Castleman Disease

Frits van Rhee, MD, PhD, MRCP(UK), FRCPath
Myeloma Center, University of Arkansas for Medical Sciences
Little Rock, Arkansas
The Castleman Disease Story...
The trigger...

Benjamin Castleman, pathologist in Boston

...lymphoid tissue, hyperplastic to be sure, with many germinal centers surrounded by mature lymphocytes. Many of these germinal centers contained hyalinized foci,...

Dr. Chapman: This is a new disease syndrome that you are presenting to us!
First Description

LOCALIZED MEDIASTINAL LYMPH-NODE HYPERPLASIA RESEMBLING THYMOMA

Benjamin Castleman, M.D., Lalla Iverson, M.D., and V. Pardo Menendez, M.D.

Cancer, 1956

Mediastinal mass in 13 young adults
What is Castleman Disease?

- Group of rare lymph node disorders which share the same histopathology
- Unicentric vs multicentric
- Multicentric disease in some patients, often HIV positive, driven by HHV8
- In multicentric disease, symptoms and laboratory abnormalities caused by cytokines especially interleukin-6 (IL6)
Hyaline Vascular Variant

Dysplastic Germinal Center

Increased Blood Vessel Formation

Hyaline Vascular Variant
Lollipop Follicle in Hyaline Vascular CD
CD Classification

<table>
<thead>
<tr>
<th>Unicentric Castleman Disease (UCD)</th>
<th>HHV8-associated Multicentric Castleman Disease (HHV8+ MCD)</th>
<th>HHV8-negative “Idiopathic” Multicentric Castleman Disease (iMCD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Idiopathic; 90% no B-symptoms; occasional to severe symptoms (if it causes paraneoplastic pemphigus or cannot be resected)</td>
<td>☐ HHV8 virus drives cytokine release and causes episodes of B-signs, autoimmune manifestations, and multiple organ system impairment (renal failure, pancytopenia, fluid overload); clinically picture: from mono or sepsis</td>
<td>☐ Unknown cause drives the cytokine release and B-signs, autoimmune manifestations, and multiple organ system impairment; like HHV8</td>
</tr>
<tr>
<td>☐ HHV8 negative</td>
<td>☐ B-cell hosts HHV8, secretes vIL6, IL6</td>
<td>☐ Unknown host/pathologic cell type</td>
</tr>
<tr>
<td>☐ Surgical excision is usually curative (&gt;90% 5-year survival rate)</td>
<td>☐ Rituximab +/- etoposide +/- antivirals are effective</td>
<td>☐ Siltuximab newly approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ Rituximab and cytotoxic chemotherapy can be used off label; relapses common</td>
</tr>
</tbody>
</table>
Age Distribution in 384 HIV- Patients

A. HIV- patients n = 384

B. Centricity
- UCD n = 283
- MCD n = 101

C. Gender
- Female n = 205
- Male n = 179

D. Histopathology type
- HIV n = 223
- PC n = 161
Unicentric Castleman Disease (UCD)

- Single, slow-growing lymph node mass, e.g. neck, chest, abdomen, or groin
- Symptoms, if any, caused by pressure effect of the enlarging lymph nodes
- Usually Hyaline vascular type, usually HIV- and HHV8-negative
- Usually no progression to, or association with other tumors
- Only 10% have systemic symptoms
Relationship Between Centricity and Pathologic Subtype

Unicentric
- Usually Hyaline Vascular type (90%)

Multicentric
- Mixed Cellularity type
- Plasmacytic type
UCD Therapy

- Surgery: Curative in > 95% of patients
- Combined approach: embolization, cryoablation followed by surgery
- Other (drug) therapy followed by surgery
- Radiation
Large Lymph Node Mass Displacing and Compressing Windpipe
Embolization Process

Microcatheter injection of internal pudendal showing hypervascular mass
CT performed during cyroablation shows deposition of embolic material in the mass
10cm, 600g Pelvic Mass Rendered Resectable by Embolization
Management of UCD

Evaluate for Resectability[^1,^2]

- **Resectable**
  - Surgery

- **Not Resectable**
  - Asymptomatic
    - Observe[^3]
  - Symptomatic
    - Attempt to RENDER Resectable by:
      - Embolization
      - Rituximab/Steroids
        - Resectable
        - Not Resectable
          - Surgery
          - Observe[^3,^4]
          - Consider Radiation

[^1]: No role for anti-IL6 therapy except for rare patients with pro-inflammatory syndrome.
[^2]: Consider pre-surgical embolization in large, vascular masses.
[^3]: CT-scan every 6-12 months.
[^4]: In some cases only significant debulking can be achieved.
Role of IL6 in CD in iMCD

**B Cell Growth**
- Overgrowth of B cells and plasma cells
- Increased size of lymph nodes, lymphoma, myeloma

**Elevated VEGF**
- Formation of blood vessels
- Increased blood supply to tumor
- Vascular leak syndrome

**Increased Th2 Cells**
- Autoimmune reactions
- Auto-antibodies to organs

**Inflammatory Response**
- ESR, CRP, IgG, anemia, hypoalbuminemia
- B-symptoms
Fever (51/64), hepatosplenomegaly (45/60), pleural effusion (29/38), edema (26/36)

43 plasmacytic, 26 mixed, and 23 hyaline vasculare163- pathological subtypes

Elevated CRP (70/79), anemia (76/90), hyper gammaglobulinemia (63/82), hypoalbuminemia (57/63), high IL-6 (57/63), abnormal PLTs (28 high, 14 low), renal dysfunction

3X increased prevalence of malignancy in iMCD cases than age-matched SEER controls

Autoantibodies or autoimmune hemolytic anemia reported in 38/128 iMCD patients

NR (21%), PR (42%), CR (37%) to first-line therapies;
41% failed first line (6mo)

Patients treated with corticosteroids first line experience worse survival

22% died by follow up (median: 28 months) with median OS of 26 months

Causes of death: septic shock, multi-organ failure, and malignancy
Clinical Course – Extremely Varied

- Mild, virtually asymptomatic
- Waxing and waning
- Gradually progressive
- Massive cytokine flares resulting in organ failure and death
Ascites Due to Vascular Leak Syndrome
Thrombosis of the right transverse sinus demonstrated by loss of flow signal (red arrows).

The normal left transverse sinus is easily seen (white arrows).
Castleman Disease with Osteosclerotic Bone Lesions
Ethnic Impact on Clinical Manifestations: Skin Lesions in Asian Patients
Ethnic Impact on Clinical Manifestations: Interstitial Pneumonitis in Asian patients
iMCD Overall Survival
Why is the historical outcome of iMCD poor?

- Until recently, no diagnostic criteria or treatment guidelines
- Orphan disease with incidence of 1000-1500 patients in the USA
- CD is complex with different subtypes and varied clinical presentation
- Few published systematic studies
- No uniform response criteria
- Lack of real world data
How Do You Diagnose Idiopathic Castleman Disease?
## Initial Work-up

<table>
<thead>
<tr>
<th>Critical features</th>
<th>Clinical Parameters</th>
<th>Laboratory Tests/ History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centricity</td>
<td>Unicentric vs Multicentric</td>
<td>CT-scans or CT-PET</td>
</tr>
<tr>
<td>Virology</td>
<td>HHV8 positive versus negative</td>
<td>qPCR HHV8 PB</td>
</tr>
<tr>
<td>Pathology</td>
<td>HV, MC, PC variety</td>
<td>LANA-1, EBER, IgG4 stains</td>
</tr>
<tr>
<td>Symptoms</td>
<td>B-symptomatology</td>
<td>Night sweats, fever, weight loss, anorexia</td>
</tr>
<tr>
<td>Laboratory Features</td>
<td>Inflammatory response/Organ Function</td>
<td>Hb, ESR, CRP, fibrinogen, ferritin, albumin, creatinine, platelet count</td>
</tr>
<tr>
<td>Cytokine Profile</td>
<td>Cytokine storm</td>
<td>IL6, VEGF, Interleukin 2 Receptor</td>
</tr>
<tr>
<td>Co-existent Disorders</td>
<td>POEMS, MGUS, Myeloma, Amyloidosis, Autoimmune Disorders</td>
<td>Myeloma markers, ANA, endocrine function, bone marrow</td>
</tr>
</tbody>
</table>
CDCN Consensus Diagnostic Criteria

A. Major criteria (both are required)
   ◦ Histopathologic lymph node features consistent with the iMCD spectrum
   ◦ Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations

B. Minor Criteria pertaining to symptoms and laboratory markers
   ◦ Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion

C. Exclusion of diseases that can mimic iMCD
CDCN Consensus Diagnostic Criteria:
Minor Criteria (≥ 2 of 11) and at least one lab criterion

**Laboratory**
1. C-Reactive Protein (>10mg/dL) and/or ESR (>15)
2. Anemia (Hgb<12.5 for males, <11.5 for females)
3. Thrombocytopenia or thrombocytosis (< 150K/uL; >400k/uL)
4. Hypoalbuminemia (<3.5 gm/dL)
5. Renal dysfunction (estimated EGFR<60) or proteinuria >150mg/100ml
6. Hypergammaglobulinemia (>1700mg/dL)

**Clinical**
1. Constitutional Symptoms: Sweats, fever (>100.5), weight loss, fatigue (≥ 2 CTCAE score for B-symptoms)
2. Large spleen and/or liver
3. Edema/anasarca, effusions
4. Eruptive Cherry Hemangiomata or violaceous papules
5. Interstitial pneumonitis
Related Conditions Must Be Ruled Out

- Autoimmune conditions: RA/JIA, IgG4, SLE, HLH-MAS, AOSD
- Malignancy: M-HLH, ALPS, HL/NHL, FDC Sarcoma, POEMS Syndrome
- Infection: V-HLH, HHV-8 MCD, Acute EBV, Acute HIV

CDCN: Castleman Disease Collaborative Network
CDCN Algorithm for the Clinico-Pathological Diagnosis of Castleman Disease

ADAPTED FROM DAVID C. FAJGENBAUM ET AL. BLOOD 2017;129:1646-1657
How Do You Treat Idiopathic Castleman Disease?
iMCD Therapy

Corticosteroids

Antibodies
- Rituximab
- Anti-IL6 antibody therapy: tocilizumab, siltuximab

Chemotherapy:
- Like for lymphoma: R-CHOP,
- Like for myeloma: VDT (P) ACE

Immunomodulatory agents: α-interferon, ATRA, bortezomib, thalidomide, lenalidomide, cyclosporin, sirolimus, anakinra

Stem cell transplantation
Is the therapy of Castleman Disease a maze?
Rationale for Rituximab Therapy

HYALINE VASCULAR CD STAINED WITH CD20 ANTIBODY

CD20+ B-lymphocytes
MCD Post-Rituximab/Steroids

5-18-2004 Pre-therapy
8-20-2004 Improving
2-28-2005 Normal
Which data support the role of rituximab in iMCD?

- Very limited data in iMCD (case reports)
  - Systematic studies and prolonged follow-up data lacking
- Still a favorite for many oncologists: familiar drug, effective in lymphoma and HHV8-associated MCD
- Limited course of ‘single shot therapy’
IL6 is a pleiotropic cytokine with multiple functions
How Anti-IL6 Antibody Therapy Works
Interleukin-6
Tocilizumab Reduces Lymphadenopathy

Size of swollen LN

Short axis (mm)

Baseline  4 months  1 year

NORIHIRO NISHIMOTO ET AL. BLOOD 2005;106:2627-2632
Impact of Tocilizumab on Inflammatory Markers
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Siltuximab, an Anti-Interleukin 6 Monoclonal Antibody, in Patients with Multicentric Castleman Disease


¹Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, Hong Kong; ²Fred Hutchinson Cancer Research Center, Seattle, WA; ³Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; ⁴Peking University Third Hospital, Beijing, China; ⁵The Norwegian Radium Hospital, Oslo, Norway; ⁶North Shore Hospital, Takapuna Auckland, Auckland, New Zealand; ⁷Hospital Mãe de Deus, Porto Alegre, Brazil; ⁸Department of Hematology, West China Hospital, Sichuan University, Chengdu, China; ⁹Mackay Memorial Hospital, Taipei, Taiwan; ¹⁰Singapore General Hospital, Singapore, Singapore; ¹¹Beijing Cancer Hospital, Beijing, China; ¹²Seoul St. Mary's Hospital, Seoul, South Korea; ¹³Peking University First Hospital, Beijing, China; ¹⁴The Christie NHS Foundation Trust/University of Manchester, Manchester, United Kingdom; ¹⁵Janssen Research & Development, Spring House, PA; ¹⁶Janssen Research & Development, Washington, GA; ¹⁷Janssen Research & Development, Beerse, Belgium; ¹⁸Janssen Research & Development, Leiden, Netherlands; ¹⁹Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Siltuximab in Multicentric Castleman Disease

First and only multi-national, randomized, double-blind, placebo-controlled, study in MCD

**MCD subjects**
- Symptomatic
- Central confirmed pathology
- HIV, HHV8 negative
- Treatment naïve or pretreated

Primary study analysis planned at 48 weeks after last patient enrolled

*All patients received best supportive care allowing up to 1mg/kg of prednisone

VAN RHEE F LANCET ONCOL, 2014
Primary Endpoint Analysis: Durable Tumor and Symptom Response

- Placebo (N=26)
- Siltuximab (N=53)

P=0.0012

50% of patients remained on siltuximab
## Siltuximab Statistically Superior Across Major Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=26)</th>
<th>Siltuximab (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable tumor and symptom response (Central Review)</td>
<td>0%</td>
<td>34.0%</td>
<td>0.0012</td>
</tr>
<tr>
<td>Durable tumor and symptom response (Investigator)</td>
<td>0%</td>
<td>45.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor response (Central Review)</td>
<td>3.8%</td>
<td>37.7%</td>
<td>0.0022</td>
</tr>
<tr>
<td>Tumor response (Investigator)</td>
<td>0%</td>
<td>50.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin increase ≥ 1.5 g/dL at Week 13</td>
<td>0%</td>
<td>61%</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
Time to Treatment Failure

- Median TTF:
  - Placebo: 134 days
  - Siltuximab: not reached

HR=0.418
p=0.0084

Survival probability

Time to Treatment Failure (Days)

- Placebo
- Siltuximab

Median TTF:
- Placebo: 134 days
- Siltuximab: not reached

HR=0.418
p=0.0084
In siltuximab-treated subjects, improvement in MCD related laboratory abnormalities are observed:

- CRP, ESR and Fibrinogen levels decrease
- Hemoglobin and Albumin increases

**CRP = C-REACTIVE PROTEIN; ESR = ERYTHROCYTE SEDIMENTATION RATE**

Anti-IL6 Therapy: Siltuximab

At diagnosis

After 2.5 years of Siltuximab therapy
Skin Lesions Improving with Siltuximab

(Baseline)  
After 2 doses  
(12 mg/kg q3wk)  
After 6 doses
Limitations of Siltuximab

- Therapy is life long and not a ‘cure’
- Treatment intervals can eventually be spaced out
- Relapse occurs on cessation of therapy
Can we predict who will respond to siltuximab?
Responders to siltuximab have a clear inflammatory response by laboratory markers.
Predicted Probability of Response Based on Model Comprising Hb, CRP, IgG and Fibrinogen

Correctly classified
- Response: 15/18 (83%)
- Treatment Failure: 19/22 (86%)
How to utilize the different therapies?
CDCN Criteria for Evaluation of iMCD Severity

Severe iMCD

- ECOG ≥ 2
- Stage IV renal dysfunction (eGFR < 30; Creatinine >3.0)
- Anasarca and/or ascites and/or pleural/pericardial effusion (effects of hypercytokinemia/low albumin)
- Hemoglobin ≤ 8.0g/dL
- Pulmonary involvement/interstitial pneumonitis w/dyspnea
### iMCD Clinical Case Series of 344 Patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients (n)</th>
<th>Response/m* (%)</th>
<th>No Response/m* (%)</th>
<th>Treatment Failure/m* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Therapies</td>
<td>344</td>
<td>281/461 (61)</td>
<td>180/461 (39)</td>
<td>163/367 (44)</td>
</tr>
<tr>
<td>Corticosteroid Monotherapy</td>
<td>117</td>
<td>53/114 (46)</td>
<td>61/114 (54)</td>
<td>62/115 (54)</td>
</tr>
<tr>
<td>Corticosteroid or Cytotoxic Chemotherapy (not distinguished)</td>
<td>19</td>
<td>12/19 (63)</td>
<td>7/19 (37)</td>
<td>NA</td>
</tr>
<tr>
<td>Cytotoxic Chemotherapy (any time used)</td>
<td>135</td>
<td>102/131 (78)</td>
<td>29/131 (22)</td>
<td>44/105 (42)</td>
</tr>
<tr>
<td>Anti-IL-6 mAb (without cytotoxic agent or rituximab)</td>
<td>147</td>
<td>88/144 (61)</td>
<td>56/144 (39)</td>
<td>32/100 (32)</td>
</tr>
<tr>
<td>Immunomodulator (without cytotoxic agent)</td>
<td>27</td>
<td>18/26 (69)</td>
<td>8/26 (31)</td>
<td>10/26 (38)</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>8/13 (62)</td>
<td>5/13 (38)</td>
<td>12/15 (80)</td>
</tr>
<tr>
<td>No treatment/Follow-up Only</td>
<td>18</td>
<td>0/14 (0)</td>
<td>14/14 (100)</td>
<td>11/14 (79)</td>
</tr>
</tbody>
</table>

m = Total number of regimens evaluated (479)

m* = Number regimens assessed for stated outcome

CDCN Criteria for Evaluation of iMCD Severity

Management of iMCD

Non-Severe
- Siltuximab ± Steroids
- Tocilizumab ± Steroids
- Rituximab ± Steroids*
  - PR/CR
  - Continued Therapy
    - Siltuximab ± Steroids
    - Tocilizumab ± Steroids
  - Inadequate Response
    - Rituximab ± Steroids ± Immunomodulatory Agent
      - PR/CR
      - Continued Immunomodulatory Agent ± Steroids
      - Seek Expert Advice/Consider Immunomodulatory Agent

Severe
- Siltuximab + HD Steroids
  - Tocilizumab + HD Steroids
    - (1 week, daily assessment)
  - PR/CR
  - Continued Therapy
    - Siltuximab ± Steroids
    - Tocilizumab ± Steroids
  - Inadequate Response
    - Combination Chemotherapy†
      - x1 cycle
    - Individualized Further Therapy
    - Refer to Center of Excellence or Consult CD Expert

*Category 1 Evidence
†Category 2A Evidence
‡Category 2B Evidence
State of CD Research in 2018

- 407 physicians; 32-member SAB; 5 largest ever meetings
- First ever R01 for CD awarded! 18 studies launched to investigate etiology, cell types, and pathways; 7 more in development
- Diagnostic criteria published! ICD-10 code established! International iMCD consensus treatment guidelines published! Published largest series! New subtype described!
- Siltuximab approved in 2014!
- New disease model guiding Research Agenda
- Over 6,000 patients and loved ones connected!
- Real-world natural history registry advancing research!
- Identified a promising therapeutic approach
Conclusions

- Accurate diagnosis of iMCD is of paramount importance
- Tailor therapy to the severity of the disease
- Severely afflicted patients may require combination chemotherapy
- On-going research may identify biomarkers for responders to anti-IL6 mA therapy.
- Alternative therapeutic targets for IL6-non-responders
Thank You

David Fajgenbaum
Eric Oksenhendler
Sheila Pierson
Elaine Jaffé
Corey Casper
Thomas Uldrick
Raymond Wong
Peter Voorhees
Angela Dispenzieri
Makote Ide

Katie Stone
Amy Greenway
Samina Waheed