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Case Report

TAFRO Syndrome Mimicking Solid Cancer and Successfully Treated by Tocilizumab: A Case and Literature Review

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Abstract

TAFRO syndrome, or now formally termed idiopathic multicentric Castleman disease (iMCD) with thrombocytopenia, anasarca, fever, renal insufficiency or reticulin fibrosis, and organomegaly (iMCD-TAFRO), describes a unique subtype of iMCD. Hypersecretion of pro-inflammatory cytokines, such as interleukin-6, plays a critical role in this disease. Several anti-inflammatory medications are used for treatment, such as tocilizumab, siltuximab, and rituximab, and they have demonstrated efficacy in some cases; however, the disease remains incurable. Here, we report a 56-year-old woman who presented with ileus and progressive ascites formation. She received several operations for suspected secondary peritonitis, but thrombocytopenia, lymphadenopathy, and anasarca progressed. It took 1 year to reach the diagnosis of iMCD-TAFRO, and tocilizumab was given soon after the diagnosis. After tocilizumab treatment, her symptoms improved dramatically. Due to the heterogeneous clinical manifestations of iMCD-TAFRO, awareness of iMCD-TAFRO and a multidisciplinary team approach are required for a timely and accurate diagnosis of iMCD-TAFRO.

Keywords: Idiopathic multicentric Castleman disease, TAFRO syndrome, tocilizumab

Introduction

Multicentric Castleman disease (MCD) is a group of systemic polyclonal lymphoproliferative disorders characterized by the proliferation of morphologically benign lymphocytes, plasma cells, and vessels due to the excessive production of cytokines, especially interleukin-6 (IL-6).[1] TAFRO syndrome, now termed idiopathic MCD (iMCD)-TAFRO, was first reported in 2010 as a variant of iMCD characterized by thrombocytopenia, anasarca, fever, reticulin myelofibrosis, and organomegaly.[2,3] It has a more aggressive nature and is associated with dismal outcomes.[4] Due to its rarity (0.9–4.9 per million individuals in Japan[5] and only eight Caucasian cases reported[6]), most clinicians are unfamiliar with iMCD-TAFRO, and consequently, it is likely to be under- or misdiagnosed. In this article, we present a case of iMCD-TAFRO who was initially treated as secondary peritonitis or metastasis of unknown origin, thus delaying an accurate diagnose.

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Case Report

A 56-year-old woman was transferred to our hospital due to massive ascites and fever. Before this transfer, she has been admitted several times at three different hospitals over a 6-month period with initial presentations of anorexia, abdominal pain, and flatulence. Ileostomy was done for ileus, after which she had a recurrent fever and acute kidney injury requiring transient hemodialysis. Ascites developed overtime, and she also had anemia, thrombocytopenia, and bilateral pleural effusion. Generalized subcutaneous edema worsened, and she was finally transferred to our hospital 6 months after her initial presentation.

After transfer, computed tomography (CT) showed multiloculated fluid collection at the perihepatic space and left lower quadrant area, hepatosplenomegaly, and enlarged para-aortic lymph nodes [Figure 1a-c]. An atypical bacterial infection or metastasis of unknown origin was suspected. A hemogram showed normocytic anemia (hemoglobin 9.5 g/dL [normal range 13–18 g/dL]) and thrombocytopenia ($30 \times 10^3/\mu L$ [normal range 143–349 $\times 10^3/\mu L$]) [Table 1]. Fever and ascites were recurrent and unresponsive to antibiotic treatment and drainage. Exploratory laparotomy was thus repeated, during which many blood clots, necrotic tissue, and ascites were debrided and evacuated, but no peritoneal carcinomatosis or tumor lesions were noted. Mycobacterium and bacterial cultures of ascites were negative, and the ascites cytology was negative for malignancy.

One year after the initial presentation, her thrombocytopenia ($13 \times 10^3/\mu L$) and renal function (creatinine level 2.19 mg/dL) deteriorated [Table 1]. Immune thrombocytopenic purpura was suspected, and corticosteroids were prescribed with a partial (platelet level elevated to $31 \times 10^3/\mu L$) but fluctuating response. Repeated abdominal CT revealed the development of inguinal and iliac lymph nodes [Figure 2a]. A right inguinal lymph node excisional biopsy was done, and the pathology showed increased plasma cells and histiocytes in the interfollicular area with hyalinized vascular proliferation in the interfollicular area. Grocott's methenamine silver and acid-fast staining failed to demonstrate pathogens. Immunohistochemically, CD3 and CD20 stains showed normal distribution of T and B cells. Human herpesvirus 8 (HHV-8) stain was negative, and immunoglobulin G4-positive cells were identified at around 30–40/HPF. The plasma cell type of Castleman disease was pathologically diagnosed [Figure 2b-e], and a bone marrow biopsy showed myelofibrosis (fibrosis Grade 1) with a silver stain [Figure 2f]. We checked the autoimmune and viral infection profiles [Table 1], but the findings were negative. Taking the clinical and pathological findings together, the patient fits the diagnostic criteria of iMCD-TAFRO. She was given 200 mg of tocilizumab every 2 weeks as an alternative to siltuximab, and the only U.S. Food and Drug Administration approved anti-IL6 inhibitor for MCD, which was not available in Taiwan. After two doses of tocilizumab, her platelet level dramatically elevated from $12 \times 10^3/\mu L$ to $106 \times 10^3/\mu L$. In addition, the fever, lymphadenopathy, pleural effusion, and impaired renal function were relieved. Tocilizumab was tapered to 200 mg every month after her condition stabilized. Although she still has perihepatic loculated ascites, she is now followed at our clinic with good performance and better quality of life.

Discussion

TAFRO syndrome, a rare variant of iMCD, is associated with the hypersecretion of cytokines and chemokines such as IL-6 and interferon-γ-induced protein 10 kDa.[7] The presence of four clinical criteria is necessary to make a diagnosis of TAFRO syndrome, including thrombocytopenia, anasarca (e.g., pleural effusion, ascites, or subcutaneous edema), fever or hyperinflammatory status, and organomegaly (e.g., lymphadenopathy [≤2 cm] in more than two regions, hepatomegaly, or splenomegaly on CT). The pathologic criteria include lymph node histopathology consistent with features of international iMCD diagnostic criteria, including one of the following minor criteria: renal insufficiency, hyperplasia of megakaryocytes, or reticulin fibrosis in bone marrow.[3] Nevertheless, the diagnosis remains difficult for iMCD-TAFRO, and due to the hyperinflammatory status, it resembles an infectious process or autoimmune disease. Lymphadenopathy and hepatosplenomegaly can also mislead the diagnosis toward other malignancies. Currently, there is no specific biomarker for this disease. Because of thrombocytopenia and bleeding tendency, tissue diagnosis is usually delayed. Furthermore, the pathology of lymph node

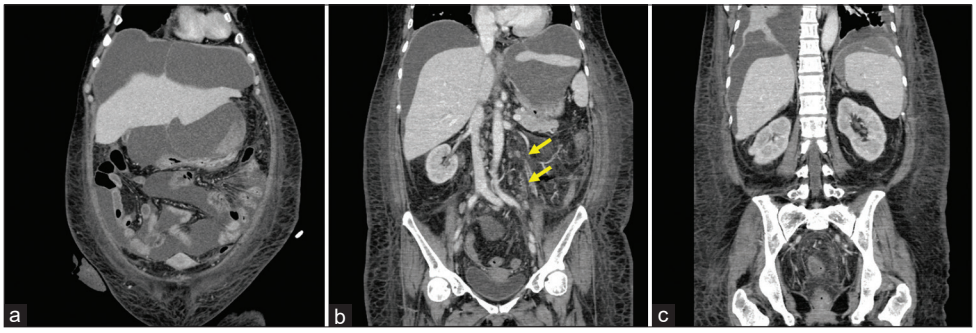

Figure 1: Computed tomography image of the patient's abdomen before tocilizumab treatment. (a-c) Computed tomography images of the abdomen performed 6 months after the initial presentation. Significant anasarca and lymphadenopathy are seen. (a) Loculated ascites, especially at the perihepatic area. (b) Multiple para-aortic lymphadenopathy. (c) Bilateral pleural effusion. The yellow arrow pointed out para-aortic lymphadenopathy

Table 1: Laboratory data before and after treatment

	6 months after initial presentation	12 months after initial presentation	2 months after treatment	Normal range
Hemogram				
Hemoglobin (g/dL)	9.5	9.2	11.8	11.0–15.0
Platelet (10^3/μL)	30	13	106	157–392
Biochemistry				
Albumin (g/dL)	2.6	3.5		3.5–5.2
Creatinine (mg/dL)	1.17	1.07	0.69	0.50–0.90
Total bilirubin (mg/dL)	0.4	2.0	0.5	≤1.2
ALT (IU/L)	45	69	-	≤35
LDH (IU/L)	-	340	216	135–225
ALP (IU/L)	947	530	175	35–104
Immunologic test				
IgG (mg/dL)	-	1300	-	751–1560
IgA (mg/dL)	-	99.8	-	82–453
IgM (mg/dL)	-	105.0	-	46–304
C3 (mg/dL)	69.2	-	-	58–147
C4 (mg/dL)	17.6	-	-	11–35
ANA	-	1:40 (negative)	-	
Anti-dsDNA (IU/mL)	-	0.1	-	
Virology				
EBV IgM	-	1:10 (negative)	-	
HSV IgM	-	0.347 (negative)	-	Negative: <0.8
VZV IgG	-	3.651 (positive)	-	Positive: ≥1.1
HCV IgG	0.71 (nonreactive)	-	-	Nonreactive: <0.9 COI
HBV viral load	<20 IU/mL (not detected)	-	-	

MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, APTT: Activated partial thromboplastin, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, γ-GTP: γ-glutamyl transferase, IgG: Immunoglobulin G, C3, 4: Complement 3, 4, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double strand DNA antibody, EBV: Epstein–Barr virus, HSV: Herpes simplex virus, VZV: Varicella–zoster virus, HCV: Hepatitis C virus, HBV: Hepatitis B virus, IgA: Immunoglobulin A, IgM: Immunoglobulin M, COI: cut off index

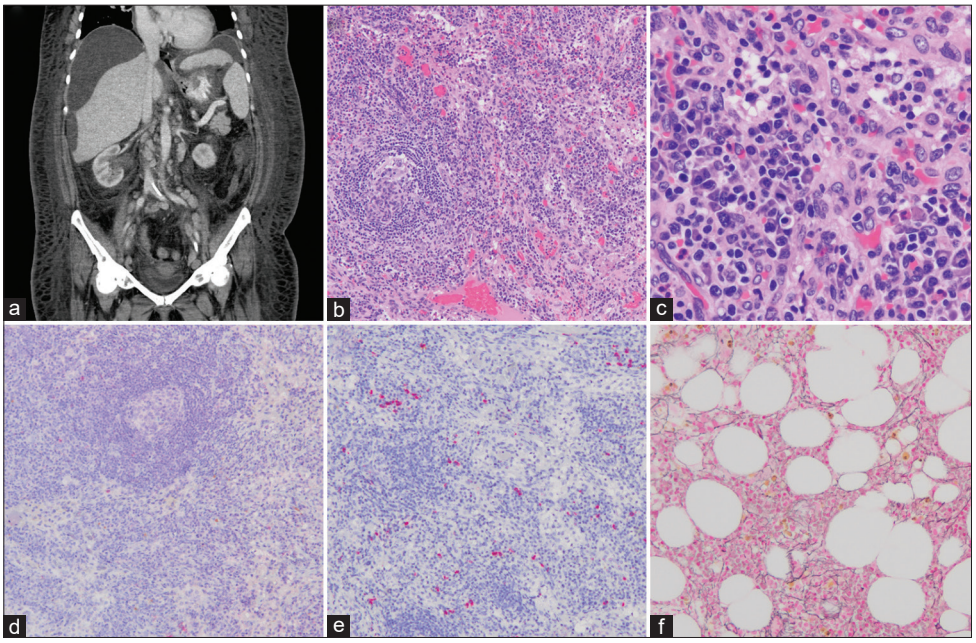

Figure 2: Computed tomography image of progressive lymphadenopathy, pathology of lymph node biopsy, and bone marrow biopsy. (a) Progressive enlargement of lymphadenopathy 1 year after the initial presentation. Inguinal lymphadenopathy progressively enlarged, and pathology of inguinal lymph node biopsy is shown in b-e. (b) Low-power hematoxylin and eosin (H and E stain; ×100) and (c) high power of the interfollicular zone (H and E stain; ×400). Sheets of plasma cells and prominent endothelial venules were seen in the interfollicular zone. Some eosinophils were present. There was follicular/germinal center hyperplasia with a sharply defined marginal zone. (d) HHV-8 stain, which was negative. (e) Immunoglobulin G4 stain measured positive 30–40 in one high-power field. (f) Silver stain of a bone marrow biopsy. Reticulin fibers were stained, and myelofibrosis score was measured as Grade 1

biopsy in iMCD-TAFRO mimics other inflammatory disorders and requires an experienced pathologist to make the diagnosis. Awareness of iMCD-TAFRO and a multidisciplinary team approach are needed for a timely and accurate diagnosis of iMCD-TAFRO.

In our case, it took 1 year to make an accurate diagnosis and start appropriate treatment with the IL-6 inhibitor tocilizumab. For patients with iMCD-TAFRO, anti-IL6-directed therapy is the indicated first-line therapy.[8] Second-line and beyond options include rituximab, cyclosporine, sirolimus, or cytotoxic regimens. Tocilizumab is a humanized monoclonal antibody which blocks IL-6 receptors to prevent cytokine binding. In a systematic review including 31 iMCD-TAFRO patients treated with tocilizumab, 51.6% of the patients achieved a complete response, 15 patients showed a partial or no response, and 4 patients (12.9%) died of the disease. Two patients were in drug-free remission at the last visit, and five patients maintained in remission on tocilizumab monotherapy. The findings of the review showed that tocilizumab was a safe agent which could be tolerated by most patients.[9] The other anti-IL6-directed therapy for iMCD-TAFRO is siltuximab, which demonstrated improved progression-free survival and durable symptomatic response in a phase 2 trial.[10]

In conclusion, iMCD-TAFRO is a rare but unique disease characterized by clinical symptoms of thrombocytopenia, anasarca, fever, reticulin fibrosis or renal insufficiency, and organomegaly. It is a syndrome diagnosed by clinical and pathologic criteria. iMCD-TAFRO can be difficult to diagnose due to its mimicry of infection, autoimmune disease, or other malignancies. Therefore, it is important for clinical practitioners to be aware of the disease. This case reminds us of the importance of making an accurate and timely diagnosis to provide an opportunity for recovery.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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