TAFRO
A unique variant of multi-centric Castleman’s disease

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Conflict of interest

- No conflict of interest to disclose
TAFRO

- Case discussion
- Introduction and classification of Castleman’s disease
- Diagnosis of TAFRO
- Treatment of TAFRO
Case

- 20 yo M with Asperger’s disease and ADHD, presented to local hospital with abdominal pain, SOB, cough, wheezing, leg swelling, easy bruising, epistaxis, n/v, subjective fever, and weight loss ~80lbs

- He was intubated at local ER for hypoxemic respiratory failure. Bronch with BAL grew MSSA, for which he received appropriate antibiotics.

- Admit labs were notable for Hb 5.1, MCV 69.1, WBC 46K, plt 400. Positive DAT. Haptoglobin WNL. LDH elevated at 409. Retic not sent.

- He received PRBC transfusion and responded appropriately. Followed by steroid for hemolytic anemia.

- Cr elevated to 3.

- Hemodialysis was started for acute anuric renal failure.

- ALP elevated to 300s. Hepatitis workup all negative.
Case

- Imaging was notable for pleural effusion, ascites, large pericardial effusion, diffuse lymphadenopathy and mild splenomegaly.

- Thoracentesis with 2.5L plural fluid removed, culture negative.

- ESR was WNL, CRP not sent. Autoimmune workup include ANA panel, ANCA, C3/C4 were all negative.

- Infectious workup all negative, include HIV, EBV, Hep B, Hep C, CMV, HSV, parvovirus, Lyme titer, syphilis, malaria smear

- Serum protein: total protein 6.2, albumin 2.9, alpha-1 0.3, alpha-2 0.7, beta fraction 0.6, gamma 1.7

- 5 days later Plt dropped from 400 to 100s, HIT negative.

- After 1 wk of steroid: Hb stable, no further transfusion. Pleural effusion and Cr did not improve, remained intubated, requiring repeat thora and HD.
Case

- Left groin lymph node core bx (s/p 1 week of steroid): extramedullary hematopoiesis.
- BM Bx (2 days s/p 1w of steroid): inconclusive.
  - Hypercellular marrow (cellularity 90%) with megakaryocytic hyperplasia, mild relative myeloid hyperplasia, and mild reticulin deposition.
  - Flow cytometry: No abnormal B cell, T cell, NK cell, or myeloid blast population.
  - Cytogenetics: normal male karyotype.
- He was transferred to UWMC for further management.

What is your differential?

- Autoimmune?
- Myeloproliferative disorder?
- Lymphoma?
- IgG4 related disease?
- Systemic inflammatory disorder: Castleman’s disease?
at UWMC

- He was extubated the next day. But required a repeat thoracentesis.
- He continued to be anuric requiring hemodialysis.
- Retic 1.1%, Ab Retic 30.
- Coagulopathy corrected by mixing study.
- HHV-8 PCR negative; sIL-6 elevated at 138.2 (normal <17.4).
- VEGF elevated at 632 pg/mL (normal 9-86), CRP elevated.
- Peripheral CALR, MPL, JAK2 – all negative
- Reviewed his lymph node core biopsy and BM biopsy, nonspecific and not diagnostic for Castleman’s disease.
- Discussed IL-6 inhibitor with high-cost medication committee but won’t be approved unless pathologic diagnosis is made.
- Coordinated with ICU, Gen Surg, Cardiac anesthesia, Cardiology for excisional lymph node biopsy - takes effort to make the biopsy happen.
Right inguinal lymph node excisional biopsy
(on a Saturday...)

...sion, mantle zone lymphocytes arranged in onion-skin-like concentric whorls, with expansions...
Atretic follicles

Penetrating vessels
CD21: tight/concentric and expanded/disrupted pattern of follicular dendritic cells
Diagnosis

• Right inguinal lymph node, excisional biopsy:
  • Reactive hyperplasia with features of Castleman’s disease
  • Extramedullary hematopoiesis of uncertain significance
  • No evidence of lymphoma
  • Flow cytometry: No abnormal B or T cell population
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Castleman’s disease

- Dr. Benjamin Castleman (1906-1982), best known for describing Castleman’s disease (angiofollicular lymphoid hyperplasia) in 1954
- Pathologist at Mass. General Hospital, who edited weekly Clinicopathologic case presentations


1954 NEJM report

Figure 1.

Figure 2. Photograph of the Mass of Mediastinal Lymph Nodes, Showing Two Large Lymph Nodes Bisected.
What is Castleman’s Disease?

- Rare systemic lymphoproliferative disorder in which immune cells become activated to produce excess of cytokines, particularly IL-6
  - The proinflammatory proteins induce B cell and plasma cell proliferation, VEGF secretion and angiogenesis, acute phase reaction
  - Subset of cases related to HIV or HHV-8 (or Kaposi sarcoma Herpes virus, KSHV)
  - Estimated incidence 6,502-7,696 annually
- Wide heterogeneity of symptoms in the disease, ranging from asymptomatic to Multisystem organ dysfunction:
  - Lymphadenopathy; gammaglobulinemia, microcytic anemia, elevated CRP
  - B symptoms (fatigue, weight loss, night sweats, etc.)
  - Dysfunction of vital organs, including liver, kidney, and bone marrow (fluid gain, confusion, bruising, bleeding)
- Significant morbidity and death (sepsis, multi-organ failure, lymphoma, etc.)

Munshi et al. Leuk Lymphoma. 2015. 56(5):1252-60
How to Diagnose Castleman’s Disease?

- No consensus diagnostic criteria currently exist
- No disease specific histopathologic features or biomarkers
- Lymph node histologic features can be seen in other diseases
  - Infectious diseases (EBV, HIV, etc.)
  - Autoimmune diseases (SLE, RA, etc)
  - Neoplasms (non-Hodgkin, Hodgkin lymphoma, myeloma, clear cell meningioma, etc)
- Careful clinical and pathologic correlation is required for diagnosis

Subclassication

- Unicentric (UCD)
  - Young adults (median 3\textsuperscript{rd}-4\textsuperscript{th} decade)
  - Localized mass
  - Often asymptomatic
  - High cure rate with surgical excision
- Morphologic variants
  - Hyaline-vascular (HV): 76-91%
  - Plasma cell (PC): 9-24%
  - Mixed: features of both HV and PC

Cronin et al. Adv Ana Pathol. 2009. 16(4):236-246
Subclassification

• Multicentric (MCD)
  • Age variable (median 4\textsuperscript{th}-5\textsuperscript{th} decade)
  • Generalized lymphadenopathy
  • Constitutional symptoms, hematologic/immunologic abnormalities

• Morphologic variants
  ✎ Hyaline-vascular (HV): 17-49%
  ✎ Plasma cell (PC): 46-77%
  ✎ Mixed: 4-20%
  ✎ Plasmablastic: HHV-8+

TAFRO

• TAFRO syndrome is a unique clinicopathologic variant of MCD that was first reported in 2010 in Japan by Takai et al:

Thrombocytopenia, Anasarca, microcytic Anemia, Fever, Reticulin fibrosis, Renal dysfunction, Organomegaly

• Kojima first classified Japanese MCD into Idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL type) and non-IPL type in 2008

• Kawabata et al. (2013) proposed the clinical term “TAFRO” syndrome, Fukushima (福島市) and Nagoya (名古屋市) meetings. It was also referred as Castleman- Kojima disease, as it is a subtype of non-IPL MCD.

• These pt frequently presented with ab pain, elevated ALP, acute renal failure, without hypergammoglobulinemia, with high mortality rate (3/25 in 9 mon in a recent report).

Hawkins JM et al. Blood. 2015.126(18):2163
Takai K et al. Rinsho Ketsueki, 2010; 51, 320-325
Diagnosis of Castleman’s Disease

- It was proposed that MCD can be further classified beyond HHV-8 status.
- HHV-8 infects B-cells and expresses a viral homolog of IL-6, drives the disease.
- HHV-8 negative iMCD may be further stratified into iMCD with TAFRO features.

Schematic representation of histologic characteristics of different types of CD and multicentric CD (MCD).

TAFRO: atrophic GC, expansion of the interfollicular zone, proliferation of highly dense endothelial cell.
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Diagnosis of TAFRO

- TAFRO is characterized by a more aggressive clinical course, corticosteroid-refractoriness, thrombocytopenia, higher frequency of anasarca, elevated level of ALP, and normal gammaglobulin levels.

- These unique clinical and laboratory features suggest that TAFRO-iMCD is a distinct entity within the larger entity of iMCD, featuring immunological abnormality beyond the ordinary spectrum of MCD.

- Total of ~50 cases reported (majority in Japan), 6 reported death. 3 cases from US reported so far (1 case report from MD anderson; 2 cases from U Penn included in a Japanese report).

- Age 15-78 yo; M>F; 76% PS>=2; 96% anasarca.

Jain et al. AJH 2015; 90: 1091
Diagnosis of TAFRO

- TAFRO-iMCD patients must fulfill the histopathological criteria, all three major criteria and one or more minor criteria.

**TABLE III. Proposed Diagnostic Criteria for TAFRO-iMCD**

1. Histopathological Criteria;
   - Compatible with pathological findings of lymph nodes as TAFRO-iMCD®
   - Negative LANA-1 for HHV-8
2. Major criteria;
   - Presents 3 of 5 TAFRO symptoms
     - ✓ Thrombocytopenia
     - ✓ Anasarca
     - ✓ Fever
     - ✓ Reticulin fibrosis
     - ✓ Organomegaly
   - Absence of hypergammaglobulinemia
   - Small volume lymphadenopathy
3. Minor criteria need 1 or more;
   - Hyper/normoplasia of megakaryocytes in bone marrow
   - High levels of serum ALP without markedly elevated serum transaminase

- Largest series of TAFRO (25 cases).
- The first description of TAFRO in U.S.
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Treatment (our case)

- Started steroid after he had excisional biopsy.
- Although it takes time to order Siltuximab but able to “borrow” from SCCA outpatient pharmacy on the day of diagnosis.
- Clinical symptoms after 1st dose of Siltuximab:
  - Pericardial effusion improved
  - Off hemodialysis, Cr normalized
  - Persistent pleural effusion requiring thoracentesis but less frequent
  - Taper steroid off
- HTN and tachycardia requiring CCB and beta blockers
- Developed RSV PNA 2 days after 2nd dose of Siltuximab
Response of CRP and Cr to IL-6 inhibitor

1st dose of Siltuximab

2nd dose of Siltuximab
IL-6 level interfered by Siltuximab

1st dose of Siltuximab
Case report of treatment

Upfront regimen:

- **Steroid**
  - Relapse during steroid taper

- **Tocilizumab**
  - 12 cases report since 2013 to 2016, one patient died of relapse.
  - 8 cases in CR. 4 cases in PR, changed treatment to R+CVP, RCyA, +thal, +R, respectively
  - No clear association between IL-6 conc and effectiveness of anti-IL-6 therapy

- **Rituximab**
  - R alone (AM J Hema 2015, Rinsho Ketsueki 2014) or Combination with tocilizumab (JCEH 2013)

  - 3 case reports with good response (including first report of TAFRO); one case from Italy did not respond and pt died.

- **CHOEP** (JCEH 2013)
  - Patient died of septic shock
Case report of treatment (cont.)

Tocilizumab-resistant:
- Thalidomide for Tocilizumab-resistant ascites (Clin Case Rep 2015)
- R+CVP (Exp Hematol Oncol 2015)
- +R
- RCyA

Recent large cohort of 25 patients (Am J Hem 2016)
- 23 pt received steroid; 12 of 23 pt received additional therapy, including CsA (n=7), Tocilizumab (n=6), Rituximab (n=4), Siltuximab (n=1). → thalidomide (n=1), vincristin (n=1), Sirolimus (n=1), VDT-ACE-R (n=1), IVIG (n=1).
- 1 case: refractory to steroid, Rituximab, Siltuximab → VDT-ACE-R → replaced on Siltuximab q3wk → VDT-ACE-R → relapsed → resplased on Siltuximab q3week and weekly VDT → 3rd cycle of VDT-ACE-R, now in remission for 21 months.
- Plasma exchange was used in 2 cases.
- 7 cases with acute renal failure requiring dialysis

VDT-ACE-R (bortezomib, dexamethasone, thalidomide, adriamycin, cyclophosphamide, etoposide, and rituximab)
Conclusion

• HHV-8 negative iMCD may be further stratified into iMCD with TAFRO features

• The etiology of TAFRO remains mostly unknown

• Wide spectrum of symptoms make it extremely difficult to diagnose. Diagnostic criteria of TAFRO was proposed and needs further validation

• Treatment standards have not been determined but IL-6 inhibitors seems to be a reasonable choice

• Global patient registry by the Cattleman Disease Collaborative Network

• 3 cases here at UWMC - maybe more?