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Case Report

CASE REPORT

Castleman's disease with TAFRO syndrome: a case report from Syria

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Abstract

Castleman's disease is a rare disorder, yet a rarer newly described syndrome called TAFRO syndrome was discovered to accompany it. TAFRO represents the constellation of symptoms (Thrombocytopenia, Anasarca, MyeloFibrosis, Renal failure, Organomegaly). Most cases were described in Japan. We present the first case of TAFRO syndrome in Syria. A 58-year-old Caucasian male with no relevant history presented with fatigue, oliguria, decreased platelets, increased creatinine level, hepatosplenomegaly, ascites, pitting edema and lymph node enlargement. Possible differential diagnoses were excluded by laboratory, radiologic and cytologic tests including TB, malignancy and autoimmune diseases. A biopsy of a supraclavicular lymph node confirmed Castleman disease. Our patient had Catleman's disease, and presented with only four diagnostic criteria for TAFRO syndrome (Myelofibrosis was absent) in addition to other minor characteristics (microcytic anemia, negative HIV and HHV-8 infections.) which make the presentation consistent with TAFRO syndrome described in the Japanese cases. The criteria for diagnosing TAFRO syndrome are still changing, and the pathophysiology behind it is unclear. We recommend further research to understand this syndrome taking into account that its prevalence might be worldwide.

BACKGROUND

Castleman's disease (CD) is a rare lymphoproliferative disorder with hyperplasia of lymph nodes and regression of germinal centers on pathology [1]. It is classified clinically to either unicentric (UCD) or multicentric (MCD) which is a systemic disease clinically characterized by diffuse lymphadenopathy, splenomegaly, anemia, thrombocytosis, hypergammaglobulinemia, elevated serum inflammatory proteins (e.g. CRP) and systemic inflammatory symptoms [2, 3]. The disease is also classified histologically to hyaline-vascular, plasma cell and mixed type [4].

It is believed that this inflammatory entity (MCD) is caused by pathologic hypercytokinemia, IL-6 in particular.

In western countries, it was found that MCD was associated with human herpes virus-8 (HHV8) in immunocompromised patients (e.g. AIDS) where the virus produces a homolog to IL-6 that drives the pathology of the disease. However, in other countries including Japan, MCD was described in HHV-8 negative patients. The etiology of this type of MCD is still unknown and controversial and the disease is referred to as idiopathic MCD (iMCD) [5].

Systemic therapies are the primary treatment for MCD, and include glucocorticoids, cytotoxic chemotherapy, rituximab and other drugs [2, 6].

TAFRO is a unique clinicopathologic variant of MCD that was first reported by Tekai *et al.* [6, 7].

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A recent meeting in Japan held by Kawabata *et al.* assigned the term 'TAFRO' to the constellation of symptoms (Thrombocytopenia, Anasarca, MyeloFibrosis, Renal failure, Organomegaly) [8].

Other characteristics of TAFRO were later proposed including: normal immunoglobulin levels, and relatively small lymphadenopathy (<1.5 cm).

Differential diagnosis for TAFRO syndrome includes multiple diseases (lymphoma, autoimmune disease and acid-fast bacillus infection) that should be excluded before the diagnosis of TAFRO can be confirmed.

Histological findings might also differentiate iMCD with TAFRO syndrome from pure iMCD without other specified characteristics (iMCD-NOS). Iwaki *et al.* mentioned that TAFRO-iMCD has atrophic germinal centers, enlarged nuclei of endothelial cells, proliferation of endothelial venules with a small number of mature plasma cell infiltrate. Whereas iMCD-NOS has hyperplastic germinal centers varying in size with sheets of proliferating mature plasma cells.

A new diagnostic criteria and disease severity classification were proposed by Masaki *et al.*, and another diagnostic criteria was proposed by Iwaki *et al.* and differs slightly from the former [5, 9].

Most cases on TAFRO syndrome were described in Japan [6, 10–12], a case in India [13], two in Italy [6, 14] and one in Tunisia [15].

In our case we are reporting a Syrian patient with iMCD and TAFRO syndrome.

CASE DESCRIPTION

A 58-year-old Caucasian male with no relevant medical, family or psychosocial history was admitted to Al-Assad University Hospital, Damascus University, for ascites.

The patient's complaint started 4 months before with productive cough of white sputum with low grade fever which was relieved with paracetamol, accompanied with fatigue and general myalgia. The cough sustained for about a month and did not respond to antibiotics nor to bronchodilators, and the patient was prescribed corticosteroids for it.

Two months later, the patient developed oliguria, melena and creatinine level was rising steadily (rising from 1.2 to 2 mg/dL).

The patient was admitted to a local hospital where he underwent some medical tests. Abdominal ultrasound showed hepatosplenomegaly, fatty liver and a small-amount ascites. Upper GI endoscopy revealed no source for bleeding.

The ascites kept rising, and the patient was put on albumin replacement therapy. Laboratory tests from this local hospital are not available.

The patient was then referred to Al-Assad University Hospital for further investigation. The timeline of the patient's

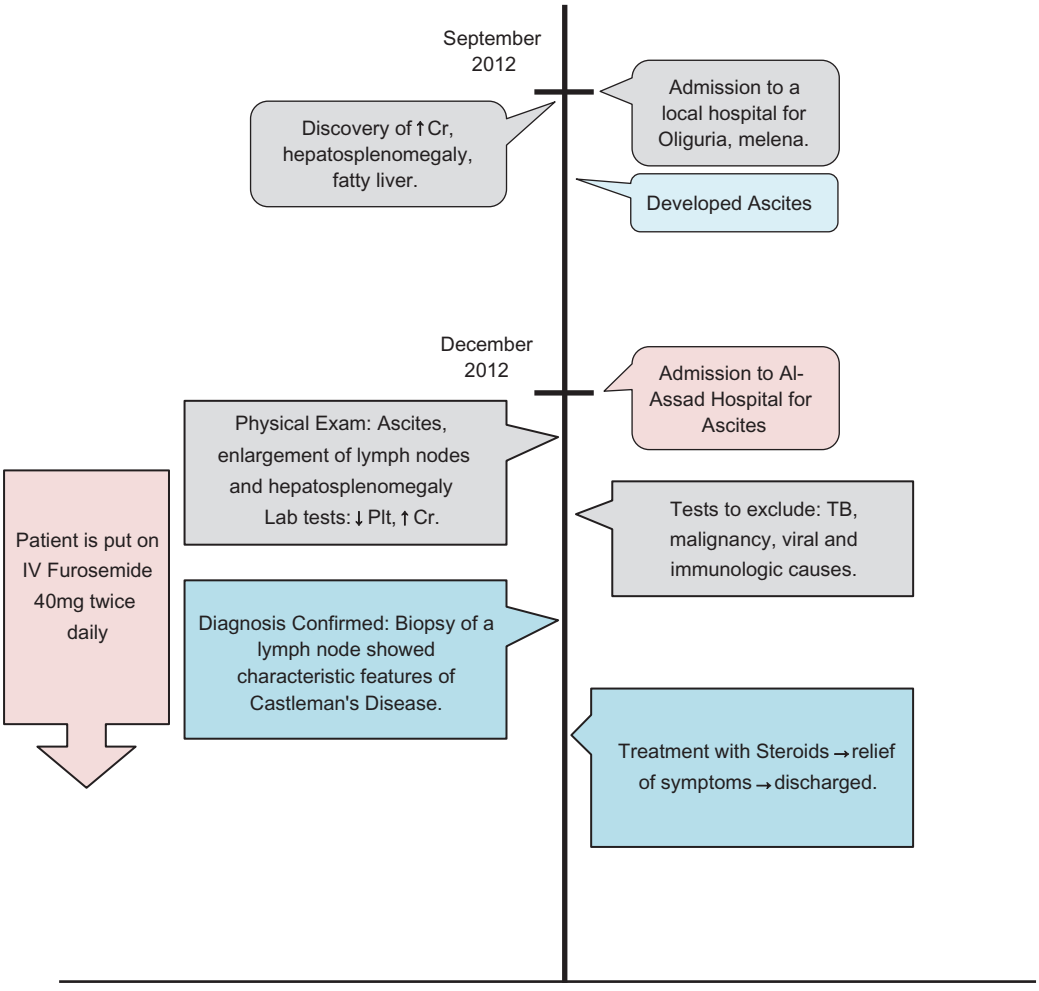

Figure 1: Timeline of patient's history, diagnostic process, intervention and outcome.

Table 1: Laboratory tests on admission

Test name	Result	Normal range
Complete blood count		
White blood cells	6010/μL	4400–11 000/μL
Neutrophils	59%	40–70%
Lymphocytes	16.2%	20–40%
Monocytes	20.6%	2–6 %
Eosinophils	2.03%	1–6 %
Basophils	2.2%	1–2 %
RBCs	2.87×10^6/μL	$4.5–5.5 \times 10^6$/μL
Hemoglobin	8.34 g/dL	13–16 g/dL
Hematocrit	24.4%	38–53 %
RBCs MCV	85.2 fL	82–96 fL
RBCs MCH	29.1 pg	27.5–33.2 pg
RBCs MCHC	34.1%	31.5–35.5 %
RBC RDW	17.9	
Platelets	47.2×10^3/μL	$150–450 \times 10^3$/ μL
Reticulocytes	2.5%	0.5–1.5 %
Coagulation test		
PT	60%	
PTT	28	
INR	1.28	1–1.5
Coombs direct	Positive (++++) IgG (+++++)	
Coombs indirect	Positive	
Blood Chemistry		
Urea	261 mg/dL	10–50 mg/dL
Creatinine	2.92 mg/dL	0.7–1.36 mg/dL
Sodium	132.2 mmol/L	135–148 mmol/L
Potassium	4.48 mmol/L	3.5–5.0 mmol/L
Chloride	101.7 mmol/L	95–105 mmol/L
ACE	36 U/L	8–52 U/L
Total protein	6.2	
Albumin	2.3	
Alkaline phosphatase (ALP)	322	
AST	23 IU/L	8–20 IU/L
ALT	16 IU/L	8–20 IU/L
LDH	497 IU/L	50–150 IU/L
ESR	73 mm/h	0–20 mm/h
CRP	4.3 mg/L	<2 mg/L
Ferritin	571.4 μg/L	20–330 μg/L
Viral markers		
HIV Ag/Ab	0.28 (negative)	Negative: up to 1 Positive: more than 1
HBsAg	0.29 (negative)	0–1
Anti HCV	0.06 (negative)	0–1
Cancer markers		
CA 15.3	Negative	
CA 19.9	Negative	
PSA	Negative	
AFP	Negative	
CEA	Negative	
Autoimmune disease serology		
ANA	Negative	
Anti-dsDNA	Negative	
Complement C3	Normal value	
Complement C4	Normal value	
Urine analysis		
Protein	+	
Glucose	–	
Hemoglobin	+	
Leukocytes	15	Normal: up to 10
RBCs	60	Normal: up to 10
Cylinders	Negative	
Ascites fluid chemistry		
Color before sedimentation	Yellow turbid	
Color after sedimentation	Yellow clear	
Leukocytes	850/μL	
Neutrophils	75%	
Lymphocytes	25%	
Eosinophils		
Monocytes		
RBCs	420/μL	
Glucose	104 mg/dL	70–100 mg/dL
Protein	3.6 g/dL	0.3–4.0 g/dL
Albumin	1.5 g/dL	
Ascites fluid microbiology and cytology		
Culture	No growth of bacteria after incubation for 48 h	
Mycobacterium tuberculosis DNA by real-time PCR	Negative	
Malignant cell	No malignant cells were detected	

history, diagnostic process, intervention and outcomes are illustrated in Fig. 1.

On admission in December 2012, the patient suffered from general fatigue, muscle pain, oliguria, decreased platelets count, increased creatinine level, hepatosplenomegaly, ascites, pitting edema (grade +2), and neck, axial, and inguinal lymph node enlargement.

The patient was then put on a diuretic (40 mg of intravenous furosemide twice daily).

Repeated abdominal ultrasound and Doppler confirmed the presence of splenomegaly (homogenous, 15 cm), moderate hepatomegaly, pelvic fluid and ascites. No increased portal tension or varices were detected.

CXR showed bilateral pleural effusion.

Repeated MSCT scans showed generalized lymphadenopathy with enlargement of jugular nodes (0.5–1 cm), mediastinal (a node in the anterior mediastinum was 4×2.5 cm^2 in diameter), and small peri-aortic nodes.

Ascites fluid analysis revealed elevated leukocytes with prominent neutrophils, SAAG > 1.1 (Table 1). Further investigation with echo Doppler showed normal vena cava-portal vein pressure gradient with no retrograde flow.

Ascites fluid was free of malignant cells, and TB test came negative.

Viral serology (HIV, HBV and HCV) and cancer markers were undertaken and came back negative as well.

Tests for HHV-8, EBV and other viruses were not performed.

Immunological tests were performed. ANA and anti-dsDNA were negative and cryoglobulin was elevated.

Some routine serologic tests were also undertaken, showing elevated CRP and ESR values and normal complement and elevated alkaline phosphatase (ALP) and lactate dehydrogenase (LDH).

All Lab test results are demonstrated in Table 1.

Serum protein electrophoresis showed low albumin with normal alpha1, alpha2, beta and gamma globulins.

A bone marrow biopsy was performed and the result was in the normal range with no infiltrative lesion, and Congo red staining was negative.

Biopsy of a supraclavicular lymph node was performed to make a definitive diagnosis and showed a partial alteration in the general structure, small polymorohic follicles with hyalinized germinal centers, lymphocytes of the mantle zones arranged in concentric rings around the germinal center ('onion-skinning') and follicles radially penetrated by a blood vessel ('lollipop' follicle), also a large non-atretic infiltrate of plasma cells was found in the interfollicular region (Fig. 2).

Glucocorticoids were administered to our patient and most of the symptoms and signs were relieved, after which he was discharged. No further follow up is available.

DISCUSSION

CD is a lymphoproliferative disorder that was first described by Castleman *et al.* [16].

CD is classified to UCD or MCD which is a systemic disease clinically characterized by diffuse lymphadenopathy, splenomegaly, anemia, thrombocytosis, hypergammaglobulinemia, elevated serum inflammatory proteins (e.g. CRP) and systemic inflammatory symptoms [2, 3], and histologically to hyaline-vascular, plasma cell or mixed CD.

HIV with HHV-8 leads to aggressive and often fatal cases of MCD in western countries [17–19], and is believed to do so by producing a homolog to IL-6, whereas MCD is seen in patients free of HIV and HHV-8 in Japan [5, 11].

TAFRO is a new syndrome that is similar to but distinct from MCD [7].

A recent meeting declared the symptoms and signs of this syndrome which include ascites, thrombocytopenia, microcytic anemia, renal dysfunction, low level of LDH, relatively mild polyclonal hypergammopathy, ALP elevation, immunological abnormalities (such as positivity for RF, COOMBs test, anti-thyroid antibodies), myelofibrosis, increased megakaryocytes in bone marrow.

Later, Masaki *et al.* proposed a revised diagnostic criteria for TAFRO syndrome and disease severity classification [9], and Iwaki *et al.* described histological differences between iMCD and TAFRO-iMCD.

Our patient was tested for different etiologies for his non-specific symptoms, and was eventually diagnosed with MCD based on the lymph node biopsy and clinical characteristics.

On revision of the case we discovered the unique manifestations that appeared to go along with the newly described entity of TAFRO syndrome.

Our patient fulfilled four out of five major characteristics of TAFRO syndrome as mentioned by Takai *et al.* At the same time he fulfilled the three major criteria recently proposed by Masaki *et al.* (anasarca, thrombocytopenia and CRP $\geq$ 2 mg/dl), and three out of four minor criteria (CD-like features on lymph node biopsy, mild organomegaly, including hepatomegaly, splenomegaly and lymphadenopathy and progressive renal insufficiency) where the authors required only two for the diagnosis.

In addition, we excluded malignancies including lymphoma and myeloma by performing lymph node biopsy and protein electrophoresis.

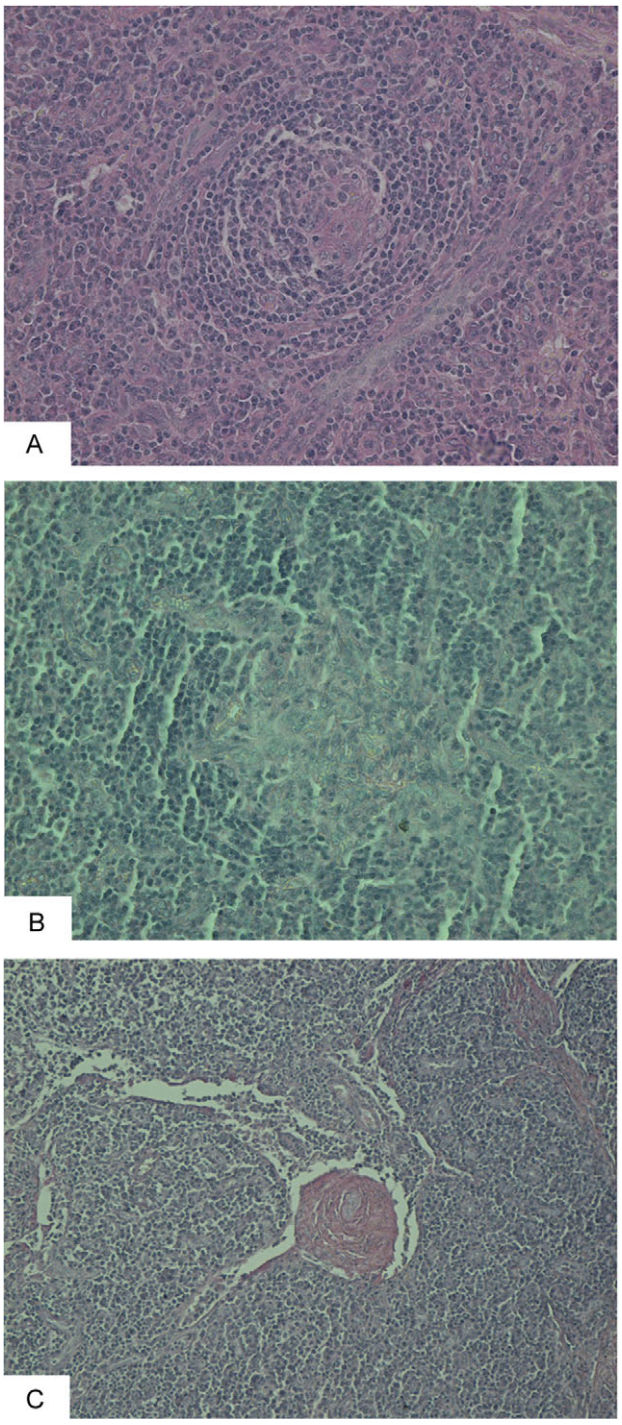

Figure 2: A biopsy of a lymph node. The microscopic photos above show the histology of a supraclavicular lymph node using hematoxylin and eosin staining. A lymphoid follicle appears and in which the mantle zone is arranged in concentric rings around the germinal center 'onion-skinning' (**A**) penetrated radially by hyalinized blood vessels (**B** and **C**) indicating Castleman's disease of the hyaline-vascular type.

We also excluded tuberculosis; other infectious diseases were not pursued due to the lack of clinical manifestations supporting an infective etiology.

The patient was tested for HIV infection with PCR and he was negative. And with no immune deficiency in the patient,

Table 2: Comparison of symptoms and laboratory test between iMCD-NOS, TAFRO-iMCD and our patient

Clinicopathologic findings	iMCD-NOS	TAFRO-iMCD	Our case
Symptoms			
Fever	±	++	–
Anasarca	±	++	++
Lymphoid adenopathy	+	±	+
Hepatosplenomegaly	+	+	+
Laboratory tests			
Blood platelet count	Increased	Severely depleted	Severely depleted
Hypergammaglobulinemia	Present	Absent	Absent
Serum ALP	Lower	Higher	Higher
Histopathological			
Germial center (GC)	Hyperplastic GC with sheets of proliferating mature plasma cells	Atrophic GC with hyaline vessels, proliferation of endothelial venules and a small number of mature plasma cell infiltrate	Small GC with hyaline vessels
LANA-1 for HHV-8	±	–	N/A
Interfolicular area	Plasma cells	Proliferation of small vessels	Atretic infiltrate of plasma cells
Bone marrow	Immunoblast, plasma cells	Megakaryocytes hyperplasia	Normal
Treatment	Corticosteroid, tocilizumab	Corticosteroid, cyclosporin A	Corticosteroids

–, none; ±, often; +, mild; ++, marked.

PCR and latency associated nuclear antigen (LANA-1) for HHV-8 were not tested.

VEGF and IL-6 which are thought to be responsible for the pathogenicity of MCD and were both elevated in TAFRO-iMCD as described by Iwaki *et al.* [5]. However, these two tests were not performed as they are not part of routine workup in our hospital and little evidence was available at the time of diagnosis.

Some autoimmune diseases were excluded through clinical presentation and serology. Characteristic symptoms of SLE and rheumatoid arthritis were absent along with negative ANA and Anti dsDNA for the former. POEMS syndrome might accompany Castleman disease, but most of its basic signs and symptoms were absent as there were no polyneuropathy, endocrinopathy, monoclonal gammopathy nor skin changes.

Polyarteritis nodosa, Wegner's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome were not considered as primary diagnoses options because patient's signs and symptoms didn't suggest them (no history of eye inflammation, nasal crusting or discharge, epistaxis, oral ulcers, sinusitis, acute foot drop or wrist drop, palpable purpura) along with normal lungs on CXR and unspecific urine sediment collected using Foley catheter. And after the confirmation of Castleman disease, no extra workout was done to firmly confirm their exclusion, and neither p-ANCA nor c-ANCA tests were performed.

In this patient, a high level of cryoglobulins was detected. However, the possibility of having cryoglobulinemic vasculitis is problematic. The patient's levels of cryoglobulin were not followed to establish a firm diagnosis. Based on Brouet classification, we can exclude Type I cryoglobulinemia as it is associated with isolated monoclonal Ig typically resulting from multiple myeloma or Waldenström's macroglobulinemia, both of which are negative based on protein electrophoresis and lymph node and bone marrow biopsies. Type II and III on the other hand result from a variety of conditions (connective tissue diseases, chronic inflammatory states, viral infections like HCV and HIV, and lymphoproliferative disorders) all of which were excluded except the lymphoproliferative disorder where actually Castleman disease of our case fits, and the association of Castleman disease with cryoglobulinemia is mentioned in literature [20]. Classical cryoglobulinemic vasculitis includes a wide variety of symptoms which were absent in our patient as there were not any cutaneous manifestation, sensory changes or weakness due to peripheral neuropathy, arthralgia that's exacerbated by cold exposure nor arthritis [21].

And it should be mentioned that cutaneous manifestations (palpable purpura due to cutaneous vasculitis, erythematous macules to purpuric papules, Raynaud phenomenon, livedo reticularis, ulcerations and necrosis) develop in nearly all patients with cryoglobulinemias type II syndromes [22].

That leaves renal dysfunction with proteinuria and hematuria as the only manifestation that are present in our case (casts were negative).

In the recent history of the patient, there was a persistent cough that did not respond to antibiotics nor to bronchodilators, but seems to have responded to corticosteroids, which might also be an early presentation of cryoglobulinemia and the systemic inflammatory state of the patient.

Along with what's described above, the values of complement C3 and C4 were normal, which decreases the possibility of the formation of immune complexes that mediate the pathogenicity of cryoglobulinemic vasculitis.

Based on this analysis we cannot exclude the presence of cryoglobulinemic vasculitis with atypical characteristics. However, as the majority of known causes for cyroglobulinema were excluded, the only remaining explanation is the lymphoproliferative entity (CD).

We would like to note some points from our case: no hypergammaglobulinemia in serum protein electrophoresis was detected which favors TAFRO to MCD, but histological findings where typical for MCD and did not fit the difference described by Iwaki *et al.*

Both Iwaki *et al.* and Masaki *et al.* mentioned that in TAFRO, the size of lymph node did not exceed 1.5 cm. In our case one lymph node was larger ($4 \times 2.5\ cm^2$) which is not typical and has been mentioned in only one case report before [23].

Elevated ALP with normal transaminases was present.

LDH level was elevated, and we noticed that its levels were higher than what was mentioned in the two new case series

[5, 9] as it did not exceed 400 IU/L while in our case it was 497 IU/L on admission and rose to 650 IU/L in the next following days. Unfortunately LDH subtype was not analyzed.

Based on the disease severity classification for TAFRO patients suggested by Masaki *et al.*, our patient's disease is slightly severe (grade 3) with 7 points for (anasarca, platelets <50000, CRP ≥ 2 and < 10 mg/dL, GFR < 60 mL/min/1.73 m^2).

Glucocorticoid, immunosuppressant or tocilizumab are being used for TAFRO management.

We compare in Table 2 between typical TAFRO-iMCD, iMCD-NOS and our patient.

Glucocorticoids were used as a principle treatment in this patient and were effective leading to the relief of symptoms. Other more specific treatments for CD were inconvenient to use.

CONCLUSION

As the pathophysiology of TAFRO syndrome has not been known yet, and the criteria of diagnosis are not clear enough; the discovery of this case in Syria and the divergence in its presentation rises the opportunity to discover more cases of TAFRO and to make better criteria for the diagnosis.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not required.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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GUARANTOR

Prof. Mayssoun Kudsi.

REFERENCES

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital Weekly Clinicopathological Exercises: Case 40011. *N Engl J Med* 1954;**250**:26–30.
2. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and management of Castleman disease. *Cancer Control* 2014;**21**:266–78.
3. Herrada J, Cabanillas F, Rice L, Manning J, Pugh W. The clinical behavior of localized and multicentric Castleman disease. *Ann Intern Med* 1998;**128**:657–62.
4. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. *Cancer* 1972;**29**:670–83.
5. Iwaki N, Fajgenbaum DC, Nabel CS, Gion Y, Kondo E, Kawano M, *et al.* Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol [Internet]* 2016;**91**:220–6. http://www.ncbi.nlm.nih.gov/pubmed/26805758.
6. Tedesco S, Postacchini L, Manfredi L, Goteri G, Luchetti MM, Festa A, *et al.* Successful treatment of a Caucasian case of multifocal Castleman's disease with TAFRO syndrome with a pathophysiology targeted therapy—a case report. *Exp Hematol Oncol* 2015;**4**:3.
7. Takai K, Nikkuni K, Shibuya H, Hashidate H. [Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly]. *Rinsho Ketsueki* 2010;**51**:320–5.
8. Kawabata H, Takai K, Kojima M, Nakamura N, Aoki S, Nakamura S, *et al.* Castleman-Kojima disease (TAFRO syndrome) : a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly : a status. *J Clin Exp Hematop* 2013;**53**:57–61.
9. Masaki Y, Kawabata H, Takai K, Kojima M, Tsukamoto N, Ishigaki Y, *et al.* Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol [Internet]* 2016;**103**:686–92. http://www.ncbi.nlm.nih.gov/pubmed/27084250.
10. Inoue M, Ankou M, Hua J, Iwaki Y, Hagihara M, Ota Y. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after immunosuppressive therapies using corticosteroids and cyclosporin A : a case report. *J Clin Exp Hematop* 2013;**53**:95–9.
11. Masaki Y, Nakajima A, Iwao H, Kurose N, Sato T, Nakamura T, *et al.* Japanese variant of multicentric castleman's disease associated with serositis and thrombocytopenia—a report of two cases: is TAFRO syndrome (Castleman-Kojima disease) a distinct clinicopathological entity? *J Clin Exp Hematop* 2013;**53**:79–85.
12. Kubokawa I, Yachie A, Hayakawa A, Hirase S, Yamamoto N, Mori T, *et al.* The first report of adolescent TAFRO syndrome, a unique clinicopathologic variant of multicentric Castleman's disease. *BMC Pediatr* 2014;**14**:139.
13. Koduri PR, Parvez M, Kaza S, Pappu P, Anuradha S. Castleman-Kojima disease in a South Asian adolescent. *J Clin Exp Hematop* 2014;**54**:163–6.
14. Allegra A, Rotondo F, Russo S, Calabro L, Maisano V, Bacci F, *et al.* Castleman-Kojima disease (TAFRO syndrome) in a Caucasian patient: a rare case report and review of the literature. *Blood Cells Mol Dis* 2015;**55**:206–7. United States.
15. Naifar M, Messedi M, Elleuch A, Snoussi M, Gouiaa N, Turki M, *et al.* Syndrome de TAFRO et gammapathie monoclonale: association inhabituelle. *Curr Res Transl Med [Internet]* 2016;**64**:43–7. http://www.ncbi.nlm.nih.gov/pubmed/27140598.
16. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. *Cancer*. 1956;**9**:822–30.
17. Cesarman E, Knowles DM. The role of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in lymphoproliferative diseases. *Semin Cancer Biol* 1999;**9**:165–74.
18. Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, *et al.* HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood* 2000;**95**:1406–12.
19. Frizzera G. Atypical immunoproliferative disorders: when of age? *Virchows Arch A Pathol Anat Histopathol [Internet]* 1993;**422**:261–3. http://link.springer.com/10.1007/BF01608333.
20. Trejo O, Ramos-Casals M, López-Guillermo A, García-Carrasco M, Yagüe J, Cervera R, *et al.* Hematologic malignancies in patients with cryoglobulinemia: association with

autoimmune and chronic viral diseases. *Semin Arthritis Rheum [Internet]* 2003;**33**:19–28. http://www.ncbi.nlm.nih.gov/pubmed/12920693.

21. Peng SL, Schur PH. Overview of cryoglobulins and cryoglobulinemia. In: Post T, ed. *UpToDate [Internet]*. MA: UpToDate in Waltham, 2016. https://www.uptodate.com/contents/overview-of-cryoglobulins-and-cryoglobulinemia. (2 March 2017, date last accessed).
22. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med [Internet]* 1974;**57**:775–88. http://www.ncbi.nlm.nih.gov/pubmed/4216269.
23. Nagano M, Matsumoto J. A case of TAFRO syndrome with a large mediastinal mass treated with debulking surgery. *Surg Case Reports [Internet]* 2016;**2**:61. http://www.ncbi.nlm.nih.gov/pubmed/27316721.