlarged lymph nodes at neck, axillary fossa, and inguinal groove. Antibiotics did not work well. Methylprednisolone was administrated in a local hospital for 25 days; therefore, body temperature and edema were both improved. However, abdominal distention was later apparent, and a 10 kg loss of body weight was observed despite increased symptoms.

On examination, the patient was febrile with maximum 39.1°C. Petechiae were observed on knees, sacrococcygeal region, and left popliteal fossa. Enlarged lymph nodes were at bilateral submandibular areas, right axillary fossa, and bilateral inguinal grooves. Breath sounds were low in both lower lungs. The liver was palpable 9 cm below the right costal margin with slight tenderness. Splenomegaly was noted with line I 12.2 cm, line II 15 cm, and line III − 3.8 cm without pain while pressed. A shifting dullness and fluid thrill was revealed after the examination of the abdomen. Edema of lower extremity was no noticeable. Other complaints included night sweats, malaise, lower extremity edema, enlarged lymph nodes at neck, axillary fossa, and bilateral inguinal grooves. Breath sounds were low in both lower lungs. The liver was palpable 9 cm below the right costal margin with slight tenderness. Splenomegaly was noted with line I 12.2 cm, line II 15 cm, and line III − 3.8 cm without pain while pressed. A shifting dullness and fluid thrill was revealed after the examination of the abdomen. Edema of lower extremity was no noticeable.

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IL-8 407 pg/ml (<62). Vascular endothelial growth factor was 484 pg/ml (<600). Echocardiogram showed normal cardiac function with a mild aortic insufficiency. A computed tomography scan revealed bilateral pleural effusion, enlarged lymph nodes in the mediastinum, hilum of lung, neck, axillary fossa, inguinal groove as well as in the retroperitoneal region, hepatosplenomegaly and ascites. Peripheral blood smear: erythrocytes ranging in size with some irregular shape, the central indiffERENCE zone of red blood cell expanding. WBC morphology normal and PLTs rare. Bone marrow aspiration showed neutrophilic and megakaryocytic hyperplasia. Bone marrow biopsy revealed fibrosis with positive reticulin stain [Figure 1d]. The biopsy of the enlarged lymph node in the right axillary fossa showed a histological picture consisted with CD of the hyaline-vascular (HV) variant [Figure 1a and 1b]; immunohistochemical stain for HHV-8 was negative [Figure 1c]. A diagnosis of idiopathic (HHV-8 negative) MCD (HV variant) was therefore made. With the constellation of manifestations of thrombocytopenia (T), anasarca (A), myelofibrosis (F) and proteinuria and organomegaly (O), a final diagnosis of TAFRO syndrome was thus confirmed.

Along with supportive treatment (e.g. transfusion), two courses of TCP (thalidomide 100 mg qw, cyclophosphamide 300 mg/m² qw and prednisone 1 mg/kg d1–2 qw) regimens were administrated with aspirin 100 mg qd to prevent thromboembolism. After the treatment, her enlarged lymph nodes, liver and spleen partly shrank with abdomen circumference decreased. However, due to neutropenia, cyclophosphamide was discontinued at the accumulation dosage of 1.6 g (her neutrophil count recovered after the discontinuation of cyclophosphamide). Despite the above-mentioned improvement, unfortunately, her PLT and hemoglobin levels were not improved. Without effective means to improve her anemia (other than transfusion), the general status of the patient deteriorated. The patient died with cardiac arrest which was possibly due to severe anemia 2 months after diagnosis.

TAFRO syndrome is a unique subtype of HHV-8 negative MCD (iMCD) with high mortality,[1] first reported by Takai et al. in 2010.[2] In the beginning, TAFRO stood for Thrombocytopenia (T), Anasarca (A), Fever (F), Reticulin fibrosis (R), and Organomegaly (O) which was consistent with the clinical presentation of our patient.[4] In 2012, a diagnostic criterion was proposed for TAFRO syndrome at the Fukushima and Nagoya meeting, and some slight changes were made for the acronyms: F presented myelofibrosis and R for renal dysfunction.[4] This criterion was composed of 11 items [Table 1] which included both clinical and laboratory parameters. Rather than a “diagnostic criterion,” these 11 items can be more properly referred as the clinical manifestations of TAFRO syndrome. Moreover, the diagnosis of TAFRO syndrome is a clinical diagnosis which does not require to fulfill all the 11 criteria. However, with a thorough review of the reported cases so far, it is worth mentioning that once an iMCD patient fulfills at least 4 of 5 key components (T, A, F, R, O) and has other manifestations listed in Table 1, a diagnosis of TAFRO syndrome should be highly suspected.

As a rare clinical entity, there are only a few cases of TAFRO syndrome reported in English literatures: mostly in the Japanese and occasionally in the Caucasians. Although the Chinese shares similar origin with the Japanese, TAFRO syndrome in Chinese population was not reported so far. Maybe hematologists in China need more time to recognize this disease. We herein report the very first case of TAFRO syndrome in China. Since the patient had pancytopenia and TAFRO syndrome was a possible explanation for this laboratory finding, a bone marrow biopsy was performed, which revealed myelofibrosis which was a key criterion of this syndrome.

One important reason that TAFRO syndrome should be distinguished from other MCD patients is its aggressive and lethal characteristics with hardly effective regimens. There was no “standard treatment” for MCD by now. IL-6 targeted therapy seems to be effective, but neither tocilizumab nor siltuximab was approved in China. Rituximab might be effective but was very expensive and

**Table 1: Diagnostic criteria for TAFRO syndrome**

| 1. Blood count abnormalities: Low platelets and/or red blood cells; thrombocytopenia, microcytic anemia |
| 2. Systemic inflammation: Polyserositis (pleuritic/peritonitis); inflammation of the tissue lining the lungs or abdominal cavities; pleural effusions, ascites |
| 3. Renal dysfunction |
| 4. Myelofibrosis |
| 5. Immunologic disorder: Rheumatoid factor, platelet-associated IgG, antithyroid antibody, and positivity on direct coombs test |
| 6. Antinuclear antibody |
| 7. Rare polyclonal hyper-globulin: <4000 mg/dL |
| 8. Laboratory data abnormalities: Elevated level of alkaline phosphatase and decreased level of lactate dehydrogenase |
| 9. Elevated levels of IL-6 and the vascular endothelial growth factor in serum or effusions |
| 10. Lymphadenopathy: Generally of mild degree (<1.5 cm in diameter) |
| 11. Histology of mixed-type and less frequently HV-type CD |

IgG: Immunoglobulin G; HV: Hyaline-vascular; CD: Castleman’s disease; IL-6: Interleukin-6.
not covered by medical insurance in China. Thalidomide-based treatment was a relatively inexpensive treatment option which might still be efficacious in MCD patients. In this patient, who was from the rural area of China, we chose thalidomide-based treatment, trying to provide her with an economical therapy. Unfortunately, this treatment seemed not very helpful.

In conclusion, we report the case of TAFRO syndrome in China which might help to enrich the clinical spectrum of this rare and unique subtype of MCD. We anticipate more cases to be reported in the future.

Declaration of patient consent
The patient was a participant of our registered clinical trial which was approved by the Institutional Ethical Review Board of Peking Union Medical College Hospital (ZS-1159), and informed consent was achieved from the patient and her relative.

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Conflicts of interest
There are no conflicts of interest.

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