

A life-threatening case of TAFRO syndrome with dramatic response to tocilizumab, rituximab, and pulse steroids

The first case report in Latin America

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Abstract

Rationale: This is the report of the first case of TAFRO syndrome (Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction, Organomegaly) in Latin America.

Patient concerns: The patient was a 61-year-old white woman of Ashkenazi Jewish descent, who presented with a history of 8 days of nausea, vomiting, and fever; severe pitting edema in both legs, ascites, splenomegaly, and palpable axillary lymph nodes.

Diagnoses: Abdominal computed tomography (CT) showed bilateral pleural effusion and retroperitoneal lymph node enlargement.

Interventions: Anasarca and worsening of renal function led to admission to the intensive care unit (ICU) with multiple organ failure, requiring mechanical ventilation, vasopressor medications, and continuous renal replacement therapy (CRRT). Diagnosis of TAFRO syndrome was made on day 18 after admission, based on clinical findings and results of bone marrow and lymph node biopsies. She was treated with methylprednisolone, tocilizumab, and rituximab. One week after the first tocilizumab dose, she had dramatic improvements in respiratory and hemodynamic status, and was weaned from ventilator support and vasopressor medications.

Outcomes: After 2 weeks of therapy, CRRT was switched to intermittent hemodialysis. On day 46, the patient was discharged from the ICU to the general ward, and 3 months after admission, she went home.

Lessons: Provided the interleukin-6 measurement is available, this approach is suggested in cases of TAFRO syndrome, in order to customize the treatment.

Abbreviations: CD = Castleman disease, CRP = C-reactive protein, CRRT = continuous renal replacement therapy, CT = computed tomography, FDG = fluorodeoxyglucose, GGT = gamma-glutamyltranspeptidase, HHV-8 = human herpes virus 8, HV = hyaline-vascular, ICU = intensive care unit, IL6 = interleukin 6, IMCD = idiopathic Castleman disease, MCD = multicentric Castleman disease, PC = plasma-cell, PET-CT = positron-emission tomography, SUV = standard uptake value, TAFRO = Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction, Organomegaly, WBC = white blood cell count.

Keywords: edema, giant lymph node hyperplasia, primary myelofibrosis, renal insufficiency, thrombocytopenia

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1. Introduction

Castleman disease (CD) is a relatively rare, nonmalignant lymphoproliferative disorder^[1] that is histopathologically subclassified into hyaline-vascular (HV), plasma-cell (PC), and mixed types. The disease has also been classified into unicentric CD and multicentric CD (MCD), based on the clinical presentation.^[1] Human herpesvirus 8 (HHV-8) is an established etiologic agent in the pathogenesis of MCD.^[2] HHV-8 is found almost universally in patients with HIV-associated MCD, and in a variable portion of patients with HIV-negative MCD.^[1,2] It has recently been proposed that patients with MCD who are negative for both HIV and HHV-8 should be termed idiopathic MCD (IMCD).^[1] It is considered that most clinical manifestations of MCD are the result of increased production of pro-inflammatory cytokines (primarily interleukin-6, IL-6).^[1] The source of IL-6 production in HHV-8 positive MCD is HHV-8 infected plasmablasts,^[3] while the source in IMCD is currently unknown.

In the last 3 years, several published papers, mainly from Japan, have reported on patients who developed a previously

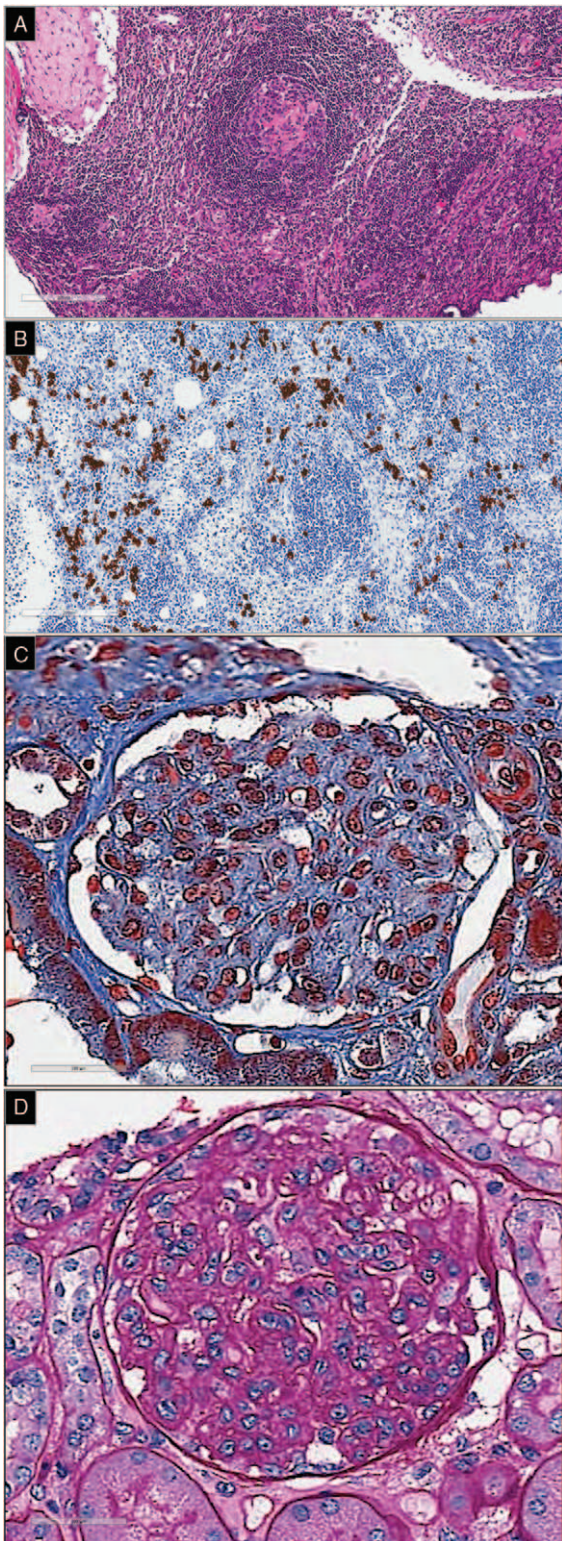


Figure 1. Histopathological examination of the lymph node, with immunohistochemical evaluation. (A) Lymph node with involuted and hyalinized germinal center. Vascular proliferation of the interfollicular area. Hematoxylin and eosin stain, 100x magnification. (B) CD138 stain (MI15, Dako) of lymph node showing section of lymph node with involuted hyalinized germinal centers and interfollicular areas with vascular hyperplasia and increased scattered plasma cells. 100x magnification. (C) Renal glomerulus with turgescence of endothelial cells, mesangiolysis and subendothelial space widening, and clarification. Masson trichrome stain, 200x magnification. (D) Renal glomerulus with subendothelial mesangial interposition (double contours) of glomerular basement membranes, simulating a membranoproliferative pattern; however, no immune complexes were present. PAS stain, 200x.

undescribed clinical syndrome characterized by thrombocytopenia associated with bone marrow fibrosis, fever, renal failure associated with anasarca, hepatosplenomegaly, and lymphadenopathy.^[4–12] Histopathological analysis of the lymph nodes involved revealed a histological pattern consistent with the HV subtype of CD. No finding of HHV-8 infection could be demonstrated in any case. On the basis of these cases, Masaki et al^[11] and Kawabata et al^[12] have coined the acronym TAFRO syndrome to describe this clinical entity (TAFRO stands for Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction, Organomegaly), a variant form of IMCD. In this paper, we report the case of a white patient who developed TAFRO syndrome, the first to be described in Latin America, and give a brief literature review on this novel disorder.

2. Case presentation

2.1. Patient information

A 61-year-old white woman of Ashkenazi Jewish descent presented to our hospital with a history of 8 days of nausea, vomiting, and fever. On physical examination, there was severe pitting edema in both legs and ascites. She had splenomegaly and palpable axillary lymph nodes.

2.2. Clinical findings and diagnostic assessment

Abdominal computed tomography (CT) scan at admission showed bilateral pleural effusion and retroperitoneal lymph node enlargement. Laboratory tests revealed mild anemia (hemoglobin 10.7 g/dL) and thrombocytopenia ($118 \times 10^9/L$). They also showed hypoalbuminemia (2.8 g/dL) and elevated C-reactive protein (CRP; 84.5 mg/L). Alkaline phosphatase (134 U/dL) and gamma-glutamyltranspeptidase (GGT) (98 U/day) were elevated. HIV and HTLV-1 virus serologies were negative, and a polymerase chain reaction (PCR) test did not detect the presence of HHV-8. The patient was positive for anti-citrullinated protein antibody, complement levels were normal, and there was neither hypergammaglobulinemia nor monoclonal immunoglobulin by serum immunofixation. The IL-6 serum level was significantly elevated at 75.9 pg/mL (reference range 0–7 pg/mL).

The patient underwent surgical biopsy of an enlarged lymph node on the left axilla. Histopathological examination of the lymph node revealed lymphoid hyperplasia with involution and hyalinization of the germinal center (Fig. 1A) and immunohistochemistry showed increased scattered plasma cells (Fig. 1B), suggestive of HV-subtype of CD. HHV-8 was negative by immunohistochemical analysis. Bone marrow biopsy demonstrated an increased number of megakaryocytes with dysplastic features, forming clusters, having hyper- and hypolobulated nuclei, and there was grade 1 fibrosis. She was negative for JAK2V617F and CALR exon 9 mutations, and the karyotype was diploid. She underwent a kidney biopsy that showed histopathological findings suggestive of renal thrombotic microangiopathy, with mesangial expansion and duplication of the glomerular capillary basal membrane (Fig. 1C, D). A positron-emission tomography (PET-CT) scan showed increased fluorodeoxyglucose (FDG) uptake in the cervical, axillary, mediastinal, abdominal, and iliac lymph nodes [maximum standard uptake value (SUV)=5.1] bilaterally (Fig. 2A).

2.3. Therapeutic interventions and follow-up

Seven days after hospital admission, the patient developed worsening of anasarca and renal function, and had to be

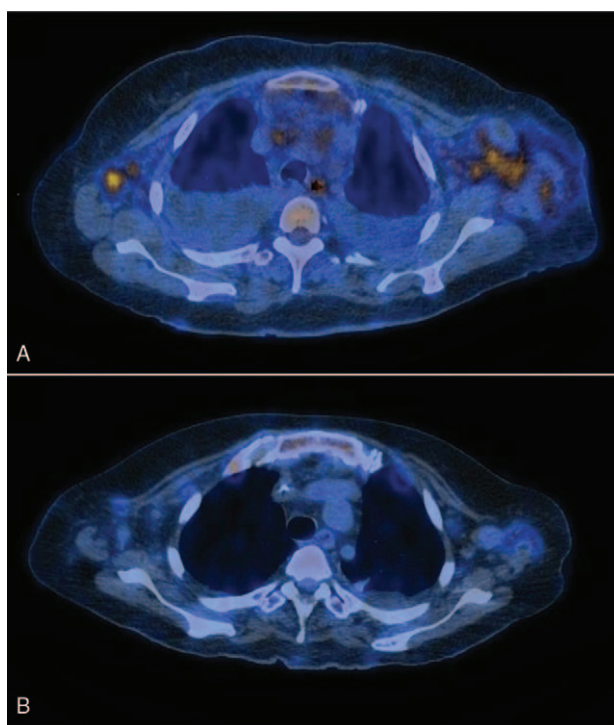


Figure 2. Positron-emission tomography (PET-CT) scan. A. PET-CT fusion image before the start of therapy at the thoracic level, showing fluorodeoxyglucose (FDG) uptake in enlarged axillary and mediastinal lymph nodes and the presence of bilateral pleural effusion. (B) PET-CT after one month of therapy showing reduction in lymph node size and FDG uptake and resolution of the pleural effusion.

transferred to the intensive care unit (ICU). She evolved with further progression of disease and developed multiple organ failure, requiring mechanical ventilation, vasopressor medications, and continuous renal replacement therapy (CRRT).

On day 18 of hospitalization, a preliminary diagnosis of TAFRO syndrome was made. At this point in time, hemoglobin was 8.3 g/dL, white blood cell count (WBC) was $17.11 \times 10^9/L$, and platelets were $21 \times 10^9/L$. Alkaline phosphatase was 205 U/L, with a GGT level of 210 U/L. Creatinine was 2.14 mg/dL, CRP was 231.2 mg/L, and IL-6 was 722.6 pg/mL. Due to the critical condition of the patient, she was started on triple therapy with pulse steroids (methylprednisolone, 1 g/day, for 3 consecutive days), weekly tocilizumab (8 mg/kg/dose), and rituximab (375 mg/m²/dose). One week after receiving the first dose of tocilizumab, she had a dramatic improvement in respiratory and hemodynamic status, and was weaned from ventilator support and discontinued vasopressor medications. After 2 weeks of CRRT, she was switched to intermittent hemodialysis. On day 46, the patient was discharged from the ICU, and after 3 months of hospitalization, she went home.

During hospitalization, the patient received 4 doses of tocilizumab and 4 doses of rituximab. A PET-CT scan after 1 month of therapy showed a significant reduction in uptake in the lymph nodes involved (Fig. 2B). The patient is currently in outpatient treatment, receives 1 dose of tocilizumab every 3 weeks, and has already tapered steroids. She has had complete resolution of the anasarca and organomegaly, and her latest complete blood count showed normalization of hemoglobin (13 g/dL) and platelet counts ($204 \times 10^9/L$). Her IL-6 levels continue to decrease, the latest measurement after 6 months being 69.3 pg/mL.

The patient described here gave her full consent for this publication and her test results.

2.4. Timeline

- (1) D1—Admission to the first aid unit, with 8 days of nausea, vomiting, fever. Edema, splenomegaly and palpable axillary lymph nodes. Mild anemia, thrombocytopenia, hypoalbuminemia, elevated CRP, alkaline phosphatase, and GGT. Elevated IL-6. Biopsies and immunohistochemistry: lymphoid hyperplasia, HC subtype CD positive, HHV-8 negative; increased number of megakaryocytes with dysplastic features in the bone marrow, grade 1 fibrosis; renal thrombotic microangiopathy. Increased FDG at PET-CT.
- (2) D7—Admission to ICU due to worsening of anasarca and renal function. Multiple organ failure. Mechanical ventilation, CRRT.
- (3) D18—Diagnosis of TAFRO. Methylprednisolone, tocilizumab, and rituximab started.
- (4) D25—Improvements in respiratory and hemodynamic status.
- (5) D39—Intermittent hemodialysis.
- (6) D46—Discharged from the ICU.
- (7) D90—Discharged from hospital.

3. Discussion

In this paper, we describe a patient with a diagnosis of TAFRO syndrome who developed multiple organ failure and was successfully treated with steroids, tocilizumab, and rituximab. We were able to find similar published cases in the medical literature, mostly in Japanese patients.^[4–12] To the best of our knowledge, only 9 cases have been described in Caucasian patients so far; ours is the first case reported in Latin America and the only one in a patient of Ashkenazi Jewish descent.

The diagnostic criteria for TAFRO syndrome are not absolutely clear, and this can lead to delays in diagnosis and treatment that may potentially affect outcome. In our case, 18 days transpired between hospital admission and the start of therapy. During this period, the patient developed multiple organ failure, requiring critical care support. To better define the clinical scope of TAFRO syndrome, Iwaki et al^[4] recently published the largest case series of this disease, with 25 cases, the majority from Japan. Almost all patients had the presence of anasarca, organomegaly, bone marrow fibrosis, and fever. On the basis of this series, the authors proposed a set of diagnostic criteria that could improve recognition of this entity in the clinical setting.^[4]

Renal failure is commonly found in patients with TAFRO, and its etiology is unclear.^[4] In our patient, kidney biopsy showed mesangial expansion, duplication of the capillary basal membrane, and other signs of capillary endothelial lesion, suggesting endothelial damage, probably secondary to the hypercytokinemia, as a potential mechanism. Other authors have previously reported on patients who developed CD, thrombocytopenia, and renal failure due to renal thrombotic microangiopathy.^[13,14] The association of Castleman, thrombocytopenia, and renal failure strongly suggests that these prior cases had undiagnosed TAFRO syndrome.

Our patient had a very aggressive clinical course, and even though the majority of patients with TAFRO syndrome have poor performance status (≥ 2) at the time of diagnosis, most do not develop multiple organ failure as occurred in our case. We were able to find 2 cases in the literature that also ran a

comparably severe course.^[4] On the basis of our and other published cases, it appears that there is a spectrum of disease that ranges from mild to severe. This heterogeneity in the clinical course might be due to the level and type of proinflammatory cytokines that are produced. Indeed, in our case, the level of IL-6 in peripheral blood at the time of admission to the ICU was found to be extremely high (722.6 pg/mL), comparable to that found in patients with septic shock.^[15]

The best treatment for patients with TAFRO syndrome is still unknown.^[4] The first cases described in Japan were responsive to steroids alone, but improvements in thrombocytopenia and anasarca were not consistently achieved.^[10–12] In the series by Iwaki et al,^[4] single-agent corticosteroids were able to control the disease in 47.8% of patients, while the remaining cases required additional therapy, most frequently anti-IL-6 antibodies (tocilizumab and siltuximab). The role of anti-IL-6 antibodies in TAFRO syndrome is not clear, as many patients show normal IL-6 levels, suggesting that other cytokines may also play a role in this disease. In our case, due to the critical status of the patient, we decided to treat her with high-dose steroids associated with weekly rituximab and tocilizumab infusions. We are maintaining her on monthly tocilizumab infusions using the IL-6 measurement and clinical parameters as guidance for decision-making. We suggest the use of this approach in other, similar cases of TAFRO syndrome, provided the IL-6 measurement is available, in order to customize treatment.

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