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Tafro Syndrome from a Single Center Outside Japan: 3 Cases and Review of the Literature

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Abstract

TAFRO is an interesting syndrome haracterized by thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly. Originally it has been reported by Takai et al in Japan patients and later this entity has been reported out of Japan. Here we reported 3 cases with TAFRO from Turkey and reviewed availabla data, diagnostic difficulties and also treatment modalities.

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Introduction

TAFRO Syndrome (TS) is a relatively new entity described firstly from Japan and later from other sites of the world. Diagnostic criteria for TAFRO must include ≥3 major criteria: thrombocytopenia, anasarca, fever, mild organomegaly/lymphadenopathy, anemia, absence of hypegammaglobulinemia, small volume lymphadenopathy and ≥1 minor criteria: high levels of serum ALP without marked increase serum transamainases, progressive renal insufficiency (creatinine >1.2 mg/dl in males, >1 mg/dl in female) [1,2]. Histopathologically it is proposed that there must be compatible pathologic findings in lymph node, negative tests for LANA-1 for HHV-8, hyper/normoplasia of megakaryocytes in Bone Marrow (BM) and Reticulin Fibrosis (RF) [3].

Case reports

Case 1

19 year-old-man admitted to department of infectious diseases with two months complaints including fatigue, fever, dyspnea and lower extremity edema in March 2015. Physical exam showed cervical, axillary and inguinal lymph nodes and respiratory findings compatible with bilateral pleural effusion. There was abdominal distension and (+++) pretibial edema. Past medical and family history were unremarkable. Abnormal laboratory findings were mild anemia, thrombocytopenia, high BUN, uric acid and creatinine, hypoalbuminemia, high ESR, CRP and LDH (Table 1). Chest X-ray showed bilateral pleural effusion. Echocardiography showed minimal pericardial effusion and pulmonary

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arterial pressure was 60 mmHg. CT scans showed bilateral cervical, axillary, mediastinal, hilar and retroperitoneal lymph nodes and also bilateral pleural effusions, hepatosplenomegaly and subcutaneous edema (Figures 1a,b,c). PET/CT showed bilateral cervical, axillary, retroperitoneal lymph nodes up to 1.5 cm with low FDG afinity (SUVmax: 2.6). At the beginning renal failure was attributed to nonsteroidal antiinflammatory drus (NSAID) using. Clinically acute viral infections (EBV, CMV etc), tuberculosis, collagen vascular diseases and lymphoproliferative disorders had been thought in the differential diagnosis. Acido-resistant bacteria and serologic tests for viral infections and autoantibodies including ANA, ANCA and also coombs test had been found to be negative. Pleural and peritoneal fluid samples were found to be compatible with transudate. There was proteinuria (630 mg/daily) and fragmentation in erythrocytes in peripheral blood smears. BMB showed hypercellularity with increased plasma cells. Although blood, urine and pleural/peritoneal fluid cultures were negative and his diagnosis was unclear, septicemia could not be excluded. He had been treated by empiric antibiotics and nonsteroid antiinflammatory drugs (NSAID) but there was no clinical benefit and patient had been followed at intensive care unit due to hypoxemia and poor clinical condition. Plasmapheresis had been performed 3 times due to his deteriorating clinical condition. At this point he was consulted by our unit and lymp node biopsy was proposed. Inguinal lymph node biopsy was done. Biopsy showed plasma cells at interfollicular area, atrophy in some follicles and increase in follicular dendritic cells (Figure 1d). HHV-8 was found as negative. CD20 and CD5 were found to be positive in reactive B and T cells. CD38 was positive in plasma cells and CD21 in dendritic cells. Bone marrow biopsy (BMB) showed mild dyserythropoiesis, increase in megakaryocytes and 95% cellularity and no BM fibrosis. Amyloid reaction was negative. Patient was defined as multicentric Castleman Disease (mCD) and rituximab, cyclophosphamide, prednisolone (R-CVP) regimen was given. After 4 cycles complete metabolic response was detected at PET/CT. Treatment was completed with 6 cycles in August 2015. Last follow up was at april 2020 and he was in remission. Figures 1a, b and c show marked pleural effusion and compression atelectasis, ascites, hepatosplenomegaly and subcutaneous edema.

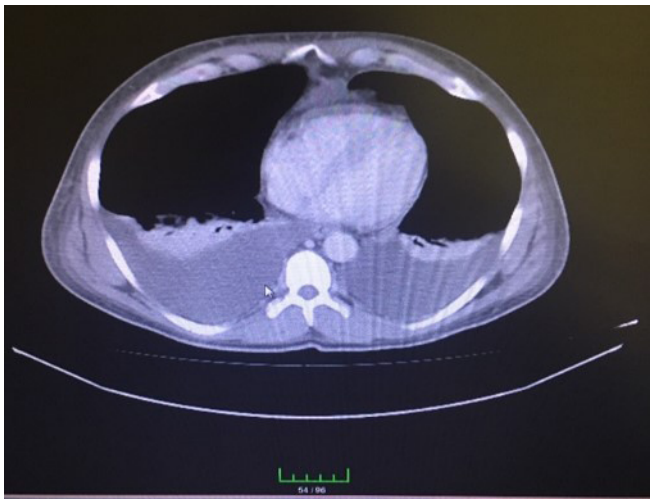


Figure 1a: Chest CT image of case 1 at the time of diagnosis showing marked pleural effusion and compression atelectasis.

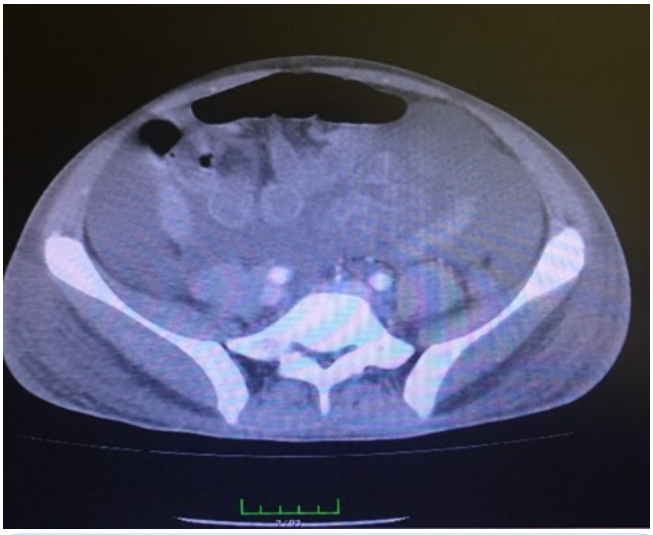


Figure 1b: Abdominal CT image of case 1 at the time of diagnosis showing ascites, hepatosplenomegaly.

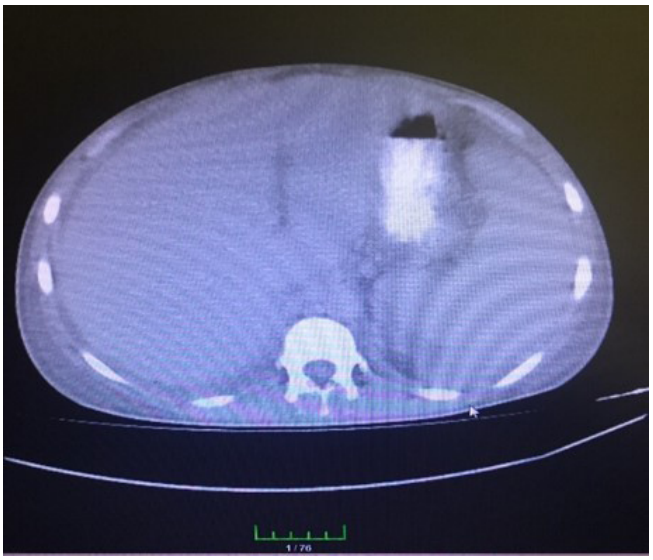


Figure 1c: Abdomen CT image of case 1 at the time of diagnosis showing subcutaneous edema.

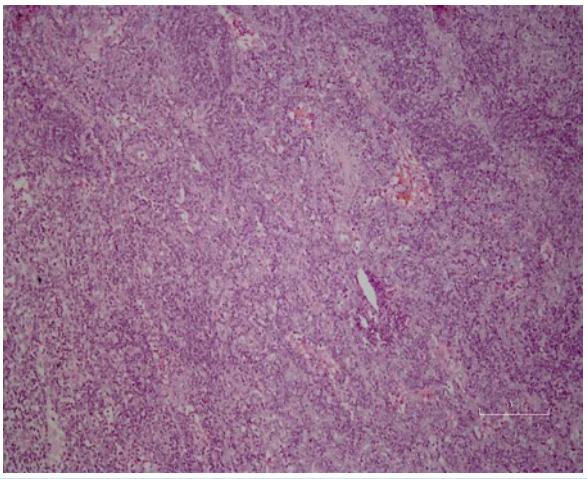


Figure 1d: Plasma cell rich infiltration in lymph node.

Table 1: Laboratoryfindings of the 3 patients at the time of diagnosis.

	Case 1	Case 2	Case 3
Leukocyte	13.4 x 10^9/L*	6.3 x 10^9/L	7.93 x 10^9/L
Hgb/hct	8.4 g/dL / 27.3%*	9.3 g/dL / 28.2%*	6.5 g/Dl*
Platelet	85 x 10^9/L*	126 x 10^9/L	22 x 10^9/L*
BUN/creatinine	29 / 2.06 mg/dL*	9 / 0.66 mg/dL	25.1 / 1.64 mg/dL*
AST/ALT	20/26 IU/mL	25 /10 IU/mL	60/53 IU/mL
ALP	255 U/L*	61 U/L	41 U/L
Sodium	133mmol/L	136mmol/L	132 mmol/L
Calcium/correctedCa	7.3 / 8.82 mg/dL	8.3 / 9.66 mg/dL	7.5 / 9.58 mg/dL
T protein/albumin	57 / 21 g/L*	40 / 23 g/L*	69.0 / 13.9 g/l*
LDH	543 IU/mL*	303 IU/mL*	228 IU/mL
ESR	41 mm/h*	120 mm/h*	81 mm/h
CRP	400 mg/L*	80 mg/L*	58 mg/L*
Ferritin	733,5ng/mL*	609,2ng/mL*	5506 ng/mL*
Beta-2 microglobulin (1.1-2.4 mg/L)	12.72 mg/L*	6.52 mg/L*	3.886 mg/L*
Proteinuria	630 mg/d*	-	162 mg/d*
CrCl	42 ml/min*	85 ml/min	47 ml/min*

*Abnormalfindingshavebeenshown as bold

Case 2

78 year-old-woman admitted to our unit with fatigue, fever up to 38°C and cough in March 2015. She had the history of breast Ca, thyrotoxicosis and hypertension. She had been diagnosed as hormone receptor positive, Her2 negative invasive ductal carcinoma in november 2013: T1N0M0 disease and had been treated modified radical mastectomy followed by aromatase inhibitor. Physical exam showed left supraclavicular and axillary lymph node, splenomegaly and ascites. CT scans showed grade I hepatosteatosis, splenomegaly and axillary, retroperitoneal, mesenteric, inguinal, iliac lympho nodes (Figure 2a). Laboratory findings have been shown in Table 1. Relapse disease was thought clinically and biopsy was done. Lymph node biopsy was reported as CD-plasmacytic type and HHV-8 was negative (Figure 2b,2c). BMB was done due to mild anemia and thrombocytopenia. Biopsy showed 90% cellularity and 2/4 reticulin fibrosis, amyloid reaction was negative. Patient was evaluated as TAFRO syndrome and she was treated by R-CVP and clinical and laboratory findings were improved after 4 cycles. Complete response was found radiologically. Patient was in complete remission and was receiving aromatase inhibitor with the aim of adjuvant hormone blockade. She died in June 2016 but the cause of death could not be known.

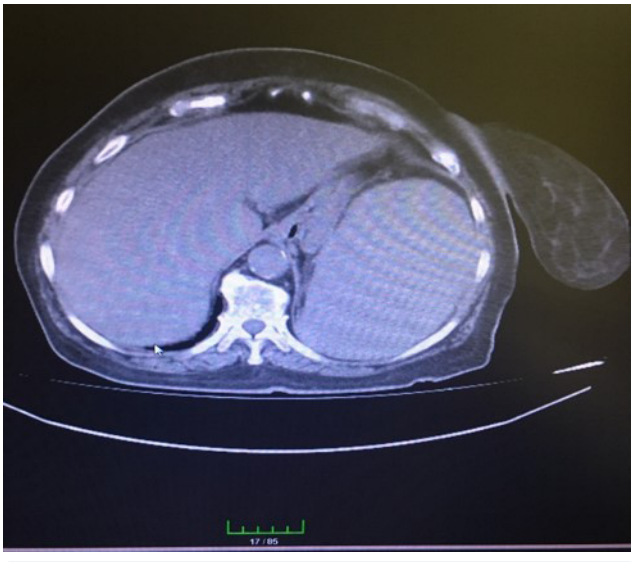


Figure 2a: Abdominal CT images of case 2 at the time of diagnosis showing organomegaly, ascites, intraabdominal lymph nodes and right mastectomy.

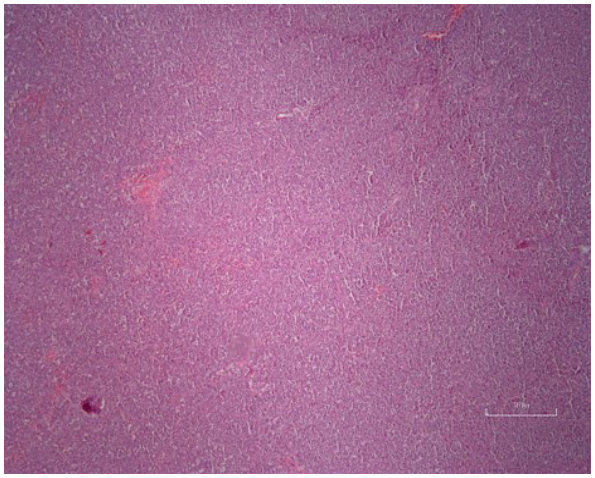
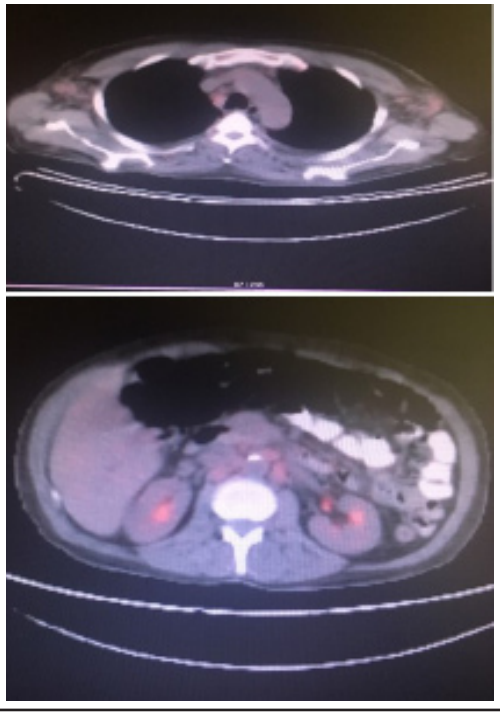


Figure 2b & C: Plasma cell rich infiltration in lymph node.

Case 3

54 year-old-man had been diagnosed as HIV infection in November 2017 and he had been treated by tenofovir alafenamide + emtricitabine + elvitegravir + cobisistat. He had been referred due to fever and bicytopenia to our hospital. Physical exam showed pallor, disseminated lymph nodes and polypoid skin lesions. BMB was done due to bicytopenia in December 2017 and there was dyserythropoiesis, hypercellularity and increase in plasma cells (20%). Plasma cells showed polytypic staining for kappa and lambda. Intravenous immunoglobulin was given due to thrombocytopenia. Infectious etiology was excluded with negative acute viral infection markers and cultures. CT scans showed bilateral cervical, axillary, inguinal, mediastinal, mesenteric lymph nodes, and hepatosplenomegaly, pleural effusion and ascites. PET/CT showed hypermetabolic axillary, mediastinel, intraabdominal and inguinal lymph nodes (SUVmax 3.85-4.70) (Figure 3a). Inguinal lymph node biopsy was reported as CD with plasmacytic type. HHV-8 was found as positive. CD3, CD20, CD38 and kappa/lambda were stained as polytypic (Figure 3b). Biopsy was done for polypoid skin lesion and it was reported as Kaposi sarcoma (KS). Patient was evaluated as KS and mCD and he was treated by 6 cycles of R-CVP plus pegylated lyposomal doxorubicin (PLD). After treatment there was complete metabolic response at PET/CT.



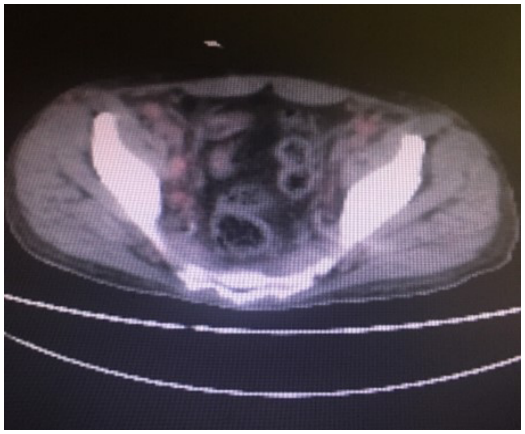


Figure 3a: PET CT shows hypermetabolic axillary, mediastinal, intraabdominal and inguinal lymph nodes (SUVmax 3.85-4.70) (Case 3).

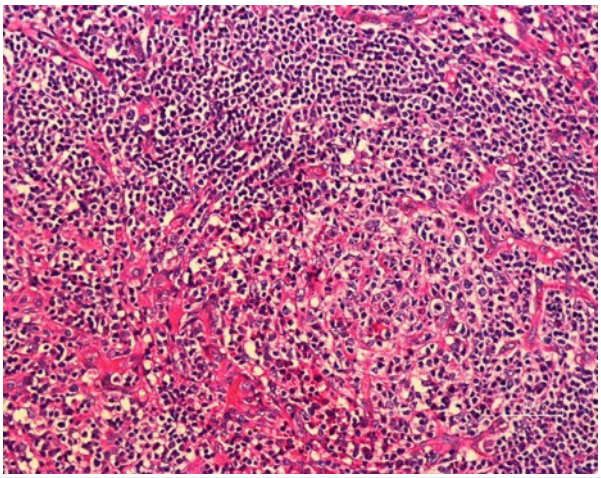


Figure 3b: Inguinal lymph node biopsy showing CD with plasmacytic type.

Discussion

TAFRO has been described in Japan cases in 2013 by Japan scientist Takai but later this interesting entity has been reported from Western countries [3,4].

Here we presented 3 cases with TAFRO syndrome from one center in Turkey. The first step is to exclude the rheumatologic syndromes, neoplastic and infectious diseases, We investigated in detail in our all 3 cases these diseases with clinical presentation and findings, biochemical tests, serologic tests for autoinflammatory diseases and virologic assessments for viral infections and also detailed cultures for other infections. However these steps are important but may not be sufficient especially in cases seronegative collagen vascular diseases mimicking TAFRO syndrome and also some infections including tuberculosis. Recent paper published from Japan is very informative at this setting. Because 69 year old male had all the criteria for TAFRO and strated to treatment by prednisolone but Mycobacterium genavence was isolated 10 weeks later by sequencing analysis [5]. This case suggest that TAFRO syndrome is an important syndrome but may mimick other entities and patients must be followed up carefully.

Neoplastic disorders were excluded in our cases with careful histopathologic examination of lymph nodes. However in our third case had HIV infection and polypoid skin lesions were compatible with KS associated with HIV. Second case had the

history of breast cancer but her disease was in remission and did not show relapse during follow up.

Anemia and thrombocytopenia are the major findings in TAFRO syndrome. Our all 3 cases had anemia and mild to severe thrombocytopenia. In our first case, infectious disease and/or collagen vascular diseases were thought clinically at first presentation. He was treated by empiric antibiotics and even plasmapheresis due to septic clinical condition which is not rare in cases published in available literature. However he did not recover with these measures and lymph node biopsy showing CD and other accompanying clinical/laboratory findings suggested TAFRO syndrome and this entity was confirmed by his clinical, radiologic and laboratory findings. He was our first case with TAFRO and was interesting for us; because he had been hospitalized by department of infectious diseases and had been consulted to us after a widespread search and longer follow up.

In our cases, HHV-8 was negative in 2 cases and positive in one case having HIV infection. Our 2 cases included all 5 major criteria, 4 in 1 case, and minor criterias were detected in 2 cases and 1 in 1 case (Table 2). Anemia was found in all of our cases and normocytic/normochromic. LDH levels are high in our 2 cases. ALP levels must be high in the absence of high liver enzyme levels. ALP was high in onlyone of our cases one and his liver enzymes were normal. CRP levels show in inflammatory status are generally high and CRP were found to be very high all of our cases and was very high in our first case who had the most prominent findings for inflammation [6]. IL-6 levels are generally high and also in one case who only had checked [5]. Autoantibodies are generally necessary to exclude the collagene vascular diseases and all the the tests for autoantibodies were found to be negative in our cases [7,8].

According to the 2015 severity criteria [9], our first case had slightly severe, second case had mild severe and third case had severe disease. These criteria are important and probably will be informative to planning treatment and follow up guidelines.

Imaging modalities in this entity are CT scans and PET/CT imagings [10]. However iodinated contrast materials must be used carefully especially in cases with renal dysfunction and PET/CT may be more appropriate in cases with renal dysfunction. PET/CT is also useful to determine the response/relapse to therapy [11] as in our first and third cases.

TAFRO is a relatively rare entity and differential diagnoses must include systemic inflammatory syndromes including autoimmune diseases, lymphomas, POEMS, APS, ITP, TTP, DIC and also systemic infections including disseminated tuberculosis [12,13]. In fact TAFRO is an exclusion entity among many systemic diseases. For this reason time to diagnosis may be longer and even many patients are undiagnosed and treated with different diagnoses, especially systemic inflammatory diseases with unknown etiology [12,13]. In our first case had been diagnosed as TAFRO a longer period after hospital admission. Our third case is very interesting and he had been referred due to severe thrombocytopenia and HIV diagnosis. Multiple lymph nodes, thrombocytopenia, anemia, fever, and anasarca related with severe hypoalbuminemia had been attributed to HIV and its complications. However reticulin fibrosis accomanying these signs alerted us for TAFRO diagnosis. Important point in this case was the presence of KS which is very unusal finding in cases with TAFRO and for this reason HHV-8 was found to be positive in lymph node biopsy.

Treatment of TAFRO syndrome is not clear and must be individualized according to the severity of the disease and also accompanying findings [2,3,14-16] We treated our first 2 cases with R-CVP protochol due to their severe systemic symptoms and complete response was achieved. However we added PLD to this regimen due to accompanying KS which is preferred drug by NCCN in cases with KS associated with HIV [17,18].

In conclusion TAFRO syndrome is a complicated systemic disease for clinicians including internists, hematologists, oncologists, rheumatologists, infectious disease specialists and also emergency medicine doctors. TAFRO must be included in differential diagnosis in cases presenting inflmmatory signs and symptoms and accompanying progressive renal dysfunction and reticulin fibrosis.

Table 2: Diagnostic criteria and disease severity classification of 3 cases.

Criteria	Case 1	Case 2	Case 3
Histopathologic	CD plasmacytic HHV-8 (-)	CD plasmacytic HHV-8 (-) RF 2/4	CD plasmacytic HHV-8 (+) Hyperplastic BM with increased mega karyocytes
Major criteria	Thrombocytopenia Anemia Fever Anasarca Small volume LAP/ mildorganomegaly	Anemia Fever Absence of hypergammaglobulinemia Small volume LAP	Thrombocytopenia Anemia Fever Anasarca Small volume LAP/ mildorganomegaly
Minor criteria	Progressive renal insufficiency High ALP	Anemia	Progressive renal insufficiency
Severity	3+1+3+1: Slightly severe-Grade 3	1+1+2+0: Mild severe-Grade 2	3+2+3+1: Severe-Grade 4
Treatment/outcome	R-CVPX4/remission 4.5 years+	R-CVPX4/remission	R-C-PLD-OPX6/Remission 3.5 years+

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