To the Editor,

Castleman disease (CD) is a lymphoproliferative disease that is characterized by angiofollicular lymph node hyperplasia and clinically presents with unicentric or multicentric involvement [1]. Unicentric CD is the benign type, which is usually characterized by mediastinal involvement in young people and treated with surgical excision [2,3,4].

In contrast, multicentric CD is a systemic disease that is classified into two categories as human herpes virus-8 (HHV-8)-associated CD or idiopathic (HHV-8-negative) CD [3,4,5]. The most commonly preferred agents in the first-line treatment of multicentric CD are anti-CD20 (rituximab) and anti-IL-6 (siltuximab, tocilizumab) agents with or without steroids. Antiretrovirals should be added to the treatment for patients with HHV-8-associated multicentric CD. Chemotherapy is usually reserved for second or later lines [4,5,6,7].

TAFRO syndrome is a rare variant of idiopathic multicentric CD that involves thrombocytopenia, anasarca edema, fever, reticulin fibrosis, and organomegaly [8,10,11]. In this letter, a case of TAFRO syndrome is presented.

A 48-year-old man with coronary artery disease was admitted to our emergency department with complaints of weakness, intermittent fever for 6 months, dyspnea for the last 1 month, and generalized edema. Blood analysis showed white blood cell count of 9600/µL with 71% neutrophils, hemoglobin of 7.2 g/dL, hematocrit of 23.6%, mean corpuscular volume of 79.9 fl, and platelet count of 98000/µL. Biochemical test results were as follows: aspartate transaminase, 26 U/L; alanine transaminase, 19 U/L; alkaline phosphatase, 132 U/L; gamma-glutamyl transferase, 87 U/L; total protein, 6.9 g/dL; albumin, 2.64 g/dL; creatinine, 2 mg/dL; serum C-reactive protein, 200 mg/L; procalcitonin, 14 ng/mL. The patient had acute kidney injury that presented with oliguria at admission. On physical examination, the patient was pale and had 3+ edema in the pretibial regions. The spot urine protein/creatinine ratio was 2 g/day. His abdomen was distended due to marked ascites. Paracentesis was performed, revealing exudative ascites. The viral serological markers of HBsAg, anti-HBs, anti-HCV, anti-HIV, HHV-8, EBV VCA IgM/G, and CMV DNA were negative. Serum protein electrophoresis showed polyclonal gammopathy and hypergammaglobulinemia. Free kappa (355.8 mg/L) and free lambda (231.9 mg/L) light chain levels were increased, but their ratios were normal. The IgG level was 2263 mg/dL and it was high in favor of subgroups G1 and G4. Serum and urine immunofixation results were normal. The β2-microglobulin level was high (18 mg/L).

In thorax computed tomography (CT), multiple pathological lymph nodes were seen in the bilateral cervical region, axillary region, and mediastinum. Abdominal CT showed hepatosplenomegaly and multiple pathological lymph nodes in the bilateral iliac chains and para-aortic region.

Positron emission tomography (PET)/CT showed multiple lymph nodes with mildly to moderately increased fluorodeoxyglucose (FDG) uptake in the cervical, axillary, mediastinal, and paraaortic areas as well as the bilateral common iliac and external iliac lymphatic stations (Figure 1). Increased FDG uptake was observed in multiple lymph nodes of millimetric/subcentimetric size in the bilateral cervical chain and supraclavicular area (SUV_{max}: 3.2). There was also involvement in multiple lymph nodes, the largest diameter of which was 2 cm, in the bilateral pectoral region and axillary area (SUV_{max}: 3.8). There was involvement in the para-aortic region in the abdomen, mostly in subcentimetric lymph nodes (SUV_{max}: 3.9), and in lymph nodes of the bilateral common iliac and external iliac chain with sizes of 1.3 cm (SUV_{max}: 4.3).

We performed a bone marrow biopsy that revealed normo-mild hypercellular bone marrow with patchy interstitial mild lymphoplasmocytosis and focal dysplastic changes in the megakaryocytic series. A heterogeneous reaction was observed with CD3 and CD20 in the lymphoid population and the ratio of CD3-positive T lymphocytes was dominant. There was no co-expression with CD5 on B lymphocytes. The rate of
CD138-positive plasma cells was around 10% with a patchy interstitial distribution. In kappa and lambda light chain studies, polytypic reactions were obtained in plasma cells. Bone marrow biopsy showed reticulin fibrosis and an increased number of megakaryocytes.

Considering the metabolic activity in PET/CT, an excisional lymph node biopsy was performed from the left axillary area. Lymphadenopathy was characterized by dense plasmacytosis showing germinal centers with a regressive character. CD3 and CD5 were positive in the perifollicular T-cell population. CD20 was positive in lymphoid follicles and had a regressive character. An interfollicular dense plasma cell population was detected with CD38 and CD138. Plasma cells were polytypic in kappa and lambda light chain studies and the ratio of IgG-positive plasma cells was significantly dominant (Figure 2). HHV-8 examination was repeated twice and the results were negative.

These findings were compatible with idiopathic multicentric CD. The patient was subsequently evaluated in terms of TAFRO syndrome and met all relevant diagnostic criteria including thrombocytopenia, anasarca edema, systemic inflammation (fever, high acute-phase reactants), reticulin fibrosis, and organomegaly [8,9].

Steroid treatment was planned for this patient with TAFRO syndrome. Cytopenia regressed after the initiation of dexamethasone administration at 80 mg. However, he was hospitalized in the hematology service to plan anti-IL-6 (tocilizumab) treatment because of ongoing generalized edema. The proteinuria and edema regressed, and the need for paracentesis also ended with tocilizumab treatment. In addition, his IL-6 level decreased from 61 pg/mL to 10 pg/mL with treatment. The patient was closely followed at 3-month intervals.

In conclusion, the etiology of TAFRO is not clear, but the symptoms are the result of cytokine storms, and especially IL-6. The most common type of idiopathic multicentric CD with clinical features of TAFRO is a rapidly progressive form that can lead to death within weeks. Although there is no optimal treatment, dexamethasone, chemotherapeutic agents, anti-IL-6 treatment, and immunosuppressive therapies can be beneficial. TAFRO syndrome must be considered in the differential diagnosis of infections, malignancies, autoimmune diseases, and especially lymphoma and lymphoproliferative diseases. TAFRO syndrome may have an aggressive clinical course. The case presented here highlights the fact that TAFRO syndrome should be considered
in the differential diagnosis of patients with similar signs and symptoms.

**Keywords:** Lymphoproliferative diseases, Castleman disease, TAFRO syndrome

**Anahtar Sözcükler:** Lenfoproliteratif hastalıklar, Castleman Hastalığı, TAFRO sendromu

**Ethics**

Informed Consent: Obtained.

**Authorship Contributions**

Concept: Ü.A.G., E.Ü., A.A., A.M., S.E.; Design: Ü.A.G., E.Ü., A.A., A.M., S.E.; Data Collection or Processing: Ü.A.G., E.Ü., A.A., A.M., S.E.; Analysis or Interpretation: Ü.A.G., E.Ü., A.A., A.M., S.E.; Literature Search: Ü.A.G., E.Ü., A.A., A.M., S.E.; Writing: Ü.A.G., E.Ü., A.A., A.M., S.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

**References**

1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph node hyperplasia resembling thymoma. Cancer 1956;9:822-830.
2. Wong RSM. Unicentric Castleman disease. Hematol Oncol Clin North Am 2018;32:65-73.
3. Dispenzieri A, Armitage JO, Loe MJ, Geyer SM, Allred J, Camoriano JK, Menke DM, Weisenburger DD, Ristow K, Dogan A, Habermann TM. The clinical spectrum of Castleman’s disease. Am J Hematol 2012;87:997-1002.
4. Bowne WB, Lewis JJ, Filippa DA, Niewizky S, Brooks AD, Burt ME, Brennan MF. The management of unicentric and multicentric Castleman’s disease: a report of 16 cases and a review of the literature. Cancer 1999;85:706-717.
5. Liu AV, Nabel CS, Finkelman BS, Ruth JR, Kurzrok R, van Rhee F, Krymskaya VP, Kelleher D, Rubenstein AH, Faigenbaum DC. Idiopathic multicentric Castleman’s disease: a systematic literature review. Lancet Haematol 2016;3:163-175.
6. Faigenbaum 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.
7. Dispenzieri A, Faigenbaum DC. Overview of Castleman disease. Blood 2020;135:1353-1364.
8. 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.
9. Masaki Y, Kawabata H, Takai K, Tsukamoto N, Fujimoto S, Ishigaki Y, Kurose N, Miura K, Nakamura S, Aoki S; Japanese TAFRO Syndrome Research Team. 2019 Updated diagnostic criteria and disease severity classification for TAFRO syndrome. Int J Hematol 2020;111:155-158.
10. van Rhee F, Voorhees P, Dispenzieri A, Fossá A, Srkalovic G, Ide M, Munshi N, Schey S, Streety M, Piardethy HL, Mukherjee S, Shillings D, Stone K, Greenway A, Ruth J, Lechowicz MJ, Chandrakasan S, Jeyanthan R, Jaffe ES, Leitch H, Pemmaraju N, Chadburn A, Lim MS, Elenitoba-Johnson KS, Krymskaya V, Goodman A, Hoffmann C, Zinzani PL, Ferrero S, Terriou L, Sato Y, Simpson D, Wong R, Rossi JF, Nasta S, Yoshizaki K, Kurzrok R, Uldrick TS, Casper C, Okenhendler E, Faigenbaum DC. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018;132:2115-2124.
11. Paydas S. Tafro syndrome: critical review for clinicians and pathologists. Crit Rev Oncol Hematol 2018;128:88-95.