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CASE REPORT

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A case of TAFRO syndrome with DIC and neurologic and cardiac involvement

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Key Clinical Message

We highlight a novel case of TAFRO syndrome with disseminated intravascular coagulation, neurologic changes, and non-ischemic cardiomyopathy. Through this clinical vignette, we hope to raise awareness of TAFRO syndrome and encourage providers to maintain a high level of suspicion for it when evaluating patients who meet the diagnostic criteria.

KEYWORDS

anemias, cytokines, DIC, thrombocytopenia

1 | INTRODUCTION

TAFRO syndrome is a rare, severe systemic inflammatory disorder, typically characterized by thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, and organomegaly. Through this case, we unravel the intricacies of this complex condition and in narrowing the differential diagnoses, review various hematologic, infectious, and autoimmune syndromes. Additionally, this case is unique in that our patient also suffered from neurologic and cardiac complications, which have not been previously described with TAFRO syndrome in the literature.

2 | CASE HISTORY/EXAMINATION

A 46-year-old Hispanic female presented with 2 weeks of progressively worsening fatigue, mild dyspnea on exertion, abdominal pain, and swelling. Past medical history was notable for a uterine mass found incidentally on imaging after a motor vehicle accident 1 year prior (Figure 1). She was taking non-steroidal anti-inflammatory drugs for pain without relief. Upon presentation, her temperature was 98.1°F, heart rate 95 beats/min, respiratory rate 16 breaths/min, blood pressure 108/76 mmHg, and oxygen saturation 96% on ambient air. On exam, she was alert and oriented to person, place, and time. She had a soft, mildly distended abdomen with suprapubic tenderness and a firm, palpable mass in the suprapubic area. She had trace pitting edema in her bilateral lower extremities. There was no palpable lymphadenopathy or hepatosplenomegaly, nor bruising or signs of bleeding. Complete blood count (CBC) revealed hemoglobin (Hgb) of 6.7 g/dL and platelet count of 96×10^3/mL. The metabolic panel showed elevated blood urea nitrogen (44 mg/dL), elevated creatinine (1.99 mg/dL), abnormal liver function tests (aspartate aminotransferase 58 units/L, alkaline phosphatase 286 units/L), and hypoalbuminemia (1.8 g/dL). Urinalysis showed small blood, 100 protein, 11–25 squamous cells, 11–25 white blood cells, large bacteria, and 6–10 granular casts. Computed tomography (CT) of the abdomen and pelvis without contrast demonstrated a pericardial effusion, small bilateral pleural effusions, moderate abdominal ascites, and a 14-centimeter (cm)

×13.6 cm ×11.3 cm solid uterine mass. The uterine mass was smaller in size compared to 1 year prior. A renal ultrasound revealed normal kidneys without obstructive changes. She was admitted for further workup and management of a suspected uterine malignancy.

Upon admission, she underwent paracentesis, transvaginal ultrasound, transthoracic echocardiogram (TTE), and CT chest, which were all unrevealing and negative for malignancy. Shortly after, her intraabdominal ascites rapidly reaccumulated and her renal function deteriorated leading to anuria and initiation of hemodialysis. Lab workup revealed positive antinuclear antibody, positive lupus anticoagulant, elevated erythrocyte sedimentation rate (97 mm/h), elevated lactate dehydrogenase (246 units/L), and elevated fibrinogen (581 mg/dL). Complement levels were normal. She underwent renal biopsy which revealed acute thrombotic microangiopathy (TMA) with diffuse acute tubular injury and early signs of chronicity (Figure 2). Due to concern for catastrophic APLS versus atypical hemolytic uremic syndrome, she was started on methylprednisolone and underwent plasma exchange before transferring to our institution for a higher level of care.

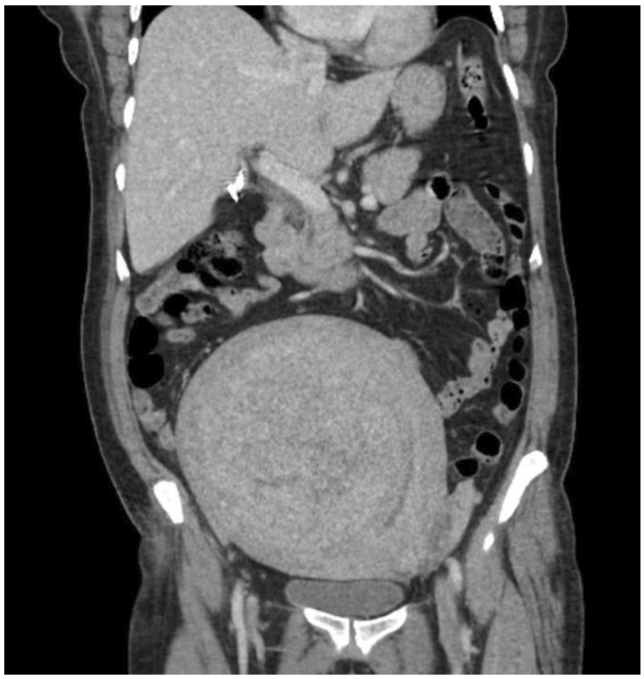

FIGURE 1 Coronal CT scan demonstrating an 18.1 cm heterogeneously enhancing thick-walled uterine mass with dilated ovarian veins.

Upon arrival to our institution, her peripheral smear was analyzed and surprisingly, schistocytes were absent. She was also found to have a positive Sjogren's syndrome-related antigen A (SSA) antibody. The consulted rheumatologist felt that the serologic studies were consistent with an undifferentiated connective tissue disease and she was started on hydroxychloroquine. Meanwhile, tense ascites and bilateral pleural effusions persisted. Blood work was consistent with evolving disseminated intravascular coagulation (DIC). Infection was ruled out as an etiology of the DIC. She also tested positive for platelet autoantibodies (anti-GP IIb/IIIa; GP Ib/IX; and GP Ia/IIa). Her fibrinogen and D-dimer levels improved with low-dose unfractionated heparin, but her platelet count continued to fall. At this point, she was still on methylprednisolone and had received two administrations of intravenous immunoglobulin (IVIG). She was also started on rituximab. A bone marrow biopsy (Figure 3) revealed slightly hypocellular bone marrow with trilineage hematopoiesis and reticulin fibrosis without evidence of malignancy. Interleukin (IL)-6 level was elevated (18.1 pg/mL). IL-2 and vascular endothelial growth factor levels were normal.

The presence of fibrosis in the bone marrow, thrombocytopenia, elevated systemic inflammatory markers, anasarca, and renal dysfunction led to the diagnosis of TAFRO syndrome. Treatment with rituximab was continued weekly for four total doses. In addition, due to

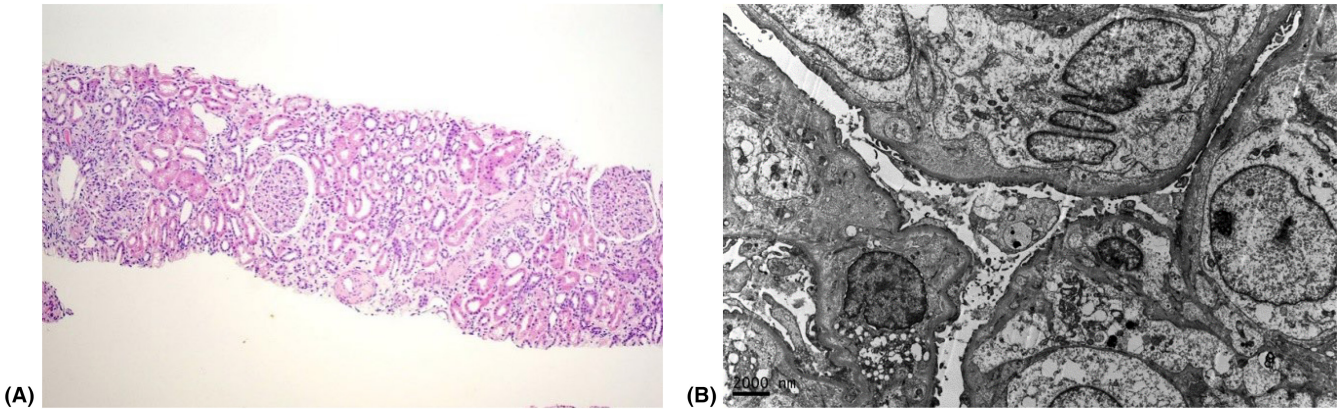

FIGURE 2 (A) Renal cortical tissue with hematoxylin and eosin stain showing acute tubular injury. (B) Left kidney biopsy showing acute thrombotic microangiopathy with diffuse acute tubular injury.

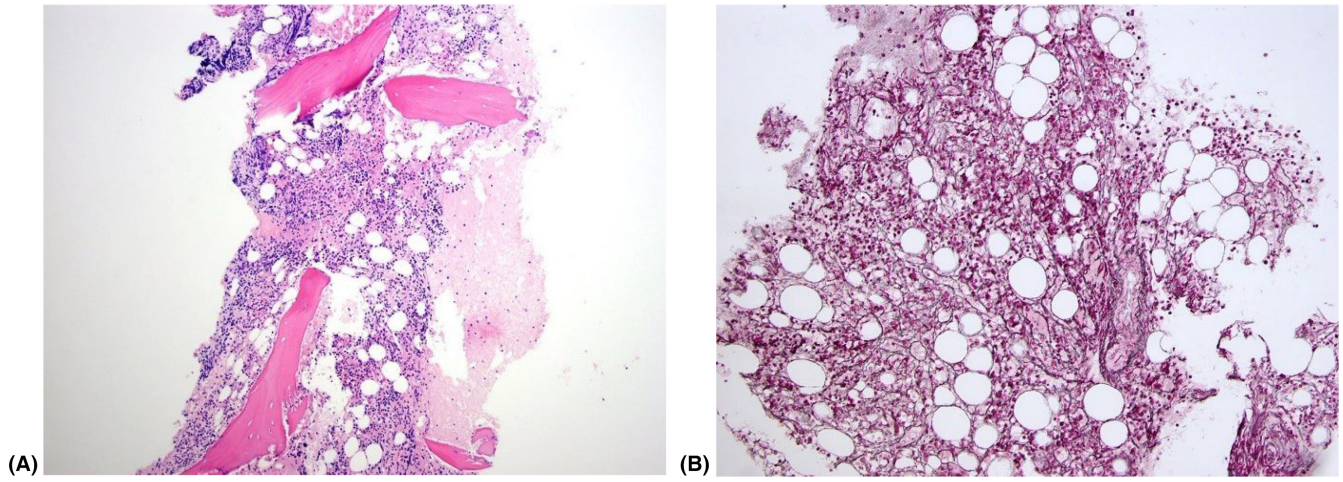

FIGURE 3 (A) Slightly hypocellular bone marrow with trilineage hematopoiesis, stained with hematoxylin and eosin. (B) Bone marrow fibrosis, stained with reticulin.

elevated IL-6 level, tocilizumab was given. With this regimen, her platelet count started to improve and her fibrinogen level normalized. Renal function recovered and dialysis was stopped. Anasarca receded and no further paracenteses were required. While she was steadily improving, she suffered an acute episode of left gaze deviation, aphasia, and diminished mental status that resolved spontaneously within a few hours. Though electroencephalograms remained unremarkable, neurology consultants attributed the transient encephalopathy to seizure activity. Levetiracetam was started without recurrence of neurologic symptoms. As part of the workup, she underwent a TTE which showed reduced ejection fraction of 35% and hypokinesis of the inferior myocardium. Three weeks prior at admission, her TTE had been essentially normal except for tricuspid valve regurgitation. CT angiogram of the coronary arteries showed normal arteries with a calcium score of zero. Cardiology consultants believed her non-ischemic cardiomyopathy was due to autoimmune myocarditis and she was placed on guideline-directed medical therapy for heart failure with reduced ejection fraction. She was first discharged to an acute inpatient rehabilitation facility and subsequently discharged home, only on low dose prednisone and hydroxychloroquine for treatment of TAFRO.

By the time she was discharged home from the acute inpatient rehabilitation facility, the ascites had almost fully resolved, platelet count was normal, and hemoglobin was steadily improving. Several weeks later, she returned for a follow-up visit in our office and was functionally at her baseline. She had no recurrence of neurologic symptoms. Lab work showed normal white blood cell count, hemoglobin, and platelets. The basic metabolic panel and inflammatory markers were normal. A repeat test for Lupus anticoagulant was negative. Coagulation tests and D-dimer were normal. Hydroxychloroquine and prednisone were discontinued. About 10 months later, a repeat TTE showed a recovered ejection fraction of 60%. For the uterine mass, she ultimately underwent an elective hysterectomy with pathology confirming a 10.1 cm leiomyoma. The postsurgical course was complicated by pulmonary emboli that were treated with apixaban. She has since completed treatment and resumed all activity without physical restrictions.

3 | DISCUSSION

The patient presented with multiple nonspecific complaints that evolved to include a variety of medical problems, each prompting thoughtful examination. Initially, the uterine mass raised suspicion for a gynecologic malignancy; however, the smaller size of the mass compared to the previous year suggested otherwise. The transudative nature of the peritoneal fluid, the concurrent renal dysfunction in the absence of obstructive uropathy, and the apparent stability of the uterine mass also suggested a different etiology than gynecologic malignancy. The severe hypoalbuminemia, ascites, bilateral pleural effusions, pericardial effusion, abnormal liver function tests, severe anemia, moderate thrombocytopenia, and abnormal renal function suggested a systemic inflammatory process for which autoimmune workup was performed.

With the renal biopsy findings, the differential for TMA was explored. Disorders associated with TMA are thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), aHUS, DIC, cancer-related TMA, drug-induced TMA, post-transplant TMA, TMA associated to underlying autoimmune disorders, and TMA due to malignant hypertension.[1] TTP is caused by a deficiency

in ADAMTS13, a protease that cleaves ultra-large multimers of von Willebrand factor (vWF).[2] Typically, this deficiency is acquired due to anti-ADAMTS13 antibodies, though rarely the deficiency may occur because of germline mutations of the ADAMTS13 gene (Upshaw-Schulman syndrome).[2] Without that protease, large vWF multimers bind to platelets and endothelium leading to fibrin-poor platelet aggregates in the small vasculature that lead to platelet consumption and MAHA.[1,2] Patients with TTP suffer ischemic end organ injury causing neurologic, cardiac, and renal sequelae.[1,2] HUS presents with the triad of hemolytic anemia, thrombocytopenia, and acute renal failure precipitated by gastrointestinal infections by Shiga toxin-producing enterohemorrhagic *Escherichia coli*.[3] In contrast, in aHUS, the MAHA, thrombocytopenia, and acute renal failure are caused by acquired autoantibodies against complement regulatory proteins.[3] Eculizumab and ravulizumab are terminal complement inhibitors used to treat aHUS.[1,3] DIC can also lead to microangiopathic thrombi formed mostly by platelets and fibrin strands.[4] Antiphospholipid antibodies including Lupus anticoagulant could lead to endothelial injury and activation of the coagulation cascade with subsequent thrombosis that may be limited to microvasculature. Vasculitis as part of a systemic inflammatory process can also be associated with DIC. Our patient did not have evidence for a MAHA on her peripheral smear, which ruled out a systemic TMA. Based on the blood work and clinical course, her picture was more consistent with ongoing DIC manifested by falling fibrinogen and platelets as well as the TMA noted in the kidney biopsy. The cause of the DIC, however, was unclear. Fortunately, no excessive bleeding was noted at any time. Treatment with low-dose heparin (400 units/hour) was recommended as well as transfusion of cryoprecipitate aiming to keep fibrinogen above 100 mg/dL.

With the bone marrow biopsy findings, the differential for reticulin fibrosis was explored. Bone marrow fibrosis is caused by the deposition of reticulin fibers and, in some cases, collagen fibers.[5] Conditions associated with isolated reticulin fiber deposition include hairy cell leukemia, HIV, pulmonary arterial hypertension, visceral leishmaniasis, and treatment with hematopoietic growth factors.[5] A suspected pathogenesis includes elevation of circulating pro-inflammatory cytokines such as tumor growth factor-beta causing promotion of malignant hematopoiesis.[5] Elevated IL-6 suggests systemic inflammation and the presence of a cytokine storm.[6]

As mentioned earlier, the presence of reticulin fibrosis, thrombocytopenia, elevated systemic inflammatory markers, anasarca, and renal dysfunction led to the suspicion for TAFRO syndrome in our patient. TAFRO syndrome is a severe systemic inflammatory process driven by high levels of IL-6 and VEGF initially described in 2010.[7,8] It is thought to be a form of idiopathic multicentric Castleman disease (iMCD), though this is currently under debate.[9,10] Classic clinical features of TAFRO syndrome are thrombocytopenia, anasarca, fever, reticulin myelofibrosis, and organomegaly, with some sources citing renal dysfunction as a defining feature.[8–12] In 2019, Masaki et al. proposed updated diagnostic criteria based on a retrospective study of over 200 cases (Table 1). Recommended first-line treatment consists of an IL-6 inhibitor (such as tocilizumab) and corticosteroids.[6,12,13]

TABLE 1 Diagnostic criteria for TAFRO syndrome.[10] Diagnosis requires all three major criteria and at least two minor criteria. Exclusion criteria are disorders that must be ruled out.

Major criteria
Anasarca: Pleural effusion, ascites, or generalized edema
Thrombocytopenia: Platelet count ≤100 K/mcL
Systemic inflammation: Fever >37.5°C and/or C-reactive protein ≥2 mg/dL
Minor criteria
Lymph node biopsy with Castleman-disease like features
Bone marrow biopsy with reticulin myelofibrosis and/or increased megakaryocytes
Mild organomegaly: Hepatomegaly, splenomegaly, and lymphadenopathy
Progressive renal insufficiency
Exclusion criteria
Malignancy
Autoimmune disorders
Infection
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy/edema, monoclonal protein, skin changes)
Hepatic cirrhosis
Thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS)

Per the diagnostic criteria set forth by Masaki et al., our patient met the three major criteria (anasarca, thrombocytopenia, systemic inflammation) and two minor criteria (bone marrow biopsy with reticulin myelofibrosis, progressive renal insufficiency). She also did not meet any of the exclusion criteria (malignancy, autoimmune, infection, POEMS syndrome, hepatic cirrhosis, TTP, or HUS). Although she had autoimmune features with positive ANA, SSA, and platelet autoantibodies, her symptoms should have improved after steroids, plasmapheresis, IVIG, and rituximab if an autoimmune process were driving her disease process. Though TTP and HUS were also considered, absence of MAHA on peripheral smear made these unlikely causes. The occurrence of DIC was thought to be a complication of TAFRO.

The mystery of this case is the underlying etiology of her systemic inflammation, as evidenced by her elevated IL-6, that led to the manifestation of TAFRO

syndrome. Current literature suggests possible causes of TAFRO syndrome as infections, germ cell mutations, or autoimmune disorders. She had an extensive infectious workup that remained negative. Additionally, she never had any overt infectious symptoms or findings. Case reports suggest an association between HHV-8 or HIV infection and the development of MCD, but our patient tested negative for HIV, and though we did not test for HHV-8, she did not have any findings suggestive of this infection. We do not believe her symptoms were caused by a germ cell mutation as our malignancy workup also remained negative. Autoimmune disease could be a possible etiology with her positive ANA and SSA antibodies as well as platelet autoantibodies, however, many patients with similar serologies do not develop TAFRO syndrome. Furthermore, her symptoms should have resolved with the use of steroids, plasmapheresis, IVIG, and rituximab. It is quite possible that we may never determine the true etiology of the inflammation that led to her cascade of symptoms. Further studies are necessary to determine if there are alternate pathogenesis associated with TAFRO syndrome.

AUTHOR CONTRIBUTIONS

Lindsay Moy: Writing – original draft; writing – review and editing. **Mauli Patel:** Writing – original draft; writing – review and editing. **Josiah Eschbach:** Writing – original draft. **Phillip Knouse:** Writing – original draft. **Ángel Gálvez:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest in relation to this manuscript. There are no relationships with industry.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICAL APPROVAL

None.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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