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Case Report

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TAFRO in Disguise: Idiopathic Multicentric Castleman Disease-Like Syndrome With Renal Thrombotic Microangiopathy and Autoimmune Overlap

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Abstract

TAFRO syndrome is a rare systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever/elevated C-reactive protein (CRP), reticulin fibrosis of bone marrow/renal dysfunction, and organomegaly. It is considered an aggressive subtype of idiopathic multicentric Castleman disease (iMCD), typically requiring lymph node (LN) histopathology for definitive diagnosis. The cases lacking LN biopsy due to accessibility or severe systemic illness but meeting all the criteria for iMCD and TAFRO are categorized as TAFRO with possible iMCD. Another category well recognized in the literature is TAFRO associated with autoimmune diseases, especially Sjogren's syndrome. We present a 29-year-old female patient with a history of seropositive rheumatoid arthritis, Sjogren's syndrome, and Barrett's esophagus who developed an abrupt onset of severe thrombocytopenia, anemia, generalized anasarca, high CRP levels, and renal dysfunction 3 weeks after a viral illness with gastrointestinal symptoms. Imaging revealed hepatosplenomegaly, retroperitoneal lymphadenopathy, and pleural effusion and ascites requiring drainage. Further analysis revealed hypoalbuminemia, elevated soluble interleukin-2 receptor (sIL-2R) and interleukin-6 (IL-6) levels, as well as negative human herpesvirus-8 (HHV-8), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) serologies. ADAM metallopeptidase with thrombospondin type 1 motif 13 (ADAMST13) and complement studies were also negative. A bone marrow biopsy showed evidence of reticulin fibrosis, but an LN biopsy was not feasible. A renal biopsy demonstrated histopathological features consistent with thrombotic microangiopathy (TMA), a finding increasingly recognized in TAFRO. Additionally, elevated anti-Sjogren's syndrome-related antigen A (SSA) antibodies were found, suggesting a possible autoimmune overlap. Given no LN biopsy, a diagnosis of "TAFRO syndrome with possible iMCD" with autoimmune overlap was entertained. The patient responded well to systemic corticosteroids, plasmapheresis, and anti-interleukin-1 (IL-1) therapy, anakinra. She was discharged in stable condition with improved clinical condition and renal function. The regimen was changed to anti-IL-6 therapy, sarilumab, in the immediate post-discharge period. This case is unique as it fulfills all six criteria of TAFRO syndrome and emphasizes the importance of recognizing it without an LN biopsy, TAFRO syndrome with possible iMCD, particularly when clinical, laboratory, and bone marrow findings support the diagnosis. This case further highlights the diagnostic complexity of TAFRO syndrome and the co-occurrence of renal TMA and autoimmune overlap, suggesting a potential interplay between multiple autoimmune cytokine-driven inflammatory processes. Prompt diagnosis and early immunosuppressive therapy are critical to improve systemic and renal outcomes in such cases with diagnostically ambiguous presentations.

Keywords: TAFRO syndrome; Idiopathic multicentric Castleman disease; Thrombocytopenia; Acute renal failure; Thrombotic microangiopathy; Reticulin fibrosis of bone marrow; Anti-IL-1 therapy; Anakinra; Anti-IL-6 therapy; Tocilizumab; Siltuximab; Cyclosporine

Introduction

TAFRO syndrome is a rare systemic inflammatory disorder driven by cytokine storms, primarily interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), and is characterized by thrombocytopenia, anasarca, fever or elevated inflammatory markers (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin), reticulin fibrosis of the bone marrow (BM) or renal dysfunction, and organomegaly [1-3]. The condition arises from aberrant immune activation, possibly triggered by viral infections, autoimmune dysregulation, or unidentified environmental or genetic factors. TAFRO syndrome is considered a subtype of idiopathic multicentric Castleman disease (iMCD), typically requiring specific lymph node (LN) histopathological characteristics for a definitive diagnosis. However, in some cases, particularly when systemic illness is severe or lymphadenopathy is inaccessible, a biopsy may not be feasible. Cases lacking an LN biopsy but meeting all the criteria for iMCD and TAFRO are classified as "TAFRO

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Table 1. Laboratory Data on Admission and Discharge

Laboratory data	Admission	Days 7 - 10	Discharge (day 33)	Normal range
White blood cells	13.9	16.2	7.2	4.8 - 10.8 × 10^3 cells/µL
Hemoglobin	9.8	6.8	8.4	13.5 - 17.5 g/dL
Platelet count	144	50	113	130 - 400 × 10^3 cells/µL
Sodium	128	129	139	136 - 145 mmol/L
Potassium	4.6	3.6	4.1	3.5 - 5.1 mmol/L
Bicarbonate	20	15	20	22 - 29 mEq/L
Blood urea nitrogen	35	93	34	8 - 22 mg/dL
Creatinine	1	3.46	0.59	0.7 - 1.2 mg/dL
Urine protein, random	157	57.5	-	mg/dL (no reference)
Urine protein-to-creatinine ratio	0.87	1.24	-	< 0.18
Hemoglobin A1c	5.5	-	-	4.4-5.6%
Total bilirubin	0.6	0.6	0.4	0.20 - 1.00 mg/dL
Aspartate transaminase	17	27	21	10 - 34 U/L
Alanine transaminase	8	10	70	10 - 44 U/L
Calcium	7.7	7.6	8.6	8.5 - 10.2 mg/dL
Total protein	6.2	5.1	5.6	6.1 - 8.2 g/dL
Albumin	1.7	2.2	3.5	3.3 - 5.2 g/dL
C-reactive protein	16.7	4.9	-	< 0.5 mg/dL
Ferritin	505	1,581	778	12 - 114 ng/mL
Erythrocyte sedimentation rate	61	12	6	2 - 37 mm/h
Anti-SSA antibodies	-	> 8.0	-	0.0 - 0.9 antibody index
Rheumatoid factor	77	-	-	< 14 IU/mL
Anti-CCP antibodies	-	230	-	0.0 - 2.9 U/mL
Lactate dehydrogenase	-	237	217	12 - 225 U/L
Interleukin-1β	-	< 6.5	-	< 6.5 pg/mL
Soluable IL-2 receptor	-	3,477	1,689	175 - 858 pg/dL
Interleukin-6	-	3.7	< 2	≤ 2.0 pg/mL
Interleukin-8	-	7.3	< 3	≤ 3.0 pg/mL
Tumor necrosis factor	-	2.2	1.7	≤ 7.2 pg/mL

CCP: cyclic citrullinated protein; SSA: Sjogren's syndrome-related antigen A.

with possible iMCD", and these cases remain diagnostically challenging and complex to treat. Another frequently overlapping category proposed in the literature is "TAFRO associated with autoimmune diseases", especially Sjogren's syndrome [3-5]. TAFRO syndrome typically manifests acutely and can lead to multiorgan failure, resulting in poor outcomes if untreated. Early recognition is critical but often delayed due to the overlap with autoimmune diseases, malignancies, infections, and other systemic inflammatory syndromes.

Case Report

We report a case of a 29-year-old Hispanic-American woman with a history of seropositive rheumatoid arthritis, Sjogren's syndrome, and Barrett's disease who presented with the sudden onset of generalized edema, fatigue, decreased urine output, and malaise 2 - 3 weeks after a viral illness with upper respiratory and gastrointestinal symptoms. She appeared acutely ill on initial assessment, showing prominent findings of generalized anasarca (thigh-high lower extremity edema, abdominal distention with abdominal wall edema, decreased breath sounds with crackles, and periorbital facial puffiness), fevers, and generalized pain/myalgias. Initial laboratory results indicated mild leukocytosis (13.9 × 10^3 cells/µL), mild thrombocytopenia (144 × 10^3 cells/µL), anemia (9.8 g/dL), hypoalbuminemia (2.2 mg/dL), hyponatremia, and normal liver enzymes (Table 1). A computed tomography (CT) of the chest, abdomen, and pelvis without contrast demonstrated bilateral pleural effusions, ascites, mild hepatosplenomegaly, bilateral perinephric stranding, and small retroperitoneal (diffuse), periaortic, and mesenteric lymphadenopathy (Figs. 1-3).

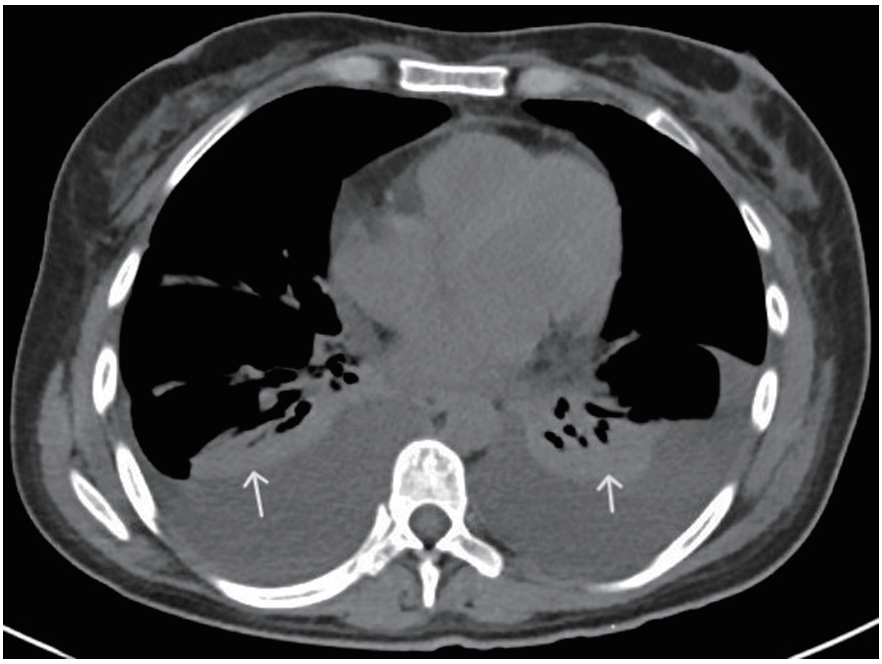

Figure 1. CT of chest with contrast (axial view) showing bilateral pleural effusions and adjacent atelectasis (white arrows). CT: computed tomography.

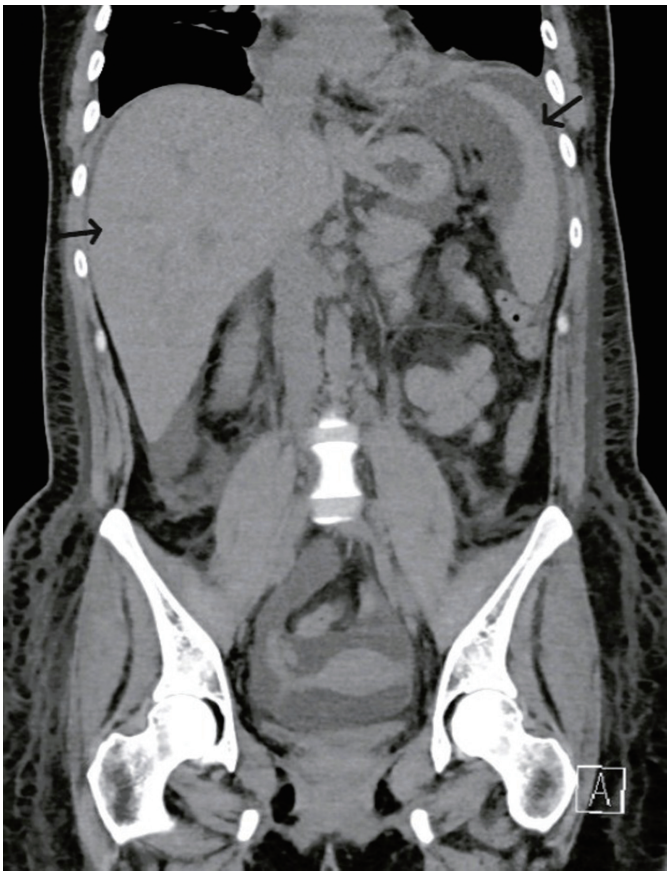

Figure 2. CT of abdomen and pelvis with contrast (coronal view) showing mild hepatosplenomegaly (black arrows). CT: computed tomography.

Urinalysis showed no hematuria and did not indicate a urinary tract infection; however, the patient was empirically initiated on intravenous (IV) ceftriaxone 1 g daily due to the CT findings. Random urine protein was elevated at 157 mg/dL, and the protein-to-creatinine ratio was 0.87. The transthoracic echocardiogram revealed normal ejection fraction and mild pericardial effusion. In addition to diuretics and albumin infusions, the patient underwent both diagnostic and therapeutic thoracentesis and paracentesis, with analysis showing noninfectious reactive fluid and negative cytology. Further laboratory analysis indicated elevated inflammatory markers (CRP, ferritin, ESR) (Table 1). The patient tested negative for influenza A and B, COVID-19, and an extended respiratory panel, including respiratory syncytial virus (RSV). Infectious diseases were consulted, and an infectious mononucleosis-like condition was suspected. The patient had a negative Monospot test and negative serologies for acute hepatitis panel, human herpes virus-8 (HHV-8), human herpes virus-6 (HHV-6), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). The antibiotics were discontinued after an empirical course of 7 days.

The patient experienced worsening thrombocytopenia (50×10^3 cells/μL) and anemia (6.8 g/dL) over the following week. She required a transfusion of one unit of packed red blood cells. Gastroenterology was consulted, and the patient underwent esophago-duodenoscopy and colonoscopy, which revealed an irregular Z-line in the esophagus, mild gastritis, a 4 mm rectal polyp, and internal hemorrhoids; pathology results were negative for *Helicobacter pylori,* metaplasia, or malignancy. A peripheral blood smear showed low platelet counts with clumping, slightly increased and enlarged megakaryocytes, and elevated polymorphonuclear cells (PMNCs). The hemolytic workup was negative, except for elevated lactate de-

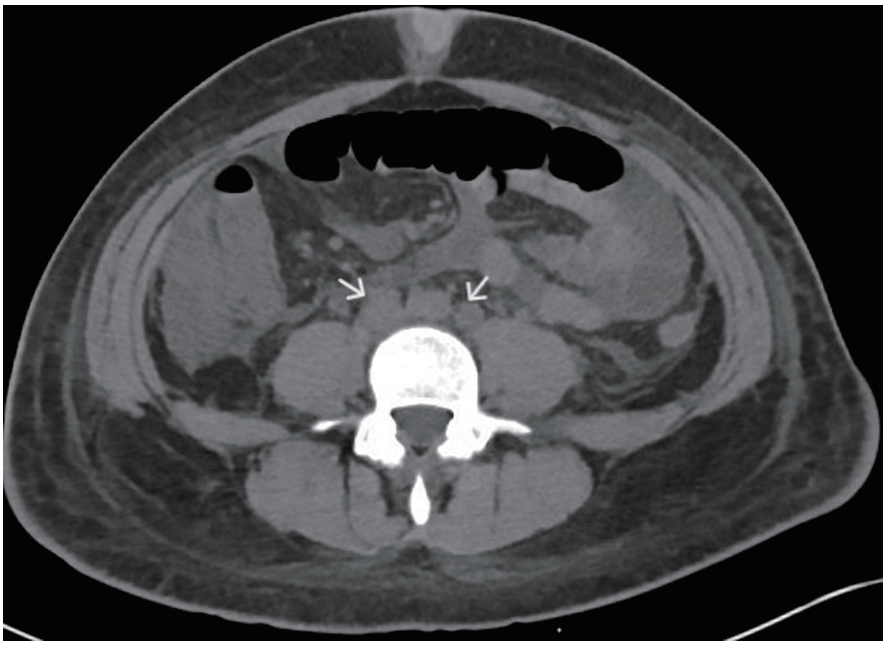

Figure 3. CT of abdomen and pelvis with contrast (axial view) showing retroperitoneal lymphadenopathy (white arrows). CT: computed tomography.

hydrogenase (LDH). ADAM metallopeptidase with thrombospondin type 1 motif 13 (ADAMST13) and complement levels were also normal. Further analysis indicated elevated cytokine levels (IL-6, IL-8, IL-13, and IL-10) and soluble interleukin-2 receptors (sIL-2Rs). The hematology/oncology team was consulted, and they recommended a BM biopsy based on the overall clinical picture. The BM biopsy revealed increased reticulin fibrosis, megakaryocytic hyperplasia with larger cells, and negative features of hemophagocytic lymphohistiocytosis (HLH) (Fig. 4).

Around the same time, following the rheumatologist's recommendation, the patient received 3 days of pulse-dose

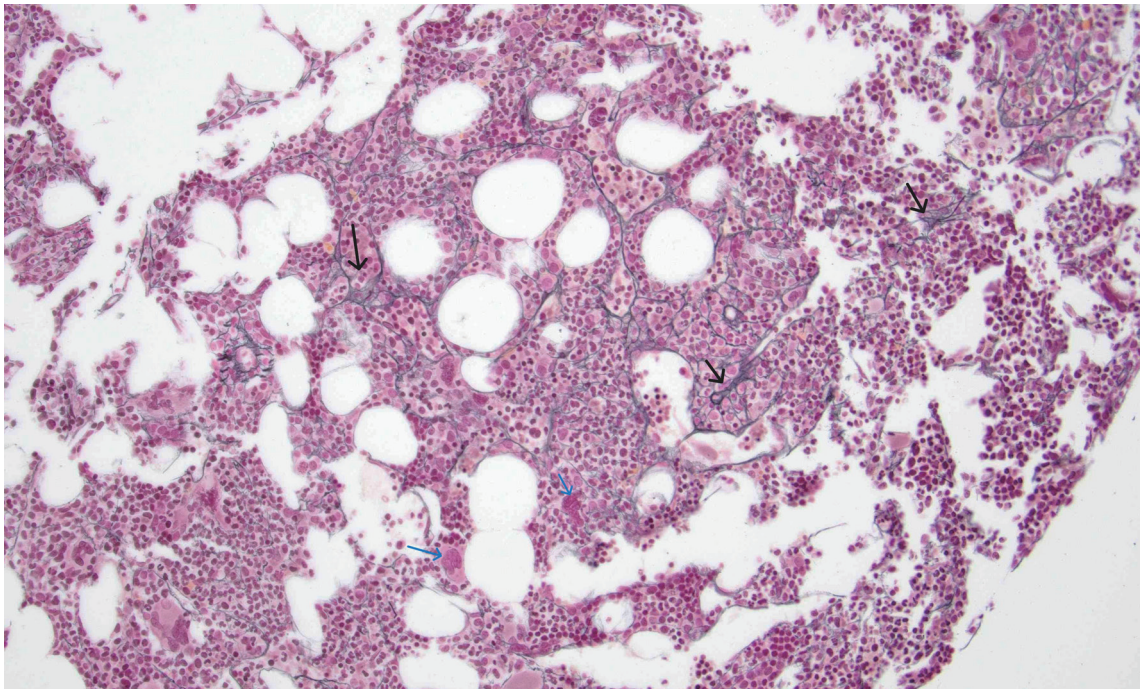

Figure 4. Bone marrow biopsy showing increased reticulin fibrosis (black arrows) and megakaryocytic hyperplasia with enlarged cells (blue arrows).

steroids, IV methylprednisolone 1 g daily, followed by IV methylprednisolone 40 mg twice daily, and was eventually transitioned to prednisone 60 mg daily. A retroperitoneal LN biopsy could not be performed due to inaccessibility. The nephrology team was consulted because the patient also had worsening renal function (creatinine 3.16 mg/dL), and a renal biopsy was recommended based on the evidence of an inflammatory autoimmune pathway. The renal biopsy revealed histopathological features consistent with thrombotic microangiopathy (TMA), a finding increasingly recognized in TAFRO. Additionally, the patient was found to have elevated anti-Sjogren's syndrome-related antigen A (SSA) antibodies, rheumatoid factor, and anti-cyclic citrullinated protein (CCP) antibodies, and considering her history of Sjogren's syndrome and rheumatoid arthritis, an autoimmune overlap was suspected to have contributed to the exaggerated autoimmune and inflammatory milieu. Multiple other autoimmune rheumatological assays returned negative results.

The patient fulfilled all clinical and laboratory characteristics of iMCD and met all the major and minor criteria of TAFRO syndrome. However, due to the absence of an LN biopsy, the diagnosis of "TAFRO syndrome with possible iMCD" overlapping with "TAFRO associated with autoimmune disease" was considered, and a plan was made to manage her as iMCD-TAFRO. The patient experienced a prolonged hospital course because of the multidisciplinary evaluations and multimodal management. She received three cycles of plasmapheresis based on the recommendations of the nephrologist and hematologist during her fourth week of stay, spaced over 5 days. Following this, she was started on anti-IL-1 therapy, anakinra 100 mg daily subcutaneously, which she received for 5 days while admitted. Anakinra (IL-1β inhibition) was chosen over IL-6 inhibitors due to the exaggerated cytokine/immune response and co-existing autoimmune conditions.

The patient responded well to systemic corticosteroids, plasmapheresis, and anakinra. She was discharged after 5 weeks of hospitalization in a stable condition, with improved anasarca and renal function. A plan was established for her to continue anakinra for five more days, prednisone at 60 mg daily for three additional weeks, and to have close outpatient follow-ups with rheumatology, nephrology, and hematology. During the follow-up visit 1 week after discharge, she showed complete clinical improvement, with resolution of signs of fluid overload, normal blood counts, and baseline renal function. The rheumatologist changed her regimen to anti-IL-6 therapy, sarilumab at 200 mg subcutaneously every 2 weeks, during the immediate post-discharge period, while continuing prednisone at 60 mg daily. A week after the discharge, Renasight (a comprehensive chronic kidney disease gene panel) was sent. It returned negative, including the complement component 3a receptor 1 (*C3AR1*) gene involved with atypical hemolytic uremic syndrome (aHUS).

Discussion

Castleman disease (CD) refers to a group of rare, heterogeneous lymphoproliferative disorders characterized by LN enlargement and systemic inflammation. It exists in two major forms, unicentric CD (UCD), affecting a single LN region, and multicentric CD (MCD), involving multiple LN areas (Table 2) [1, 4, 5]. When MCD occurs without an identifiable cause (negative HHV-8 infection), it is termed iMCD. iMCD is diagnosed after fulfilling specific clinical, laboratory, and LN histopathological criteria (Table 3) [1, 2, 4-6]. TAFRO syndrome, a subtype of iMCD, is a rare systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever or elevated inflammatory markers (such as CRP, ESR, ferritin), reticulin fibrosis of the BM or renal dysfunction, and organomegaly [4-9]. TAFRO syndrome typically requires particular LN histopathological characteristics for a definitive diagnosis [7-9]. However, in some cases, especially when systemic illness is severe or lymphadenopathy is inaccessible, a biopsy may not be possible. Cases without an LN biopsy but meeting all the criteria for iMCD and TAFRO are classified as "TAFRO with possible iMCD" [3].

TAFRO syndrome can present without exhibiting features of iMCD, and in this context, five categories of TAFRO are described in the literature: iMCD-TAFRO, TAFRO with possible iMCD, TAFRO associated with autoimmune diseases, TAFRO associated with infections, and TAFRO-like syndrome [2-4] (Table 4). Unlike classic iMCD, which has a more indolent course, TAFRO syndrome typically manifests acutely and can lead to multiorgan failure if untreated. Early recognition is critical but often delayed due to the overlap with autoimmune diseases, malignancies, infections, and other systemic inflammatory syndromes.

TAFRO syndrome was first reported in 2010 and is believed to be more prevalent in Japan. Due to the rarity of TAFRO syndrome and potential underdiagnosis, especially outside of Japan, comprehensive epidemiological studies are lacking and have a rough incidence estimate of 1 in a million [7]. Increased awareness and reporting are essential to better understand its global prevalence and clinical variations. The precise etiology of TAFRO syndrome remains elusive. Proposed mechanisms include aberrant immune activation, possibly triggered by viral infections (e.g., EBV, CMV), autoimmune dysregulation, or unidentified environmental or genetic factors. Many patients have autoantibodies such as antinuclear antibody (ANA) or anti-SSA, suggesting an autoimmune diathesis [10-12]. Genetic predispositions and polymorphisms in cytokine pathways such as IL-6 and VEGF are under investigation. Upregulation of mechanic target of rapamycin (mTOR) and interferon-1 (IFN-1) responsive genes and Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathways is implicated in some studies, forming the basis for some therapeutic targets [7]. Somatic mitogen-activated extracellular signal-regulated kinase 2 (MEK2) mutation (conferring IL hypersensitivity) and germline runt-related transcription factor 1 (RUNX1) mutation (enhancing hematopoietic self-renewal), both activating the mitogen-activated protein kinase (MAPK) pathway, are found in a study on TAFRO patients, highlighting pathogenetic overlap with histiocytoses and myeloid neoplasms [13].

The pathogenesis centers on a hypercytokinemic storm, especially involving IL-6, VEGF, and other proinflammatory

Table 2. Comprehensive Classification of CD

Type	Lymph node involvement	Histopathological subtypes	Systemic symptoms	Key features/prognosis
UCD	Single area (localized)	Hyaline vascular; plasmacytic; mixed	+/- (in few patients)	Mostly asymptomatic, may present with localized symptoms (e.g., chest or abdominal pain from mass effect). Excellent prognosis.
MCD	Multiple regions	Hyaline vascular; plasmacytic; mixed	Yes (constitutional symptoms)	Associated with IL-6-driven hypercytokinemia, organ dysfunction, hepatosplenomegaly, cytopenias. Further classified as below.
HHV-8-associated MCD	Multiple regions	Same as above	Yes	Caused by HHV-8, often in HIV+ or immunocompromised individuals. Poor prognosis without HIV control.
HHV-8-negative MCD (iMCD)	Multiple regions	Same as above	Yes	Etiology unknown, HIV and HHV-8 negative. Needs special pathological, clinical, and lab criteria for diagnosis. Variable prognosis, better with early treatment. Further subclassified below.
iMCD-POEMS	Multiple regions	Typically plasmacytic. Plasma cell neoplasm; paraneoplastic syndrome, monoclonal; often with lambda light chain restriction	Yes	Polyneuropathy, organomegaly, skin changes, endocrinopathy; often with edema and ascites. Osteosclerotic lesions on imaging. Treated as POEMS. Variable prognosis, depending on the associated genetic alteration and tumor.
iMCD-TAFRO	Multiple regions (often small)	Mixed or hypervascular	Yes, with unique lab and clinical features	Normal gamma globulins. Guarded prognosis without early treatment.
iMCD-IPL	Multiple regions	Plasmacytic or mixed	Yes	Features: thrombocytosis, hypergammaglobulinemia. Intermediate prognosis.
iMCD-NOS	Multiple regions	Variable	Yes	Does not fit POEMS, TAFRO, or IPL. Mixed clinical and lab features; etiology unknown. Variable to good prognosis.
Oligocentric CD	2 - 3 adjacent lymph node areas	Not fully defined	None or mild	Proposed subtype; overlaps more with UCD clinically and therapeutically.

CD: Castleman disease; HHV-8: human herpesvirus-8; HIV: human immunodeficiency virus; IL-6: interleukin-6; iMCD: idiopathic multicentric Castleman disease; IPL: idiopathic plasmacytic lymphadenopathy; MCD: multicentric Castleman disease; NOS: not otherwise specified; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; UCD: unicentric Castleman disease.

mediators such as TNF-α and IL-1β (Fig. 5). IL-6 drives systemic inflammation, anemia, fever, and thrombocytopenia [7, 14, 15]. VEGF increases capillary permeability, leading to anasarca, pleural effusion, and ascites. These cytokines also contribute to glomerular endothelial damage, resulting in renal dysfunction and TMA. BM often reveals reticulin fibrosis and megakaryocytic hyperplasia, signifying a reactive process. Multiple other interleukins (IL-8, IL-10, IL-13) and cell-mediated responses (B-cell, histamines) may also play a role. The interplay of individual susceptibility, cytokine-driven inflammation, endothelial injury, and tissue damage underpins the multiorgan involvement seen in TAFRO [7-9, 14, 15].

TAFRO typically presents with acute systemic symptoms and evidence of multi-organ involvement, with the initial presentation often being vague and nonspecific. The name TAFRO itself encapsulates most of the associated clinical manifestations: thrombocytopenia, anasarca, effusions, fever, BM suppression, renal dysfunction, and organomegaly [7-9, 14, 15]. BM biopsy shows reticulin fibrosis, and megakaryocytic hyperplasia. Renal biopsy typically shows TMA, and this association with renal failure in TAFRO syndrome is well studied [16-19]. Membranoproliferative glomerulonephritis (MPGN)-like injury is the next common pathological finding found in the biopsy [17, 19]. TAFRO may also present with other nonspecific findings and features of autoimmune disease, as shown in Table 5.

Diagnosis is based on clinical criteria supplemented by histopathology and exclusion of mimicking diseases. According to the 2019 international criteria, diagnosis of TAFRO is made if the patient meets all three major criteria and at least

Table 3. Diagnostic Criteria for iMCD

Criteria type	Criteria details	Explanation
Major criteria: both must be met	1) Histopathological lymph node features consistent with Castleman disease	Hyaline vascular, plasmacytic, or mixed subtype
	2) Multicentric lymphadenopathy (≥ 2 lymph node regions)	Confirmed via imaging or physical exam
Minor criteria: at least two of the following (with ≥ 1 laboratory abnormality)	Laboratory abnormalities (≥ 1 required):	
	1) Elevated CRP or ESR	Inflammatory markers
	2) Anemia	Normocytic or microcytic
	3) Thrombocytopenia or thrombocytosis	Either can occur
	4) Hypoalbuminemia	Often due to IL-6-mediated hepatic suppression
	5) Renal dysfunction	Elevated creatinine or proteinuria
	Clinical features (optional):	
	1) Constitutional symptoms (fever, weight loss, fatigue, night sweats)	Common systemic symptoms
	2) Hepatosplenomegaly	Detected clinically or via imaging
	3) Fluid accumulation (ascites, pleural effusion, edema)	Seen in TAFRO variant
	4) Lymphocytic interstitial pneumonitis or other organ involvement	Based on imaging/biopsy
Exclusion criteria	All must be excluded:	
	1) HHV-8 infection (especially in HIV+ patients)	By immunohistochemistry or PCR testing
	2) Malignancies (e.g., lymphoma, metastatic cancer)	Ruled out by biopsy or imaging
	3) Autoimmune/connective tissue diseases	E.g., SLE, Sjogren's, RA assessed via serologies and clinical history
	4) Infectious diseases (e.g., EBV, CMV, tuberculosis, sepsis)	Should not explain presenting findings
Additional laboratory abnormalities that support the diagnosis but are not required	1) Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or beta-2 microglobulin	
	2) Reticulin fibrosis on bone marrow biopsy (particularly in patients with TAFRO syndrome)	

CMV: cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HHV-8: human herpesvirus-8; HIV: human immunodeficiency virus; IL-6: interleukin-6; iMCD: idiopathic multicentric Castleman disease; LDH: lactate dehydrogenase; RA: rheumatoid arthritis; sIL-2R: soluble interleukin-2 receptor; SLE: systemic lupus erythematosus; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; VEGF: vascular endothelial growth factor.

two of the three minor criteria (Table 6). Our patient in this case report had met all six criteria. Other commonly reported laboratory abnormalities include elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or beta-2 microglobulin. Differential diagnoses are broad, and ruling them out is challenging, and forms an essential step towards appropriate diagnosis and timely initiation of management (Table 7) [7, 9, 13, 14].

The management of TAFRO syndrome involves a multimodal immunosuppressive approach tailored to organ dysfunction and disease severity (Tables 8 and 9) [7, 15, 20-46]. There are no major reports or clinical trials that studied the treatment modalities in TAFRO syndrome due to the rarity and sporadic nature of the disease. Various treatment modalities have been tried at various institutions on an individual basis. First-line therapy typically includes high-dose glucocorticoids for rapid control of inflammation [20-22]. In moderate to severe cases, IL-6 inhibitors such as tocilizumab or siltuximab are pivotal in targeting the cytokine-driven pathology for long-term remissions [23-29]. For patients with steroid-refractory disease, cyclosporine may be employed during the acute flares alone or in combination with steroids [30-32]. Rituximab is considered in acute, chronic, and relapse settings, particularly in those with refractory disease, B-cell involvement, or autoimmune overlap [33-37]. Anakinra, an IL-1 receptor antagonist, and canakinumab, a monoclonal antibody against IL-1β, have shown promise in refractory cases, particularly scenarios eliciting exaggerated cytokine storm with autoimmune overlap (Tables 8 and 9) [20, 21, 38-40].

Table 4. Five Types/Categories of TAFRO Syndrome

Type	Description	Key features
TAFRO with definite iMCD (iMCD-TAFRO)	Meets TAFRO clinical criteria with confirmed iMCD on lymph node biopsy (typically hypervascular type).	Histologically proven; IL-6 elevation; requires full workup including biopsy. Lymph nodes are usually smaller compared to other types of iMCD.
TAFRO with possible iMCD	TAFRO clinical features present but lymph node biopsy unavailable or non-diagnostic.	Clinical suspicion is high; supportive labs (e.g., IL-6, CRP); often treated as iMCD-TAFRO.
TAFRO associated with autoimmune diseases	Coexists with autoimmune diseases (e.g., Sjogren's, SLE); may mimic or overlap with iMCD.	Positive autoantibodies (ANA, SSA, etc.); may respond to immunosuppression.
TAFRO associated with infections	Associated with infections (e.g., EBV, CMV, HHV-8); clinical mimic of TAFRO syndrome.	Viral serologies positive; often younger patients; may require antiviral or supportive care.
TAFRO-like syndrome	Mimics TAFRO features but occurs in malignancies or other systemic diseases (e.g., lymphoma, MDS).	Non-idiopathic; underlying pathology explains presentation; prognosis varies widely.

ANA: antinuclear antibody; CMV: cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr virus; HHV-8: human herpesvirus-8; IL-6: interleukin-6; iMCD: idiopathic multicentric Castleman disease; MDS: myelodysplastic syndrome; SLE: systemic lupus erythematosus; SSA: Sjogren's syndrome-related antigen A; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly.

Chemotherapeutic agents, cyclophosphamide and the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone), are considered when standard therapies such as corticosteroids, IL-6 inhibitors (e.g., tocilizumab), or cyclosporine fail [41-45, 47]. Use of chemotherapy should be tailored and closely monitored due to the risk of myelosuppression, infections, and organ toxicity. Emerging therapies like JAK inhibitors are still experimental and have been tried in refractory cases [15, 20, 21, 25, 27]. Thalidomide is also considered in sporadic cases unresponsive to commonly tried treatments [41, 48]. Supportive care, including diuretics, albumin infusions, thoracocentesis, paracentesis, renal replacement therapy, electrolyte repletion, antibiotics, plasmapheresis, and transfusions, is critical in managing complications like anasarca, renal dysfunction, electrolyte imbalances, infections, and cytopenias (Tables 8 and 9) [7, 14, 15, 20, 21, 37].

TAFRO syndrome has a variable but often aggressive course, with a subset of patients having a rapidly progressing variant leading to death within a few weeks [49, 50]. Early intervention with targeted immunosuppression has improved outcomes significantly. A proposed prognostic score for iMCD (iMCD-International Prognostic Index (IPI)) could be used to stratify risk in TAFRO patients. In this, patients are divided into three risk groups based on increasing scores on five fac-

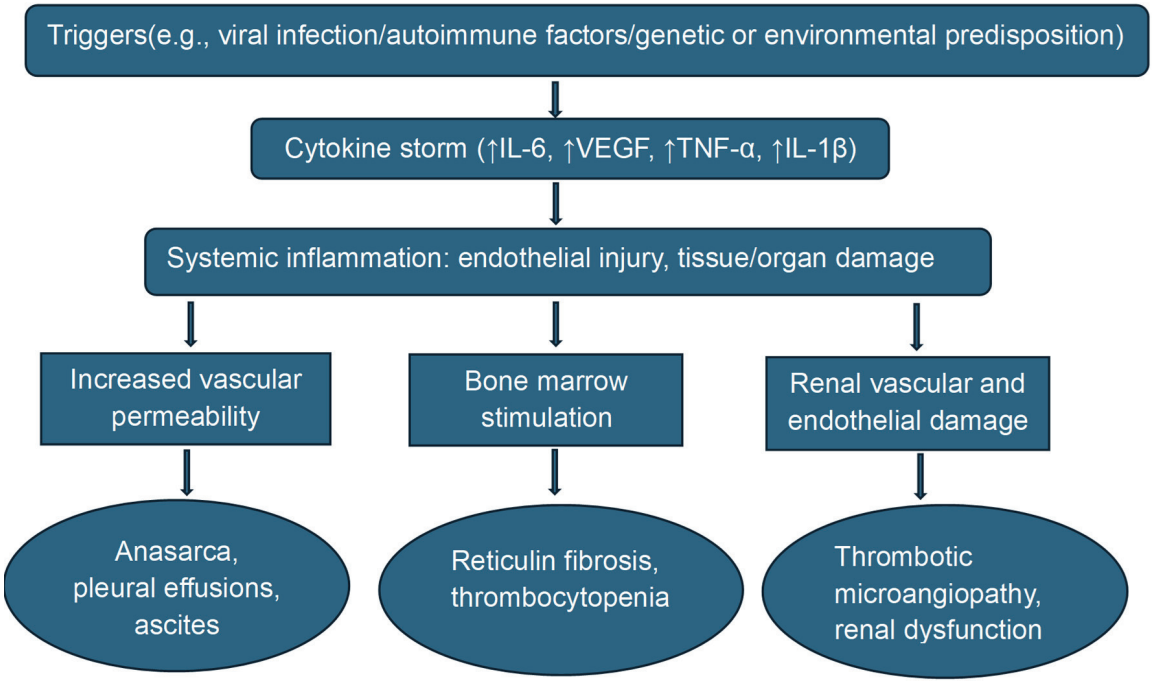

Figure 5. Pathogenesis of TAFRO syndrome. IL: interleukin; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor.

Table 5. Clinical Manifestations of TAFRO Syndrome

Manifestation	Description	Workup
Thrombocytopenia	Ranges from moderate to severe; may lead to bleeding.	Complete blood count, peripheral blood smear
Anasarca	Generalized edema, pleural effusions, and ascites. Thoracocentesis and paracentesis are often required.	Physical examination, chest X-ray, CT chest, abdomen and pelvis
Fever and systemic inflammation	High-grade fevers with elevated CRP, ESR, and ferritin.	Physical examination, laboratory analysis
Reticulin fibrosis and marrow changes	Pathology shows fibrosis and megakaryocytic hyperplasia, often with larger cells.	Bone marrow biopsy
Renal dysfunction	Acute kidney injury. TMA and MPGN on biopsy.	Laboratory analysis, urine studies, renal biopsy
Organomegaly	Mild to moderate hepatosplenomegaly, and lymphadenopathy (could be multifocal).	Physical examination, laboratory analysis, CT chest, abdomen, and pelvis
Other symptoms and findings	Fatigue, weight loss, nausea, vomiting, anemia, anorexia, and hypoalbuminemia.	Physical examination, laboratory analysis
Autoimmune overlap	Patients may meet criteria for associated autoimmune conditions, such as Sjogren's syndrome, or have features of their acute flare.	Physical examination, laboratory analysis

CRP: C-reactive protein; CT: computed tomography; ESR: erythrocyte sedimentation rate; MPGN: membranoproliferative glomerulonephritis; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; TMA: thrombotic microangiopathy.

tors: age > 40, plasmacytic subtype, hepatosplenomegaly, severe anemia (< 8 g/dL), and pleural effusion, with higher scores predicting worse outcomes [50]. Some other studies reported that TAFRO patients with severe renal impairment, persistent thrombocytopenia, or multiorgan failure have a guarded prognosis [20, 21]. Overall survival has been enhanced with IL-6 blockade and multidisciplinary care, but relapses and long-term immunosuppression pose challenges. Five-year survival rates in treated patients range from 65% to 80%, depending on the disease severity and treatment response [20, 21, 49, 51].

Conclusion

This case is unique because it meets all six criteria of TAFRO syndrome and highlights the importance of recognizing TAFRO syndrome with potential iMCD without an LN biopsy, especially when clinical, laboratory, and BM findings support the diagnosis. This case further emphasizes the diagnostic complexity of TAFRO syndrome, which requires a high index of suspicion and acknowledges the co-occurrence of renal TMA and autoimmune overlap syndromes, suggesting a potential interplay among multiple autoimmune cytokine-driven inflammatory processes. First-line treatment options include high-dose glucocorticoids, IL-6 inhibitors, anti-IL-1 drugs, cyclosporine, and rituximab or a combination of these, along with supportive care. Prompt diagnosis and early initiation of immunosuppressive therapy are crucial for improving systemic and renal outcomes in TAFRO syndrome, particularly in cases with diagnostically ambiguous presentations.

Table 6. Diagnostic Criteria for TAFRO Syndrome

Category	Criteria	Details
Major criteria	All three must be present:	
Thrombocytopenia	Platelet count ≤ 100,000/μL	Persistent or progressive.
Anasarca	Ascites, pleural effusion, and/or generalized edema	Clinically and/or radiologically detected.
Systemic inflammation	Fever ≥ 37.5 °C and/or CRP ≥ 2.0 mg/dL	Evidence of systemic inflammatory response.
Minor criteria (at least two required)	At least two must pe present:	
Reticulin fibrosis	Bone marrow biopsy findings	Bone marrow biopsy shows reticulin myelofibrosis or megakaryocytic hyperplasia.
Renal dysfunction	Elevated serum creatinine (> 1.5 mg/dL) or proteinuria	Often reflects TMA on biopsy.
Mild organomegaly	Mild hepatomegaly, splenomegaly, and/or lymphadenopathy	Less prominent than in classic MCD or other types of iMCD.

CRP: C-reactive protein; iMCD: idiopathic multicentric Castleman disease; MCD: multicentric Castleman disease; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; TMA: thrombotic microangiopathy.

Table 7. Differential Diagnosis of TAFRO Syndrome

Differential diagnosis	Key features that overlap	Distinguishing features
Classic iMCD	Lymphadenopathy, systemic inflammation	Indolent course, more prominent lymph node involvement
SLE	Cytopenias, serositis, renal dysfunction	ANA/anti-dsDNA positivity, SLE-specific criteria: anti-Smith antibody, typical malar rash, low C3/C4, positive antiphospholipid antibodies
POEMS syndrome	Organomegaly, edema, polyneuropathy	Monoclonal plasma cell disorder, VEGF levels, and sclerotic bone lesions
Lymphoma	Lymphadenopathy, constitutional symptoms	Clonal lymphoid cells on biopsy, B symptoms
Severe infection (e.g., sepsis)	Fever, multiorgan dysfunction	Positive cultures, response to antimicrobials
aHUS	Thrombocytopenia, anemia, systemic inflammation, elevated LDH, TMA, renal failure (more acute in aHUS)	Dysregulation of the complement pathway: often low C3, normal or mildly low C4, absent or minimal lymphadenopathy, organomegaly is uncommon, and anasarca is rare.
HLH/MAS	Cytopenias, fever, hyperferritinemia	Extremely high ferritin, low natural killer cell activity, HLH criteria

aHUS: atypical hemolytic uremic syndrome; ANA: antinuclear antibody; C3, 4: complement 3, 4; ds-DNA: double-stranded deoxyribonucleic acid; HLH: hemophagocytic lymphohistiocytosis; iMCD: idiopathic multicentric Castleman disease; LDH: lactate dehydrogenase; MAS: macrophage activation syndrome; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; SLE: systemic lupus erythematosus; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; TMA: thrombotic microangiopathy; VEGF: vascular endothelial growth factor.

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

Informed Consent

No patient identifiers or pictures of the patient are used in this manuscript. Verbal consent is obtained from the patient.

Table 8. Treatment Modalities for TAFRO Syndrome

Treatment modality	Indication	Complications
Glucocorticoids [7, 15, 20-22]	First-line for acute flare	Hyperglycemia, infections, and hypertension
Anti-IL-6 (siltuximab/sarilumab/tocilizumab) [24-29]	IL-6 blockade in moderate-severe disease	Risk of infection, neutropenia
Anti-IL-1 (anakinra/canakinumab) [38-40]	Refractory or exaggerated cytokine storm, autoimmune overlap, IL-6 inhibitor failure	Infections, injection site reactions
Cyclosporine [30-32]	Often used in combination with steroids; steroid/anti-IL-6 refractory cases	Nephrotoxicity, hypertension
Rituximab [33-37]	Autoimmune overlap or B-cell involvement. Used alone or in combination with siltuximab and steroids.	Infusion reactions, immunosuppression
Cyclophosphamide [41, 42]	Severe or refractory disease. Part of CHOP or in combination with bortezomib and steroids	Myelosuppression, infertility
CHOP regimen [43-45]	Suspected or confirmed overlap with lymphoma or severe inflammation	Toxicity, immunosuppression
JAK inhibitors (ruxolitinib) [25, 27]	Experimental, used in cases refractory to anti-IL-6 therapy. Successful in sporadic cases	Cytopenias, thromboembolism

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; IL-6: interleukin-6; JAK: Janus kinase; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly.

Table 9. Treatment Modalities and Patient Responses in TAFRO Syndrome

Treatment modality	Summary of patient response	Type of study
Tocilizumab (IL-6 inhibitor)	In a systematic review of 31 patients, approximately 51.6% achieved complete response, while others had partial or no response, and some succumbed to the disease [28]. In another case with severe liver dysfunction, significant clinical improvement was noted with tocilizumab, suggesting its potential utility in TAFRO syndrome [29]	Systematic review
Siltuximab (IL-6 inhibitor)	In a randomized trial, results showed that siltuximab combined with supportive care was more effective and well tolerated than supportive care alone in symptomatic multicentric Castleman disease, offering a valuable new treatment option, including TAFRO syndrome [23]. Positive response noted at 3 months in a patient with severe renal involvement [26].	Clinical trial, case report
Anakinra (IL-1 inhibitor)	Two pediatric patients with severe, rapidly progressing TAFRO syndrome achieved remission with high-dose intravenous anakinra [40]. Another adult patient with life-threatening TAFRO syndrome showed rapid clinical improvement following anakinra therapy [39].	Case reports
Cyclosporine	Three cases that were refractory to anti-IL-6 therapy, treated with corticosteroids and cyclosporine, experienced resolution of anasarca and improved renal function [30-32].	Case reports
Rituximab	In one case, a patient responded well to rituximab combined with prednisolone as first-line treatment [33]. Multiple other case reports reported use in relapsed and refractory scenarios [34-37].	Case reports
Combination therapy	Combination of tocilizumab and siltuximab was successfully used in a patient with severe disease, without the need for immunomodulators or aggressive supportive care [24]. A severe case of TAFRO syndrome was successfully treated with a combination of rituximab, steroid pulse therapy, plasma exchange, and romiplostim, with rapid improvement of renal function, anasarca, and thrombocytopenia. In a case of severe-grade TAFRO syndrome, administration of triple therapy with corticosteroid, tocilizumab, and cyclosporine achieved successful remission of the disease with discontinuation of hemodialysis by week 5 and improved platelets by week 9 [46].	Case reports

IL-6: interleukin-6; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly.

Author Contributions

All authors participated actively in this case report. They were actively involved in writing different article sections, helping with images/references, or revising the article before submission. MI (primary) started the article, actively wrote and revised different sections of the article, gathered images, conducted literature review, and added references. RIB identified the rarity of the case report, contributed to different sections of the article, and helped with proofreading (grammar) and revising the article. TFBR actively reviewed, edited, and revised the article, in the capacity of transplant nephrologist.

Data Availability

The authors declare that data supporting the findings of this case report are available within the article.

Abbreviations

ADAMST13: ADAM metallopeptidase with thrombospondin type 1 motif 13; aHUS: atypical hemolytic uremic syndrome; CCP: cyclic citrullinated protein; CD: Castleman disease; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CMV: cytomegalovirus; CRP: C-reactive protein; CT: computed tomography; C3AR1: complement component 3a receptor 1; C3: 4, complement 3, 4; dL: deciliter; ds-DNA: double-stranded deoxyribonucleic acid; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HHV-8: human herpesvirus-8; HIV: human immunodeficiency virus; HLH: hemophagocytic lymphohistiocytosis; IFN-1: interferon-1; IL: interleukin; iMCD: idiopathic multicentric Castleman disease; IPI: International Prognostic Index; JAK/STAT: Janus kinase-signal transducer and activator of transcription; LDH: lactate dehydrogenase; LN: lymph node; MAPK: mitogen-activated protein kinase; MAS: macrophage activation syndrome; MCD: multicentric Castleman disease; MEK2: mitogen-activated extracellular signal-regulated kinase 2; mEq: milliequivalent; µL: microliter; mmol: millimole; MPGN: membranoproliferative glomerulonephritis; mTOR: mechanic target of rapamycin; ng: nanogram; pg: picogram; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; RSV: respiratory syncytial virus; RUNX1: runt-related transcription factor 1; sIL-2Rs: soluble interleukin-2 receptors; SSA: Sjogren's syndrome-related antigen A; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly; TMA: thrombotic microangiopathy; TNF-α: tumor necrosis factor-alpha; UCD: unicentric Castleman disease; VEGF: vascular endothelial growth factor

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