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Case Report

Liver Cirrhosis in Castleman Disease with TAFRO Syndrome

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Abstract

Castleman Disease is a rare disorder in which benign growths form in lymph node tissue. There are various subtypes that fall under the two main manifestations of Castleman Disease: unicentric (localized) and multicentric. One subtype of multicentric Castleman disease is TAFRO syndrome which involves: Thrombocytopenia (T), Anasarca (A), Fever (F), Reticulin Fibrosis (R), and Organomegaly (O). Here we present a case of a 57-year-old Chinese woman with Castleman Disease with TAFRO syndrome who presented with fever, pancytopenia, abdominal pain, and malaise after changing dosage of her prednisone medication. She was then found to have liver cirrhosis with no significant ascites or adenopathy. Symptomatic treatment with a regimen of corticosteroids resolved the flareup of her Castleman disease. This case of a patient with Castleman disease and TAFRO syndrome who developed liver cirrhosis could provide valuable insights into a previously unknown complication of the disease, potentially expanding our understanding of its pathophysiology and guiding future research and treatment strategies.

Keywords: Castleman disease, TAFRO syndrome, Cirrhosis, Fibrosis, Pancytopenia

Introduction

Castleman Disease (CD) is a rare lymphoproliferative disorder with an unclear etiology that includes various subtypes. It can be classified as unicentric, involving a single lymph node or region, (UCD) or multicentric with the former being more common. The incidence of CD is estimated at 6500-7200 patients per year in the United States [1]. Multicentric CD (MCD) can be further classified as human herpesvirus (HHV-8)-related or HHV-8 unrelated also known as idiopathic MCD (iMCD). Roughly one-half of MCD are positive for HHV-8, and the other half negative/idiopathic. TAFRO syndrome is a newly recognized variant of iMCD that includes: Thrombocytopenia (T), Anasarca (A), Fever (F), Reticulin Fibrosis (R), and Organomegaly (O).

Some evidence regarding CD claims the etiology to be related to impaired immune regulation leading to B lymphocyte and plasma cell proliferation in lymphoid tissues. The average age of people diagnosed with UCD is 35. Whereas MCD patients are often in their 50s-60s [1]. Those with HIV have an increased risk of developing MCD. UCD typically has a good prognosis once the affected lymph node or region is removed. MCD can lead to life-threatening infections and organ failure.

Various lab tests and imaging studies are indicated in the assessment for CD. All subtypes require the following: a complete excisional lymph node biopsy with microscopic examination for CD features, lab tests for inflammatory markers, complete blood count, liver function tests, albumin, and creatinine, and imaging studies to identify enlarged lymph nodes and their activity. Diagnosis of iMCD-TAFRO requires pathology confirmation of iMCD as well as four major criteria and one minor criterion listed below [2].

A. Major Criteria

i. Anasarca (pleural effusion, ascites and generalized edema).

ii. Thrombocytopenia (<100,000/microL).

iii. Systemic inflammation (fever of unknown etiology above 37.5C and/or serum CRP concentration >2mg/dL).

iv. Organomegaly (hepatomegaly, splenomegaly, or lymphadenopathy).

B. Minor criteria

i. Reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow.

ii. Renal insufficiency.

CD can present with a wide spectrum of symptoms and severity that range from lymph node enlargement to life-threatening organ dysfunction. One noted CD mechanism for symptom onset is elevated cytokines including interleukin-6 (IL-6), however neutralizing IL-6 is not universally effective as treatment for all patients. Patients with iMCD-TAFRO often exhibit fever without obvious infection, severe anasarca or ascites, organomegaly, and abdominal pain [3]. A systematic review showed the 2-year survival rate for MCD patients with TAFRO features was 85% vs 92% for those without TAFRO features [4].

First line treatment for TAFRO syndrome is high dose glucocorticoids [5]. Treatment options also include siltuximab, IL-6 monoclonal antibody, as well as tocilizumab, IL-6 receptor monoclonal antibody [6]. For those with an inadequate treatment response to steroids and IL-6 immunotherapy, consideration may be given for chemotherapy and immunosuppressant therapy; however, efficacy for these treatments is limited to case reports and series [4].

Case Description

A 57-year-old Chinese woman with iMCD-TAFRO syndrome, diastolic congestive heart failure, and liver fibrosis presented to the emergency department with dizziness and nausea. The patient was previously diagnosed with HHV-8-negative MCD with TAFRO via lymph node biopsy. Prior to this hospitalization, her treatment regimen for CD included 3mg of prednisone. Treatment with 2mg was associated with abdominal pain and overall malaise. She had a prior episode of recent change in her prednisone dosage by her oncologist, with a decrease to 2mg that also led to similar episodes of abdominal pain and ascites development. Her oncologist decided to subsequently increase her dosage from 3 mg to 5 mg, but she still experienced abdominal discomfort with nausea, no vomiting, loss of appetite, and daily bowel movements with no constipation. She also continued to take her home diuretic medication of furosemide and spironolactone.

Additionally, the patient endorsed intermittent fever and night sweats. She also had a cough and nocturnal dyspnea when changing body position, and even noticed some blood with mucus in her mouth twice. However, she did not know whether the blood was from cough or from vomitus and she had no weight loss. The patient stated that her presenting symptoms were similar to what she had experienced in China six years ago. According to the patient, she was born and raised in China, and moved to the U.S. in 2013. Her last visit to China was in 2016. Per the patient, she received "TB treatment" ("one TB medication and several other medications for liver protection for about 6 months when she was a student in college".) In the U.S. the patient was previously treated for tuberculosis and received Isoniazid/Vit B6 for 9months in late 10/2020- late 7/2021, with management from infectious disease specialists. The patient did not travel or work since 2017, and thus international travel was noncontributory to her hospital course. Notable physical examination findings include an abdomen that is soft, nontender, nondistended, and tympanic to percussion, with no lower extremity edema.

Her blood test results were as follows: White blood cell 1.4×10^3/μL (white blood cell normal range: 3.7×10^3/μL-11.1×10^3/μL), hemoglobin 10.8g/dL (hemoglobin normal range: 11.5-15.0g/dL), platelets 23×10^3/μL (platelet normal range: 150×10^3/μL-450×10^3/μL), C-reactive protein (CRP) 2.9mg/dL (CRP normal range: 0.5mg/dL or less), sodium 129 mEq/L (135-145mEq/L). The workup was significant for hypovolemic hyponatremia. Also, abdominal CT showed liver cirrhosis and minimal ascites (Figure 1).

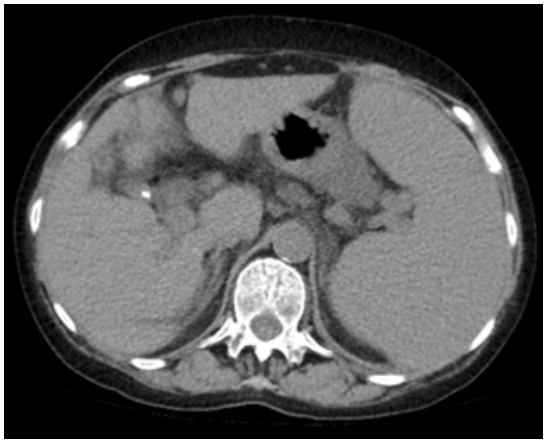

Figure 1: Abdominal Computed Tomography: Nodular liver, splenomegaly, umbilical vein recanalization, portosystemic collateral vessels.

The patient had fever and pancytopenia during this hospital course. Her nightly fever was due to unclear cause, likely related to CD flare up and less likely from infectious etiology. She was placed on cefepime. Her fever eventually resolved after completing 7 days of empiric cefepime. Her presentation was consistent with a flareup of CD with pancytopenia, as evident by enlarged lymph nodes and elevated CRP. Other surrogate markers of CD were ordered (veg F and IL-6), along with IgG and LDH as markers of disease activity.

For the patient's hematologic findings on lab studies, the hematologist inferred a recurrence of CD. Her chest CT did not show any active TB. She started on prednisone, 1mg per kilogram daily on hospital day four. Her anemia of chronic disease secondary to CD and part of her pancytopenia, were being closely monitored. The patient's pancytopenia, (ANC 500, platelets 18k) was being closely monitored as she was status-post platelet transfusion for nose bleeding during her admission. She also received Atovaquone for prophylactic treatment given her immunocompromised state.

As for the patient's abdominal bloating, initial CT did not show ascites, typically found in CD. Subsequent ultrasound showed moderate ascites likely related to a liver complication of CD. The bedside ultrasound did not show a significant enough pocket of ascites to warrant paracentesis. Her chest x-ray was clear. The echocardiogram showed normal cardiac function, despite known heart failure with left ventricular ejection fraction of 59%. The patient's abdominal girth being enlarged secondary to CD may have contributed to her anxiety related to steroid prednisone dosage changes. Clinicians offered reassurance to the patient, as well as a trial of Lasix for two days.

She noted some abdominal bloating and reflux-like symptoms associated with paroxysmal nocturnal dyspnea along with some improvement after bowel movements. Clinicians also suspected a combination of GERD, steroid-induced anxiety, and mild distention of abdomen, pushing up lung tissue. Thus, the patient was prescribed a proton pump inhibitor as well as laxative for her gastrointestinal symptoms.

As for the patient's liver cirrhosis, which she was newly diagnosed with during this hospital course, her progression of liver cirrhosis was well-documented in her medical records. The patient had two prior liver biopsies in 2017 and 2020 respectively due to issues with portal hypertension. The patient had ascites and non-bleeding varices that have been monitored for several years since her CD diagnosis. The biopsy showed only stage two fibrosis with hemophagocytic changes and recent 2022 Fibroscan, confirmed F2 fibrosis. She now has non-cirrhotic portal hypertension, presumably due to lymphoproliferative infiltration of hepatic sinusoids plus vasculature in MCD-TAFRO, with possible etiology of her current liver cirrhosis being a sequela of CD.

Discussion

TAFRO syndrome remains a challenging disease to manage given its rarity and lack of standardized treatment guidelines [7]. The patient's symptoms presented in this case align with the typical symptoms of TAFRO reported in previous literature, although her development of cirrhosis poses the possibility of a new consequence of the disorder. In regards to Castleman Disease' effect on the liver, TAFRO and CD have been reported to cause non-cirrhotic portal hypertension but not the development of liver cirrhosis [7].

The patient's progression to liver cirrhosis has been followed with diagnostic studies over the past few years prior to her current presentation. Secondary to the development of portal hypertension complications, ascites and non-bleeding varices, two liver biopsies conducted six and three years ago showed stage 2 fibrosis with hemophagocytic changes. Additionally, a Fibroscan performed in 2022 confirmed F2 fibrosis. The patient does continue to have portal hypertension, which is presumed to be due to the lymphoproliferative infiltration of hepatic sinusoids and vasculature; known to occur in TAFRO. The patient's current presentation and diagnostic studies revealing liver cirrhosis suggest a progression of her known fibrosis. TAFRO is not known to cause liver cirrhosis but given the rarity of the disease, this case may be helpful in determining if TAFRO may lead to liver cirrhosis. A case of liver cirrhosis has been reported in a child with Castleman disease, which could be indicative of an important clinical sign to consider in the workup of patients [8].

The patient's clinical picture is suggestive of a diffuse infiltration of abdominal mesenteric tissues and subcutaneous tissues, as prior liver biopsies also showed hemophagocytosis; these findings are supportive of CD [4,9]. However, it is atypical to have no significant adenopathy or ascites. Generally, the diagnosis of TAFRO syndrome includes fulfillment of four major criteria, and one minor criteria [2]. Of the major criteria, anasarca, including pleural effusion, ascites, and general edema is required. The present case patient does not have significant adenopathy or ascites, which is atypical for TAFRO. Nonetheless, our patient does have thrombocytopenia and systemic inflammation, which is part of the major criteria for TAFRO syndrome.

In terms of our patient's presentation of pancytopenia and fever, she experienced symptoms similar to individuals diagnosed with TAFRO and Castleman Disease [10]. In this case, the patient's fever was intermittent and nightly persisting until completion of empiric antibiotic regimen of cefepime for seven days total. While this patient had a history of latent tuberculosis, she did not meet criteria of reactivation of her tuberculosis during her hospital course. Interestingly, few case studies have reported a co-occurrence of tuberculosis and TAFRO syndrome.

As for our patient's general presentation of fatigue, malaise and abdominal discomfort, her treatment regimen was mostly symptomatic. The patient utilized corticosteroids, in particular prednisone, to alleviate her symptoms, and she was found to have a flare up in the setting of changes in her usual dosage. Literature studies have stated preferred first line therapy for multicentric CD to be an anti-interleukin 6 monoclonal antibody with or without steroids

[6]. Clinicians on the case were considering adding such monoclonal antibody therapies for our patient but decided against it given her eventual resolution of her flareup episode during the hospital course. The patient's treatment options for Castleman disease continues to be diminishing given her waxing and waning non-response to corticosteroid dosages. The next step would be more intensive combination chemotherapy with rituximab, or bortezomib-based regimen [6]. More severe cases require adjuvant combination chemotherapy. Given her clinical course prior has been unresponsive at times, it may be a useful option to consider repeat biopsies to clarify the patient's unique disease progression.

Conclusion

TAFRO is an inflammatory syndrome that is a subtype of iMCD and consists of: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly. The current criteria for diagnosis involves lymph node histology exhibiting CD as well as 3 of 5 TAFRO symptoms. Our patient met the diagnostic criteria and has had a poor response to treatments. The next recommendation was to begin high dose glucocorticoids 1mg/kg. CD has been reported to be associated with non-cirrhotic portal hypertension, but not liver cirrhosis. Our patient did have a history of liver fibrosis and sequelae of portal hypertension, ascites and non-bleeding varices. Upon her most recent hospital presentation, she was found to have liver cirrhosis which calls into question whether it may be a sequela of Castleman Disease. Given the rarity of CD, especially the TAFRO variant, only one other case has been reported to show the development of cirrhosis, which was in a pediatric patient. Further understanding of liver pathology in CD and CD-associated disorders may provide additional management considerations and offer insight into the pathophysiology of CD.

Acknowledgement

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Conflict of Interest

None.

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