

First European case of TAFRO syndrome associated with Sjogren disease

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To cite this article:

Lynn Antoun Abdo, Clement Philippe Morin, Rocco Paolo Collarino, Jean Paul Cabane, Marc Albert Gatfosse. First European Case of TAFRO Syndrome Associated with Sjogren Disease. *American Journal of Internal Medicine*. Vol. 2, No. 6, 2014, pp. 102-105.

doi: 10.11648/j.ajim.20140206.12

Abstract: We herein describe a case of an unusual multicentric castleman disease(MCD) accompanied by Thrombocytopenia, Anasarca, myeloFibrosis and Renal failure, compatible with TAFRO syndrome and associated with Sjogren disease. The treatment with corticosteroids dramatically improved the symptoms. The clinical features of this case were similar to those reported previously in Japan but this appears to be the first European MCD with negative HHV8 and HIV that meets the criteria of TAFRO syndrome, associated with Sjögren disease.

Keywords: TAFRO Syndrome, Sjogren Disease, Castleman Disease, Interleukin-6, Thrombocytopenia, Pleural Effusion

1. Introduction

TAFRO syndrome is a new disease concept reported by Takai et al., named from thrombocytopenia, anasarca, myelofibrosis, renal failure, and organomegaly.¹ Until now this disease was reported only in Japan, and is described as an atypical multicentric Castleman disease (MCD) with negative HHV8 and HIV.² We encountered the first case of a TAFRO syndrome associated with Sjögren disease in a European patient.

2. Case Report

An 81-year-old French patient known to have hypertension, was admitted to the hospital for fever, weight loss, asthenia, dry mouth and generalized edema for a few weeks.



Figure 1 and 2. photos showing pitting edema on the hands and ascites.

On clinical exam, he weighed 80 kg (usually 72 kg), was febrile and had anasarca (pleural effusion, ascites, edema of the lower limbs) and peripheral lymph nodes (Cf. fig1 and 2). He underwent a series of medical tests (Cf. table 1), that showed an inflammatory syndrome associated with a non

regenerative anemia, thrombocytopenia and renal failure. There was no evidence of infection. HIV and HHV8 serologies were negative. However, the anti-nuclear antibodies, anti SSA and anti SSB antibodies were strongly elevated, as well as IL6 (interleukin-6).

Table 1. Laboratory data.

	On admission	One month later	One year later		On admission	One month later	One year later
Hemoglobin (g/dl)	8.1	9.5	14.6	albumin(g/l)	20.9	26.8	
Hematocrit (%)	24	28.1	44.5	Ferritin (ng/ml)	1199		
MCV (fl)	94	95	98	IL6 (pg/ml)	18		
Reticulocytes /mm ³	77500			proteinuria(g/24h)	2.3	1.63	
White blood cells /mm ³	5473	8230	11130	ANA	1/1280		
Neutrophil /mm ³	3560	4000	7230	anti SSA	240 U/ml		
lymphocyte/mm ³	1400	1500	3340	anti SSB	58 U/ml		
Eosinophil/mm ³	20	10	0	Serum electrophoresis	Polyclonal hyper gammaglobulinemia		
basophil/mm ³	10	10	0	CRP (mg/l)	210	17	<3
Platelet count/mm ³	26000	58000	116000	creatinine(micomol/l)	141	134	138
Prothrombine time (%)	94	96	120%	Urea (mmol/l)	11		
Fibrinogen(g/l)	3.6	3.2	4.2	Triglyceride (g/l)	1.45		
Normal or negative tests	HIV, HHV8, Hepatitis B and C, HSV1 and 2, ANCA, Anti ds DNA anti RNA, anti polymerase III, Blood cultures, Coombs test, VEGF, haptoglobin, quantiFERON, antiphospholipid complements, TSH, LFTs, BNP						

Abbreviations: ANA, antinuclear antibody; CRP, C reactive protein; HIV: human immunodeficiency virus; HHV8, human herpesvirus 8; HSV, herpes simplex virus; ANCA, anti-neutrophil cytoplasmic antibody; Anti ds DNA, anti -double- stranded DNA; VEGF, vascular endothelial growth factor; TSH, thyroid -stimulating hormone; LFTs, liver function tests; BNP, brain natriuretic peptide.

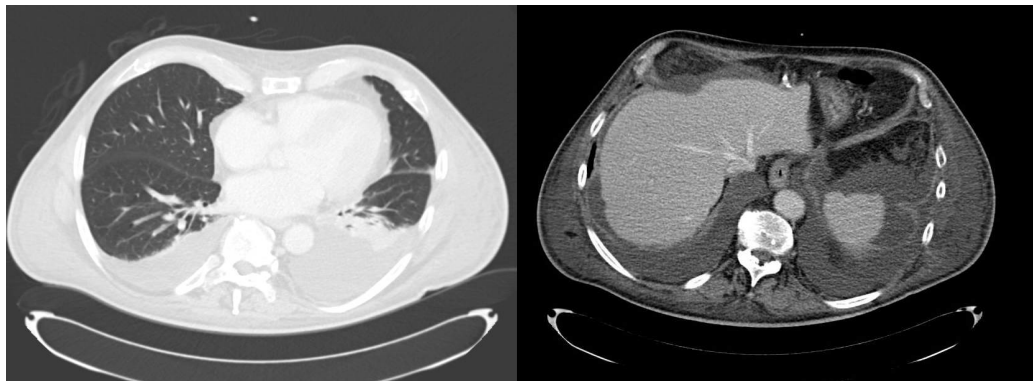


Figure 3. CT scan showing bilateral pleural effusion.

A total body scan showed bilateral pleural effusion, with mediastinal and peritoneal lymph nodes with marked ascites (Cf. fig3), and there was diffuse adenopathy with moderate hyperfixation on PET scan (SUVmax=2.3). Cardiac ultrasound was normal. Biopsies of inguinal and axillary lymph nodes were compatible with a Castleman disease of a mixed type, with negative immunohistochemical staining for HHV8 and without any argument for a lymphoma. The biopsy of the salivary glands showed focal lymphocytic infiltration of grade III according to the classification of Chisholm. The bone marrow biopsy revealed myelofibrosis without an abnormal lymphocytic infiltration.

He was then considered to have an atypical multicentric Castleman disease, compatible with TAFRO disease, associated with an autoimmune Sjögren syndrome, and was treated with corticosteroids (1mg/kg) followed by a rapid

improvement in the inflammatory markers.



Figure 4. Complete remission after treatment.

One month later, edema, anemia, thrombocytopenia and

renal function improved, and on discharge he weighed 73 kg.

One year later, he was still on a low dose of prednisone, with clinical and biological remission (Cf. fig 4).

3. Discussion

Castleman's disease (CD) is a rare systemic disorder classified among atypical lymphoproliferative disorders.³ Multicentric Castleman's disease (MCD) is a subtype with multiple lesions and systemic symptoms.⁴

As currently understood, CD is considered to be a heterogeneous entity related to conditions of immune deregulation. In this respect, it is interesting that various disorders of the immune system may be characterized by Castleman-like histological changes, such as infections (Human Immunodeficiency Virus HIV) and primary autoimmune diseases (systemic lupus erythematosus, POEMS syndrome, etc.).⁴ As it may also be occasionally associated with autoimmune manifestations and connective tissue diseases.⁵

Based on the histopathological findings of the lymph node biopsies, the laboratory data and other clinical manifestations, we diagnosed the patient as having multicentric Castleman

disease(MCD). He had an atypical presentation of a MCD associated with sjogren disease confirmed by the salivary gland biopsy. He had also multiple lymph nodes, anasarca, myelofibrosis and thrombocytopenia. The results of viral serological test for HIV and polymerase chain reaction analysis for the HHV8 sequence in peripheral blood were negative. Moreover, immunohistochemical staining for HHV8 in lymph node was also negative.

Recently, some cases, resembling MCD but with distinctive features have been reported and have been given the designation of TAFRO syndrome which stands for Thrombocytopenia, Anasarca, myeloFibrosis, Renal involvement and Organomegaly.

Our patient's clinical findings and laboratory data met the reported criteria for TAFRO syndrome, which have some common and some different characteristics from MCD. He had high levels of interleukin-6(IL6) and as a result had systemic manifestations of inflammation and an increase in acute inflammatory proteins. These findings match those of MCD. On the other hand, he had marked thrombocytopenia, anasarca and myelofibrosis which differs from typical MCD but meet the criteria of TAFRO.⁶⁻⁸ (Cf. table 2)

Table 2. Features allowing the diagnosis of TAFRO syndrome in the current case and in the three cases reported by takai *et al.*

Case no.	1	2	3	Current
Age	47	56	49	81
gender	F	M	M	M
thrombocytopenia	yes	Yes	Yes	Yes
anasarca	Yes	Yes	Yes	Yes
Reticulin fibrosis of the bone marrow	Yes	Yes	Yes	Yes
Renal dysfunction	No data	Yes	No data	Yes
organomegaly	Yes	Yes	Yes	No
HHV8	No	No	No	No
Serum IL-6 (pg/ml) (normal range < 4 pg/ml)	No data	7.2	64.9	18
Lymph node biopsy	No data	No data	hyaline vascular type CD	Mixed type CD
Treatment	cyclophosphamide, doxorubicin, vincristine and prednisolone	Prednisolone, cyclosporin A, IV immunoglobulin	Prednisolone, IV immunoglobulin	prednisolone
Outcome	survival	survival	Death caused by multiple organ failure	survival

It is postulated that the mechanism of lymphoproliferation in MCD is mediated by IL6. Lui *et al.* have demonstrated an association of CD with excess production of the cytokine interleukin-6 (IL-6).IL-6 is a pleiotrophic cytokine produced by several cell types, including activated monocytes, B cells, endothelial cells, fibroblasts and mesangial cells. Large amounts of IL-6 were shown to be produced at the germinal centers of hyperplastic lymph nodes from patients with CD and clinical improvement was observed along with decreases in IL-6 levels after the removal of the involved lymph nodes⁹ or treatment with anti-IL-6 antibodies¹⁰. Corticosteroid therapy has also been shown to reduce IL-6 levels. It thus appears that there is some other unclear pathogenesis of MCD.

It may be difficult to distinguish TAFRO syndrome from manifestations of collagen diseases that may show systemic symptoms such as fever, effusion and lymphadenopathy. Pathological findings of lymph nodes in collagen diseases are

also difficult to distinguish from those of MCD, making identification of the presence of autoantibodies important for diagnosis.¹¹ MCD may also be occasionally associated with autoimmune manifestations and connective tissue diseases.⁵ In our case, systemic lupus erythematosus specific antigens were all negative and most of the symptoms and pathologic findings couldn't have been explained by Sjögren disease alone. Reticular myelofibrosis is a rare finding in Sjögren disease.¹² The question is whether TAFRO syndrome is really a distinct entity, or instead an atypical subtype of MCD, or a yet unrecognized autoimmune disorder with secondary Sjögren disease.

There are various suggested therapeutic strategies for TAFRO including glucocorticoids, tocilizumab, cyclosporine A¹ and possibly rituximab.¹³ Our patient achieved a remission on corticosteroids alone.

4. Conclusion

In conclusion, we presented herein the first European MCD with negative HHV8 and HIV that meets the criteria of TAFRO syndrome, associated with Sjögren disease.

TAFRO syndrome is a rare and newly recognized clinical entity. It may be a specific subentity of MCD or a subentity of a connective tissue disorder, or a distinct entity that requires prompt and appropriate treatment.

Reticulin fibrosis of the bone marrow associated with thrombocytopenia, anasarca and renal failure, occurring in a typical histological setting, should raise the suspicion of TAFRO syndrome.

The etiology, pathology and strategies for optimal management of this syndrome remain mostly unknown. Therefore, we need better definition of this novel entity, criteria for diagnosis, and a therapeutic strategy.

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