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SOLVING CLINICAL PROBLEMS IN BLOOD DISEASES

A physician or group of physicians considers presentation and evolution of a real clinical case, reacting to clinical information and data (boldface type). This is followed by a discussion/commentary

Thrombocytopenia, anasarca, and severe inflammation

Amanallah Montazeripouragha[1] | Christine M. Campbell[1] | James Russell[2] | Nadia Medvedev[3] | Daniel R. Owen[3] | Alison Harris[2] | Fergal Donnellan[4] | Iain McCormick[5] | David C. Fajgenbaum[6] | Luke Y. C. Chen[7]

[1]Internal Medicine Residency Program, Department of Medicine, University of British Columbia, Vancouver, Canada

[2]Department of Radiology, University of British Columbia, Vancouver, Canada

[3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada

[4]Division of Gastroenterology, Department of Medicine, University of British Columbia, Vancouver, Canada

[5]Division of General Internal Medicine, Department of Medicine, University of British Columbia, Vancouver, Canada

[6]Division of Translational Medicine and Human Genetics, and Center for Cytokine Storm Treatment and Laboratory, University of Pennsylvania, Perelman School of Medicine, Philadelphia, USA

[7]Division of Hematology, Department of Medicine, University of British Columbia, Vancouver, Canada

Correspondence
Luke Y. C. Chen, 2775 Laurel St, 10th Floor, Division of Hematology, Vancouver General Hospital, Vancouver, British Columbia V5Z 1M9, Canada.
Email: lchen2@bccancer.bc.ca

1 | CASE PRESENTATION

A previously healthy 46-year-old East Asian male presented with back and flank pain, and abdominal bloating that began three weeks prior to admission after eating a vegan burger. He then developed fever, night sweats, and fatigue one week before presentation. Physical examination revealed normal mental status, increased abdominal girth, bilateral pitting edema, and hepatosplenomegaly. He had a fever (38.1°C), normal blood pressure, respiratory rate, oxygen saturation, and tachycardia (90–125 beats/min); He, later on, required oxygen transiently for respiratory failure secondary to pulmonary edema. While hospitalized, his mental state was almost normal. Abdominal ultrasound highlighted an enlarged heterogeneous hypoechoic liver suggestive of acute hepatitis, mild splenomegaly, and a right pleural effusion. The timeline of his symptoms is summarized in Table 1**. Initial blood work showed normal hemoglobin and platelets, white blood cells (WBC) 15.9 giga/L (4–11), neutrophils 11.8 giga/L (2.0–8.0), creatinine (Cr) 270 μmol/L (<110), C-reactive protein (CRP) 391 mg/L (<3.1), Albumin 15 g/L (34–50), normal liver transaminases, Alkaline Phosphatase (ALP) 252 U/L (30–150), Fibrinogen 5.1 g/L (1.5–4.5) (**Table 2**). A peripheral blood smear (PBS) showed neutrophilia with left shift, monocytosis, and low platelets with occasional large forms (Figure 1).**

The differential diagnosis for this patient's fever, abdominal pain, anasarca, B symptoms, and organomegaly is broad. Infections including bacterial, fungal, mycobacterial, or viral infections such as severe acute respiratory coronavirus-2 (SARS-CoV-2), autoimmune disease, malignancy such as lymphoma presenting with a hemophagocytic syndrome, liver, and renal disease, and other rare cytokine storm disorders such as catastrophic adult-onset Still's disease should be considered.[2]

He was started on empiric broad-spectrum antibiotics. Serology showed no human immunodeficiency virus (HIV), Hepatitis C infection and Human Herpesvirus-8 (HHV-8), immunity to Hepatitis B through natural infection, immunity to Hepatitis A, and negative blood and urine cultures. The Epstein Bar virus (EBV) and Cytomegalovirus (CMV) polymerase chain reaction (PCR) was less than 1000 copies/mL and undetectable, respectively. Nasal swab with COVID-19 PCR and other respiratory viruses was negative, as were stool cultures, stool Ova, and Parasite examination.

The low titer EBV result is nonspecific and can be repeated to ensure it is not raising. In the absence of a clear infectious cause, other inflammatory processes such as vasculitis, autoimmune disease, and autoinflammatory syndromes were considered the most likely cause of this patient's presentation. A comprehensive autoimmune panel and abdominal computerized tomography (CT) scan were therefore obtained. Additionally, SPEP, urine protein electrophoresis (UPEP), and free light chains (FLC) were done to look for paraproteinemia.

SPEP, UPEP, and FLC were normal. IgG by nephelometry was normal, 9.8 g/L (7–15.2), as were IgA and IgM. Autoimmune serology, including antinuclear antibody (ANA), anti-double-stranded

TABLE 1 Timeline of patient's thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, and organomegaly (TAFRO) symptoms, and different treatment modalities

Days post admission	Clinical problems and key laboratory parameters	Treatment
0	Hepatosplenomegaly, abdominal pain, fever, tachycardia, Acute kidney injury Creatinine: 312 μmol/L (normal 60–115) C-reactive protein: 288.5 mg/L (normal <3.1)	Empiric antibiotics
5	Progressive anasarca Platelets: 91 giga/L (normal 150–400)	Prednisone 1 mg/kg started with slow taper
6	Liver Biopsy: arteriolar endothelialopathy Bone marrow biopsy: hemophagocytosis, mild reticulin fibrosis D-Dimer: 3257 μg/L (normal <500) Fibrinogen: 5.1 g/L (normal 1.5–4.5) Ferritin: 1211 μg/L (15–300 μg/L) sIL-2r: 1556 U/mL (normal 241–846) C-reactive protein: 498 mg/L	IVIG 0.4 g/kg q 3 weeks initiated
7	Platelets: 49 giga/L Neutrophils: 32.8 giga/L (normal 2–8) D-dimer: 32547 μg/L	Anakinra 100 mg sc daily Cyclophosphamide 500 mg/m^1 IV × 1 dose Tocilizumab 400 mg IV × 1 dose
10–11	Creatinine: 428 μmol/L; First Hemodialysis Requiring Oxygen transiently (nasal prong 0–2 liters) C-reactive protein: 163 mg/L Ferritin: 1325 μg/L	Sirolimus 3–5 mg/day titrated to trough level 8–12 μg/L
13–15	Renal recovery (last hemodialysis); Excisional lymph node biopsy—consistent with multicentric Castleman disease	Anakinra discontinued and patient switched to siltuximab 11 mg/kg q 3 weeks
39	Discharge from hospital C-reactive protein: 1.5 mg/L D-dimer: 16615 μg/L Urine ACR: 13.4 mg/mmol (<2.0 mg/mmol)	
180	Mild arthralgias, otherwise normalization of laboratory values, patient able to work 2 days a week Platelets: 219 giga/L Creatinine:110 μmol/L C-reactive protein: < 0.2 mg/L D-dimer: 446 μg/L Urine ACR: 3.6 mg/mmol (<2.0 mg/mmol)	Siltuximab 11 mg/kg and IVIG 0.4 g/kg q 3 weeks Sirolimus titrated to trough 8–12 μg/L Prednisone 2.5 mg daily

DNA (dsDNA), anti-neutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane antibody (anti-GBM), C3-C4, anti-mitochondrial antibody (AMA), anti-smooth-muscle antibody (ASMA), transglutaminase antibody (TTG) were all negative. His CRP and ALP remained elevated with normal bilirubin and liver transaminases. Subsequent abdominal CT scan showed scattered ascites, mild peripancreatic inflammatory fat stranding suggestive of mesenteritis and panniculitis (Figure 2), normal adrenal glands, borderline enlarged lymph nodes (e.g., a portacaval lymph node measuring 15 mm in the short axis), and mild hepatosplenomegaly (Figure 3).

Without an infection source, no monoclonal band on protein electrophoresis, and a negative autoimmune panel, the etiology of his cholestatic liver enzyme elevation was likely secondary to hepatic, retroperitoneal, or intraperitoneal inflammatory process. The CT findings were relatively non-specific, with a combination of ascites and hepatosplenomegaly suggesting a congestive, hematological, or infective/inflammatory cause. Congestive causes such as portal hypertension or right heart failure may cause the abdominal imaging findings but would not explain the elevated CRP. Hematological causes may include hemoglobinopathies, polycythemia vera, leukemia, or myelofibrosis. Inflammatory/infective causes are widespread, including mononucleosis, AIDS, malaria, sarcoidosis, and collagen vascular disease. Isolated persistent elevation of ALP could pose a diagnostic challenge. While ALP concentration is highest in bone and liver, it also presents in several other organs, including kidneys and intestine. ALP concentration could also change with age, gender, ethnicity, and many other factors.[1] To work up this further, he underwent a liver biopsy.

Liver biopsy showed reactive arteriolar endothelium with vacuolated cytoplasm and hemophagocytosis by sinusoidal Kupffer cells, but no histologic evidence of steatohepatitis, autoimmune hepatitis, cholangitis, large bile duct obstruction, thrombosis, vasculitis, or malignancy. Immunohistochemical stains for CMV and Human Herpesvirus 8 (HHV8) were negative. A Congo red stain for amyloid was negative. Moreover, he also developed thrombocytopenia, platelet 90 giga/L (150–400), and anemia, hemoglobin 79 g/L (135–170),

TABLE 2 Initial laboratory values (day 1–3 of hospitalization)

Lab	Value	Reference range
Hemoglobin	138 g/L	135–170 g/L
platelets	177 giga/L	150–400 giga/L
White blood cells	15.9 giga/L	4–11 giga/L
Neutrophils	11.8 giga/L	2.0–8.0 giga/L
Creatinine	270 μmol/L	< 110 μmol/L
C-reactive protein	391 mg/L	<3.1 mg/L
D-dimer	32 547 μg/L	<500 μg/L
Albumin	15 g/L	34–50 g/L
Alanine Transaminase	28 U/L	<50 U/L
Alkaline Phosphatase	252 U/L	30–150 U/L
Aspartate Aminotransferase	25 U/L	<36 U/L
Interleukin-2 receptor soluble	1556 U/mL	241–846 U/mL
Fibrinogen	5.1 g/L	1.5–4.5 g/L
Urine ACR*	8.6 mg/mmol	<2.0 mg/mmol
Serology	**Value**	**Comment**
HIV* 1 RNA*; PCR*/NAAT*	<40 copies/ml	
HIV* 1 + 2 Ab* + p24 Ag*	Non-Reactive	No evidence of HIV* infection
Hepatitis A IgM*	Non-Reactive	
Hepatitis A Ab* total	Reactive (immune)	Immune to Hepatitis A
Hepatitis B Surface Antibody	>1000.0 mIU/ml	
Hepatitis B Surface Antigen	Non-Reactive	
Hepatitis B Core IgM	Non-Reactive	
Hepatitis B Core Antibody	Reactive	Immune to Hepatitis B through natural infection
Hepatitis E Antigen	Non-Reactive	
Hepatitis E Antibody	Non-Reactive	No Hepatitis E infection
Hepatitis C Antibody	Non-Reactive	No Hepatitis C infection
Anti CMV* IgG*	Non-Reactive	No CMV* Infection
Anti EBV* IgG*	Equivocal (below level of definitive detection)	
EBV* PCR*	<1000 copies/ml	Nonspecific for EBV* Infection
Human Herpesvirus-8	HHV8 DNA NOT detected by PCR*	No Human Herpesvirus-8 infection

Abbreviations: *AB*, *Antibody*; ACR, albumin creatinine ratio; *Ag*, *Antigen*; CMV, Cytomegalovirus; EBV, Epstein Bar virus; HIV, human immunodeficiency virus; IgG, *Immunoglobulin* G; *IgM*, *Immunoglobulin* M; NAAT, *Nucleic Acid Amplification Test*; PCR, polymerase chain reaction; RNA, Ribonucleic acid.

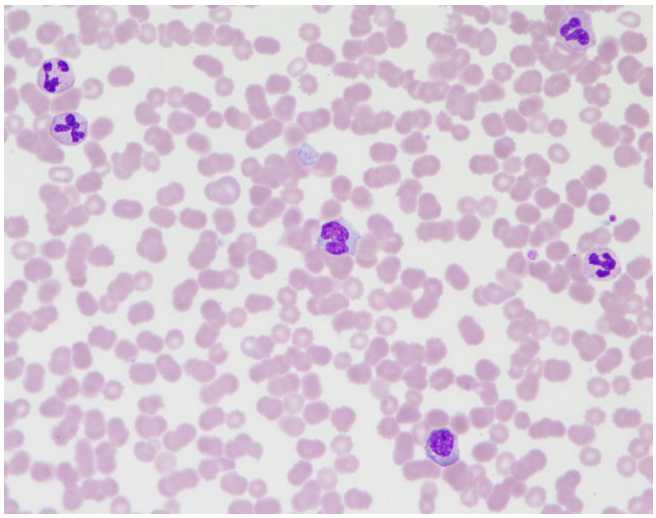

FIGURE 1 Neutrophilia with left shift, monocytosis, and low platelets with occasional large forms [Color figure can be viewed at wileyonlinelibrary.com]

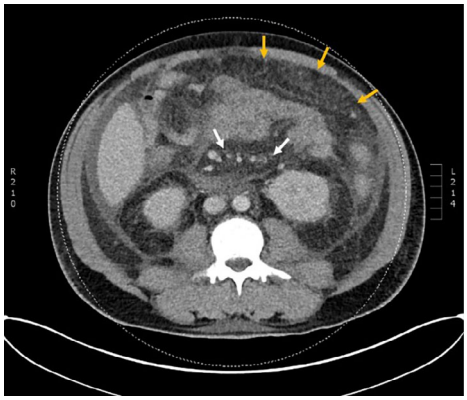

FIGURE 2 Axial computerized tomography image demonstrating soft tissue stranding within the greater omentum (yellow arrows) and small bowel mesentery (white arrows) in keeping with mesenteritis [Color figure can be viewed at wileyonlinelibrary.com]

with high ferritin 1211 μg/L (15–300 μg/L) and elevated D-Dimer 32 547 μg/L (<500 μg/L).

The possibility of thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, and organomegaly (TAFRO) syndrome was raised at this point. The arteriolar endothelialopathy in the liver biopsy likely explains the very high D-dimer in this patient, who had no evidence of venous or arterial thrombosis on imaging.[3] No clear, infectious, inflammatory, or malignant etiology was identified. When TAFRO is suspected, histological evidence of idiopathic multicentric Castleman disease (iMCD) should be sought to see if the patient has iMCD-TAFRO. The diagnosis of definite iMCD-TAFRO requires multicentric lymphadenopathy, lymph node histologic features consistent with iMCD, and four clinical criteria (thrombocytopenia, anasarca, fever, or hyperinflammatory state, organomegaly), and either renal dysfunction or bone marrow biopsy showing reticulin fibrosis or megakaryocytic hyperplasia.[4] Further supportive criteria include the absence of polyclonal hypergammaglobulinemia and an elevated ALP with mild to no

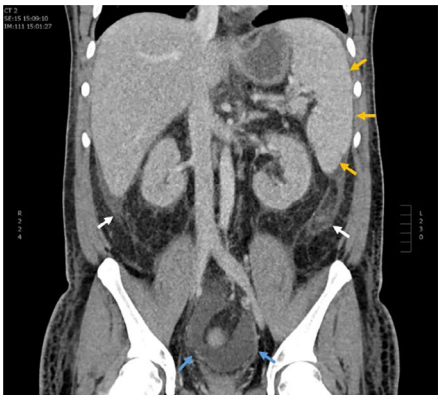

FIGURE 3 Coronal reformatted computerized tomography image demonstrating splenomegaly (yellow arrows) and ascites within both parabolic gutters (white arrows) and pelvis (blue arrows) [Color figure can be viewed at wileyonlinelibrary.com]

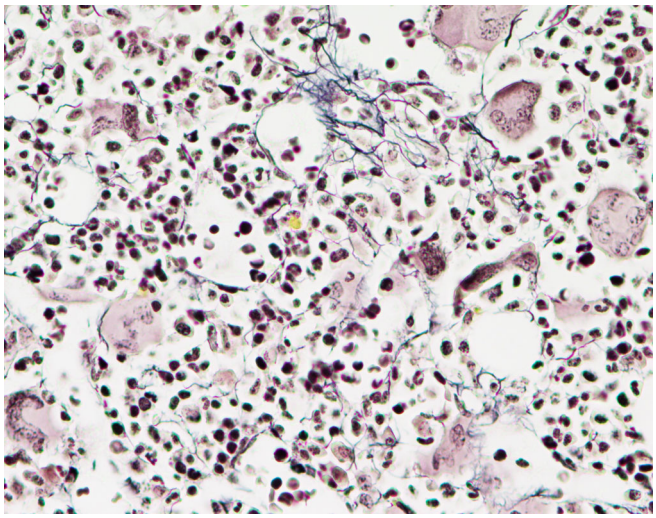

FIGURE 4 Bone marrow biopsy showing increased megakaryocytes and reticulin stain showing mild (Grade 1) fibrosis [Color figure can be viewed at wileyonlinelibrary.com]

elevation in bilirubin and transaminases.[5] Meeting pathologic criteria can be challenging as iMCD-TAFRO patients classically have small volume lymphadenopathy. Furthermore, few studies have commented on the pathologic findings of other organs involved in iMCD-TAFRO; therefore, pathological findings outside of the lymph node are excluded from diagnostic criteria. Hence, probable iMCD-TAFRO is defined as all four clinical criteria, with either renal failure/insufficiency or bone marrow reticular fibrosis, but without lymph node histological evidence because of non-performed or inconclusive lymph node biopsy.[4] If there is a high clinical suspicion for iMCD-TAFRO, empiric treatment may need to be initiated prior to pathologic diagnosis to prevent further clinical deterioration. In our case, the patient was placed on empiric treatment prior to pathologic diagnosis due to progressive thrombocytopenia and renal dysfunction.

His peripheral blood film revealed a leukoerythroblastic state with neutrophilia and monocytosis (Figure 1). Bone marrow showed sparse hemophagocytosis, an increased number of enlarged megakaryocytes, and reticulin stain showed mild grade 1 fibrosis (Figure 4). Flow cytometry showed no B cell clonality and normal T cell antigen expression. CT neck identified left supraclavicular (1.3 cm) and mild cervical lymphadenopathy (1.1 cm). Excisional lymph node biopsy of two relatively small lymph nodes (3 mm) was consistent with a chronic reactive state that can be seen with iMCD with prominent polyclonal plasmacytosis, increased vascularity, and sparse atrophic germinal centers (Figure 5).

Taken together, the patient's clinical, imaging, and pathologic features were compatible with definite iMCD-TAFRO. The hemophagocytosis noted on liver and bone marrow biopsy is suspicious for hemophagocytic lymphohistiocytosis (HLH). However, hemophagocytosis can be seen in many conditions other than HLH, such as sepsis, transfusion, and hemolysis.[6] The markedly elevated CRP and D-dimer with only modestly elevated ferritin and Interleukin-2 receptor soluble 1556 U/mL (241–846) is more consistent with iMCD-TAFRO than HLH.

The patient was started on prednisone (5 days post-admission). Yet, due to the rapid progression of the disease including hepatic, respiratory and renal failure, multiple other treatments were initiated. He briefly required hemodialysis (HD) for persistent hyperkalemia and medically refractory anasarca. Once iMCD-TAFRO was suspected, he was started on an interleukin (IL)-1 inhibitor, anakinra 100 mg sc daily, prednisone 1 mg/kg, and also given one dose of the IL-6 inhibitor tocilizumab 400 mg IV x 1 dose to rapidly control his inflammation. Table 1 **summarizes the TAFRO treatment modalities that he received and their timing. He was given sirolimus and IVIG to control his endothelialopathy. Subsquently, his C-reactive protein and D-dimer rapidly declined, and his renal function improved. Once a histological diagnosis of iMCD was made on his lymph node biopsy on day 13, he was switched from anakinra to the IL-6 inhibitor siltuximab because of local drug funding reasons. He was discharged from hospital 39 days after admission. At six month follow up, he is doing very well clinically on maintenance siltuximab 11 mg/kg and IVIG 0.4 g/kg q 3 weeks and sirolimus (titrated to serum level 8–12 μg/L), and prednisone 2.5 mg daily. All laboratory parameters have returned to normal aside from mildly elevated urine ACR 3–7 (normal <2.0).**

2 | DISCUSSION

TAFRO syndrome was initially described by Takai et al. in 2010. TAFRO is a systemic inflammatory disease characterized by thrombocytopenia, anasarca, fever, reticulin fibrosis, renal dysfunction, and organomegaly.[7] TAFRO can be associated with iMCD (iMCD-TAFRO) or can occur without iMCD. iMCD can present as either iMCD-TAFRO, which involves acute multi-system organ failure due to a severe cytokine storm, or iMCD-Not Otherwise Specified (iMCD-NOS). While TAFRO is clinically aggressive, iMCD-NOS is a chronic inflammatory syndrome, which often involved polyclonal hypergammaglobulinemia (PHGG) and thrombocytosis. It can be difficult to make a histopathological diagnosis of iMCD-TAFRO as the

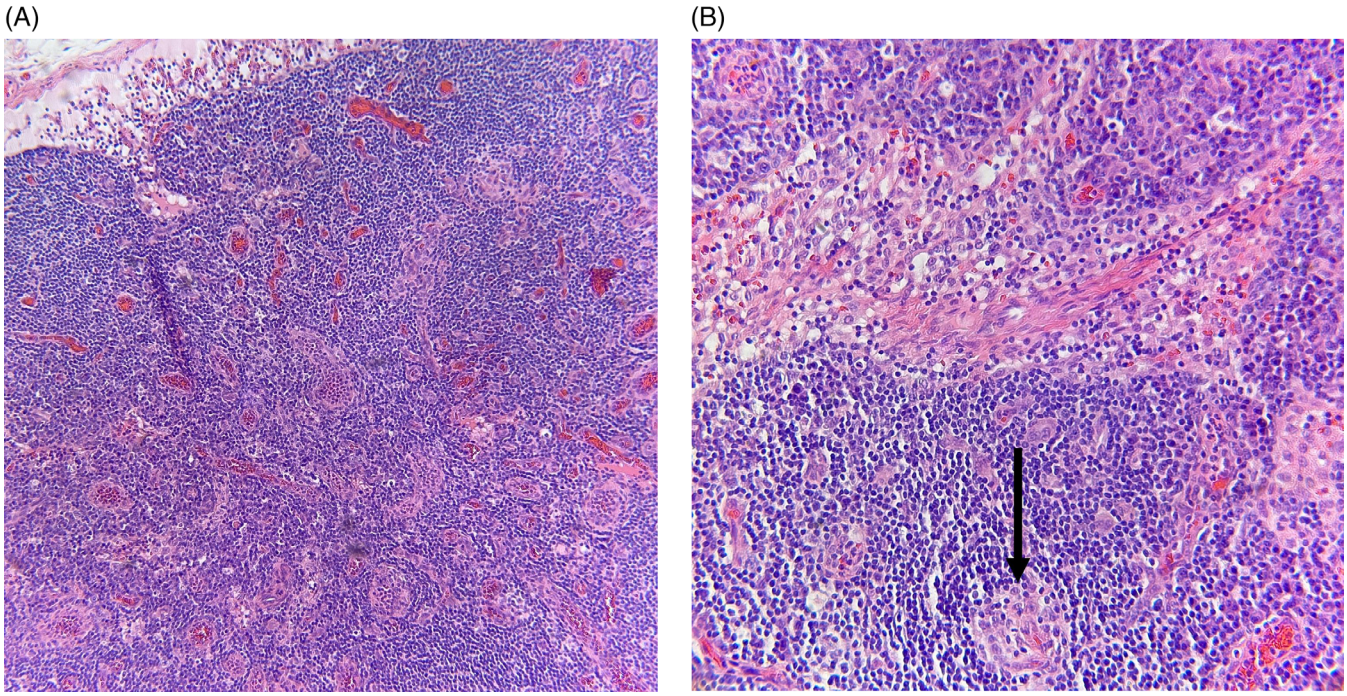

FIGURE 5 Excisional biopsy of cervical lymph node showing increased vascularity and polyclonal plasmacytosis (A, H&E, original magnification 100X). The arrow indicate a regressed germinal center (B, H&E, original magnification 200X) [Color figure can be viewed at wileyonlinelibrary.com]

lymphadenopathy and organomegaly of TAFRO are relatively mild, and the pPHGG often found in iMCD-NOS is often absent. Therefore, a high index of suspicious is needed to diagnose TAFRO.[4] Cytokine storm is an umbrella term encompassing many disorders of systemic immune dysregulation and hypercytokinemia leading to multi-organ dysfunction and high risk of mortality. This concept has gained prominence given the emergence of COVID-19 cytokine storm and the importance of immunomodulatory therapies, including IL-6 blockade and JAK-inhibition.[8]

Radiological findings of TAFRO include organomegaly, and typically mild serositis, including mesenteric panniculitis, which can mimic pancreatitis.[9] Adrenal abnormalities such as adrenalitis or adrenal necrosis are common, although adrenal biopsy is of low yield.[10,11] CT brain of this patient was within normal limits, CT chest showed findings in line with pleural edema and 5 mm stable pulmonary nodules, while an abdominal CT scan showed hepatomegaly and splenomegaly, as well as pancreatitis. In light of the normal lipase, the reported pancreatitis could have been panniculitis and mesenteritis, not true pancreatitis. While reticulin fibrosis is often part of the acronym in TAFRO, it should be noted that less than 30–65% of patients with TAFRO actually have this feature, and when present, the fibrosis is often relatively mild, as in this case.[12]

When TAFRO is clinically suspected, bone marrow and lymph node biopsies are required to mainly rule out mimickers such as HLH, lymphoma, cancer and assess for iMCD. In particular, aggressive lymphoma such as intravascular B cell lymphoma or T cell rich B cell lymphoma presenting with HLH must be ruled out, as empirically treating the cytokine storm associated with these malignancies may bring reprieve from the inflammatory cytokine storm but will not address the underlying pathology.[13] Further, exclusion of infectious etiologies such as TB is critical as immunosuppressive agents to treat the cytokine storm may worsen the infection. Definite diagnosis of iMCD-TAFRO requires excisional lymph node biopsy.[4] Unlike iMCD-NOS, lymph nodes are typically small in iMCD-TAFRO, which can make it difficult to identify a large node to confirm diagnosis quickly. Given the rapid disease progression and poor prognosis for iMCD-TAFRO, diagnosis is urgently needed to be able to promptly initiate treatment.[14–16]

Several cytokines and chemokines are elevated in iMCD-TAFRO. However, interleukin-6 (IL-6) is recognized as an essential contributor to disease pathogenesis in a large portion of patients.[17] Chemokine ligand 13 (CXCL13) is an emerging diagnostic and prognostic marker.[18] Evidence of mammalian target of rapamycin (mTOR) and Janus kinase-signal transducer and activator of transcription-3 (JAK-STAT3) activation has been found in iMCD which provides rationale for investigation of mTOR and JAK inhibitors in this disease.[11,19–22] Age greater than 60 and D-dimer ≥18 000 μg/L are poor prognostic markers.[23]

While much of the research on cytokine storms has focused on the intravascular compartment, and in particular, cytokines and other inflammatory markers, the markedly elevated D-dimer, which often occurs in the absence of overt macrovascular thrombosis, in both TAFRO and COVID-19 cytokine storm, draws attention to the role of the endothelialopathy in these conditions. In severe COVID-19, elevated markers of endothelial activation such as soluble P-selectin, soluble thrombomodulin, and von Willebrand factor antigen are associated with higher mortality, and autopsy studies have shown complex vasculopathy such as intussusceptive angiogenesis as a hallmark of a

fatal disease.[24] A recent case series of six Japanese patients with iMCD-TAFRO found many more GSK3β+CCR6+ megakaryocytes in the bone marrow compared to patients with HLH or autoimmune disease, further highlighting the complex interplay between megakaryocytes, endothelial cells, and D-dimer in this complex disease. Both COVID-19 cytokine storm and TAFRO are characterized by a central role of IL-6, markedly elevated CRP and D-dimer, and modestly elevated ferritin and sIL-2r, in contrast to HLH where ferritin and sIL-2r are markedly elevated and CRP and D-dimer are typically modestly elevated.

The standard treatment for iMCD-TAFRO is not well established, and most data come from small case series and retrospective studies. Historically, corticosteroids have been often used as the first-line agent in TAFRO treatment. Published guidelines recommend IL-6 inhibition with siltuximab or tocilizumab as first-line ± steroids, which is effective in 35%–45% of patients.[17] Severe iMCD patients, however, require high dose steroid therapy as well as IL-6 inhibition. Severe iMCD is defined as having two of the following features: Eastern Cooperative Oncology Group (ECOG) ≥2, Stage IV renal dysfunction (eGFR <30; Creatinine >3.0), anasarca and/or ascites and/or pleural/pericardial effusion Hemoglobin ≤8.0 g/dL, or pulmonary involvement/interstitial pneumonitis w/dyspnea.[17] Among non-responders, multi-agent chemotherapy is recommended for severe cases or immunomodulation with agents like cyclosporine, sirolimus, rituximab, or thalidomide for mild/moderate cases.[15–17,25,26] In summary, essential steps for patients like ours are early recognition of patients presenting with features of TAFRO, aggressively seeking a histological diagnosis of iMCD, ruling out mimickers, and early immunomodulatory therapy.

CONSENT STATEMENT

The authors have written permission from the patient to submit this manuscript for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

ORCID

Amanallah Montazeripouragha https://orcid.org/0000-0002-6294-7588

Daniel R. Owen https://orcid.org/0000-0002-1386-9624

David C. Fajgenbaum https://orcid.org/0000-0002-7367-8184

Luke Y. C. Chen https://orcid.org/0000-0002-9551-2951

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