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Case Report

TAFRO syndrome: A case report and review of the literature

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Abbreviation:
iMCD, idiopathic multicentric Castleman's disease
IL-6, interleukin-6
TAFRO, Thrombocytopenia, Ascites (anasarca), myeloFibrosis, Renal dysfunction, and Organomegaly

ABSTRACT

TAFRO syndrome is a rare clinicopathologic variant of idiopathic multicentric Castleman disease characterized by Thrombocytopenia, Ascites (anasarca), myeloFibrosis, Renal dysfunction, and Organomegaly. Here, we report a case of TAFRO syndrome in an HIV-negative young Caucasian male who presented with fever, normocytic anemia, thrombocytopenia, and acute renal insufficiency. The serum interleukin-6 (IL-6) level was elevated. Chest and abdominal CT revealed bilateral pleural effusion, ascites, splenomegaly, and multiple mildly enlarged lymph nodes. An excisional biopsy of inguinal lymph node showed a few atrophic follicles and expansion of interfollicular areas by marked vascular proliferation and polytypic plasmacytosis. HHV-8 was negative. Subsequent bone marrow biopsy was normocellular with moderately increased megakaryocytes and occasional megakaryocytic emperipolesis. His signs and symptoms improved after treatment with methylprednisolone and tocilizumab (anti-IL-6 receptor antibody). Our study confirms the distinctive nature of this syndrome, which should allow for better recognition and appropriate therapy.

1. Introduction

Multicentric Castleman's disease (MCD) is a systemic inflammatory disorder caused by excessive proinflammatory cytokines, especially interleukin-6 (IL-6). Most cases of MCD are linked to infection by HHV-8/KSHV, and the virus was identified as the cause of hypercytokinemia in MCD patients. In the past few years, a group of HHV-8 and HIV negative MCD cases with similar clinicopathologic features, namely idiopathic MCD (iMCD), were reported [1]. In 2010, Takai et al. described three cases of iMCD with the following constellation of symptoms: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly [2]. The term "TAFRO syndrome" was proposed at the Fukushima and Nagoya meetings to delineate this disorder [3]. Interestingly, the lymph nodes from TAFRO syndrome patients appeared to show features of iMCD. To date, >30 cases have been reported mostly in Japan and two cases in Europe [4,5], one in South America [6], and two in North America [7,8]. Here we present a new case of TAFRO syndrome in the United States and review recent data on this newly recognized systemic disease.

2. Case presentation

The patient was a 32-year-old Caucasian male who presented with fever, fatigue, abdominal distension, anorexia, and shortness of breath. Complete blood count (CBC) showed mild leukocytosis, mild normocytic and normochromic anemia, and severe thrombocytopenia. Acute kidney injury was demonstrated by increased creatinine and blood urea nitrogen (BUN), elevated anion gap and hyperkalemia. The workup for multiple autoantibodies and viruses were all negative. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were both increased. IL-6 level in serum was increased to 43.6 pg/mL (0–15.5 pg/mL). Serum protein electrophoresis showed no evidence of monoclonal immunoglobulinemia. Chest and abdominal CT showed splenomegaly, ascites, as well as multiple prominent retroperitoneal, iliac chain, and inguinal lymph nodes. The largest one measured up to 8 mm. Given the thrombocytopenia and acute renal insufficiency, the possibility of thrombotic thrombocytopenic purpura (TTP) was clinically suspected. The patient symptoms temporarily improved after treatment with high dose steroid and plasmapheresis.

Abbreviation: iMCD, idiopathic multicentric Castleman's disease; IL-6, interleukin-6; TAFRO, Thrombocytopenia, Ascites (anasarca), myeloFibrosis, Renal dysfunction, and Organomegaly.

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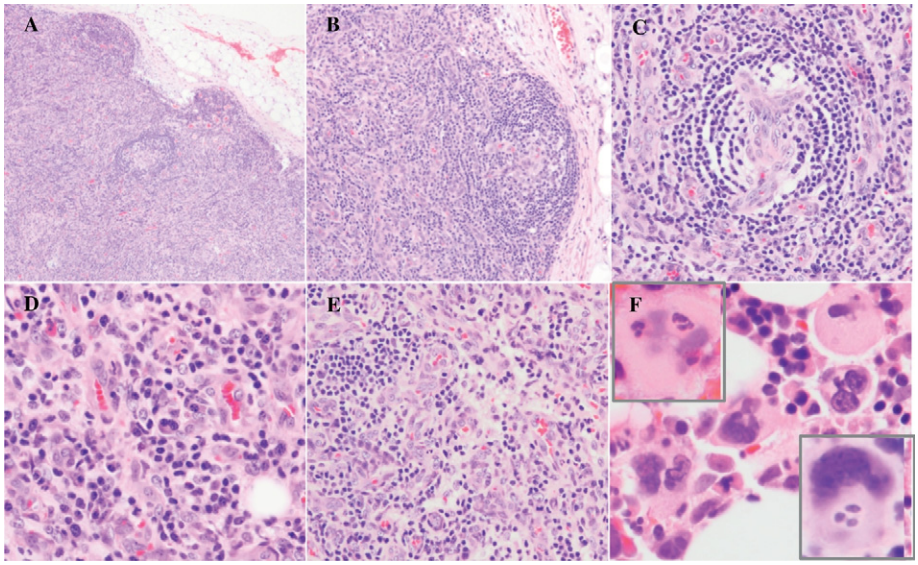

Fig. 1. Biopsy of an inguinal lymph node shows regressed germinal center with surrounded mantle zone with onion skinning change and penetrating blood vessel (A–C). Abundant histiocytes and plasma cells (D) and prominent vascular proliferation with plump endothelial cells are present in the expanded interfollicular zone (E). Bone marrow biopsy shows moderate hyperplasia of megakaryocytes (F) with occasional emperipolesis (F, inserts). A, ×40; B, ×100; C and E, ×200; D and F, ×400.

The patient returned shortly after discharge due to shortness of breath and fatigue. Repeated CT showed progressive ascites and bilateral pleural effusion. An inguinal lymph node biopsy showed small atrophic follicles with regressed germinal center surrounded by concentric rings of mantle zone. Occasional vessels penetrating through the germinal centers were noted (Fig. 1A–C). Interfollicular areas were markedly expanded by polytypic plasma cells and vascular proliferation with plump endothelial cells (Fig. 1D and E). IgG4 positive plasma cells were not increased. HHV-8 and Epstein–Barr virus-encoded small RNAs (EBER) were both negative (Fig. 2). The histopathologic features were reminiscent of multicentric Castleman disease.

PCR studies showed polyclonal T-cell receptor beta and gamma gene rearrangements. B-cell receptor gene rearrangement studies showed clonal gene rearrangement in the IgH FRIII region (one positive peak arising in a polyclonal background). The rest of the frameworks showed a polyclonal pattern. The significance of the PCR result is uncertain, and there was no evidence of monoclonality by immunohistochemistry. Also, the patient did not have other evidence of lymphoma.

A subsequent bone marrow biopsy was performed and showed normocellular marrow with moderately increased megakaryocytes. Occasional megakaryocytic emperipolesis was noted (Fig. 1F). Reticulin stain did not reveal myeloid fibrosis. Given the history of pleural effusion, ascites, anemia, thrombocytopenia, mild lymphadenopathy, splenomegaly, and renal dysfunction, the overall findings were compatible with TAFRO syndrome.

The patient was then initiated on high-dose methylprednisolone and tocilizumab. After four doses of tocilizumab, leukocytosis, anemia, and thrombocytopenia were all resolved. Electrolytes and kidney

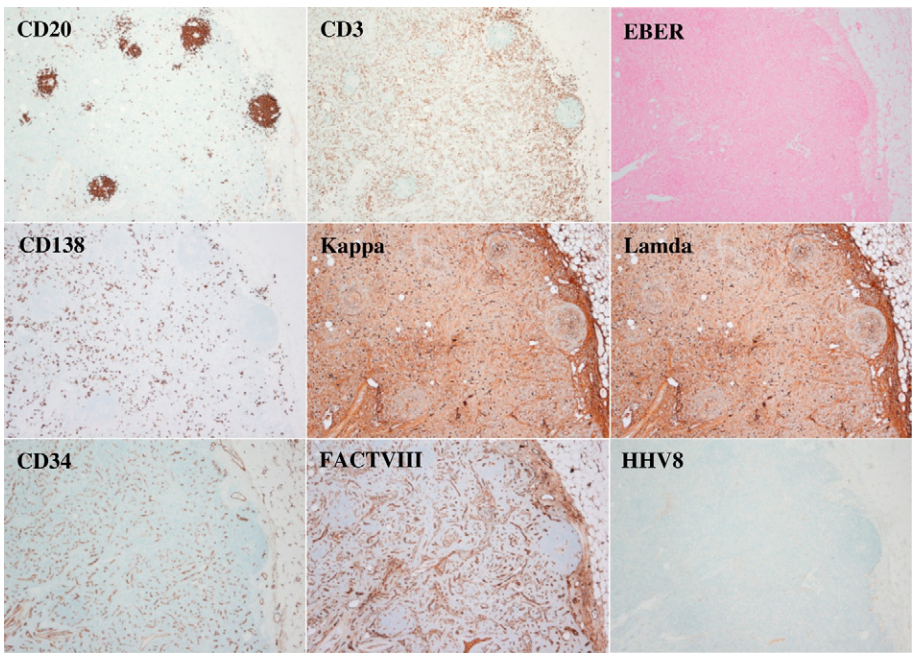

Fig. 2. Immunohistochemistry staining, ×40. CD20 shows B-cells in small follicles and CD3 highlights the unremarkable paracortical T-cells. CD138, Kappa, and Lambda show polyclonal plasmacytosis. CD34 and Factor VIII-related antigen highlight the massive proliferation of small vessels. HHV-8 and EBER are negative.