UNIVERSITA DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO-UNIVERSITARIA Città della Salute e della Scienza di Torino

DBMSS Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

EHA&EuroBloodNet Spotlight

Session 3: Idiopathic multicentric Castleman Disease (iMCD)

Simone Ferrero, MD

University of Torino, Italy, EU

15.02.2022

AMICa ASSOCIAZIONE MALATI ITALIANI CASTLEMAN-ODV

Co-funded by the Health Programme of the European Union

EHA EUROPEAN HEMATOLOGY ASSOCIATION

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

CDCN CASTLEMAN DISEASE COLLABORATIVE NETWORK

Main discussion points about iMCD

- ✓ Clinical phenotypes of the disease
- ✓ Differential diagnosis
- ✓ Relationship with TAFRO, IgG4RD, and POEMS
- ✓ Pathophysiology
- ✓ Treatment

DISCLOSURES: Simone Ferrero

- **Janssen**: consultancy, advisory board, reasearch support, speakers honoraria
- **EUSA Pharma**: consultancy, advisory board, speakers honoraria
- **Morphosys, Gilead**: reasearch support
- **Incyte, Clinigen**: advisory board
- **Servier, Gentili**: speakers honoraria

Case presentation

- 50-years-old Caucasian male with Fever of Unknown Origin (FUO) persisting for one month.
- He daily presented fever till 39.5 °C, associated with nocturnal diaphoresis, asthenia and chills.


CASE REPORT Open Access

Dichotomic response to interleukin-6 blockade in idiopathic multicentric Castleman disease: two case reports

Simone Ferrero[1,2*] and Simone Ragaini[1,2]

Journal of Medical Case Reports

(2021) 15:105

Laboratory results

- Blood count: mild anemia (11 g/dL), normal platelet count (250 k/mL) and leukocytosis (12800 /mL) with neutrophilia and monocytosis
- Inflammation markers were elevated (CRP 132 mg/L, ESR 89 mm/h)
- Slight hypoalbuminemia (3.4 g/dL).
- Blood culture and serological tests excluded infections.

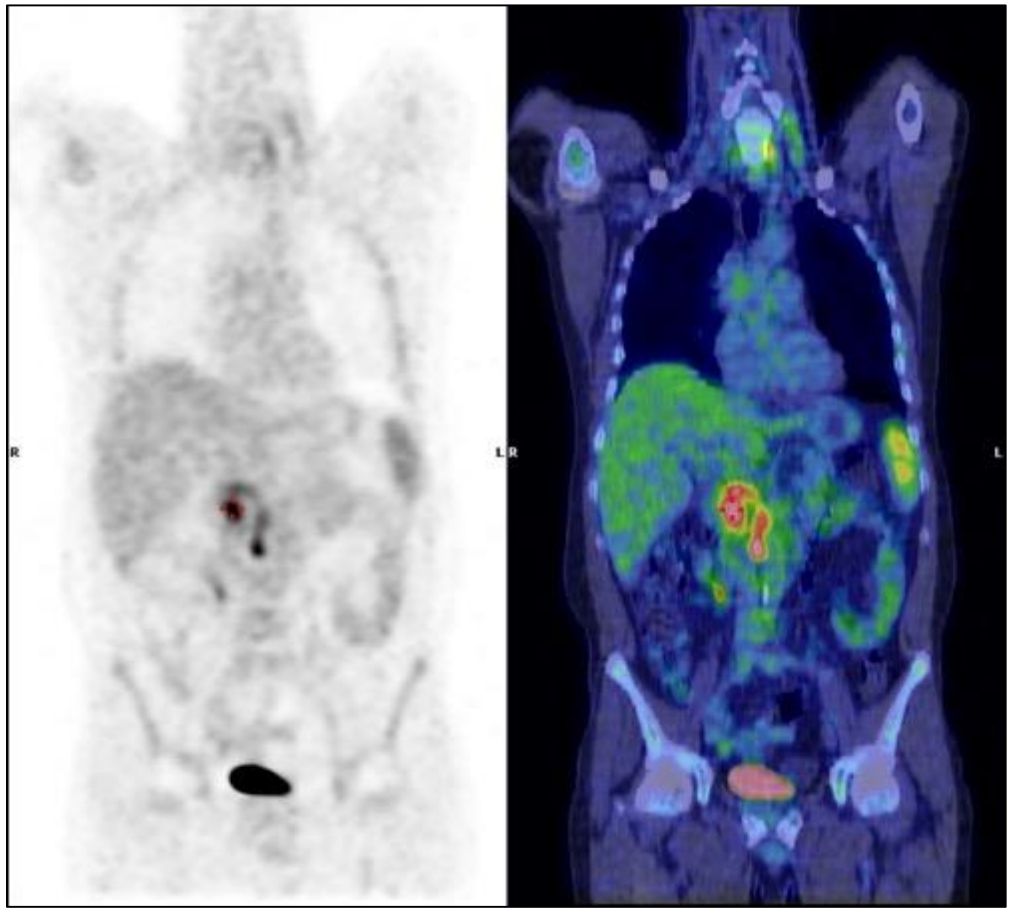
Case presentation

CT-PET scan

Evidence of contrast-enhancing, peri-pancreatic (short axis diameter 10 mm) and retrocaval adenopathies (maximum size 16 x 11 mm) with maximum SUV of 7.1

Bone marrow biopsy

- Non-necrotizing epithelioid granulomas
- Excess of interstitial and perivascular polyclonal plasma cells (about 15%).



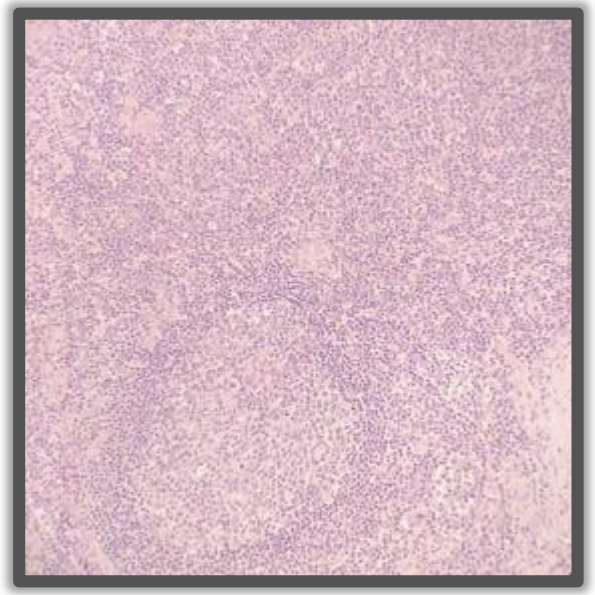
Ferrero, S. *J Med Case Reports,* 2021

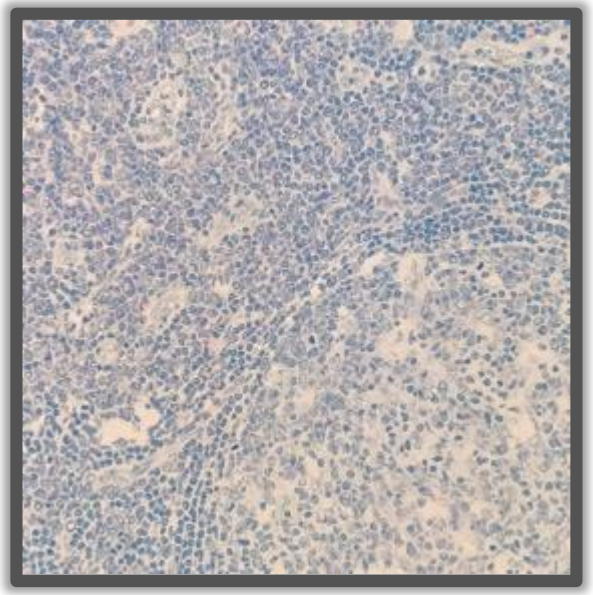
Case presentation

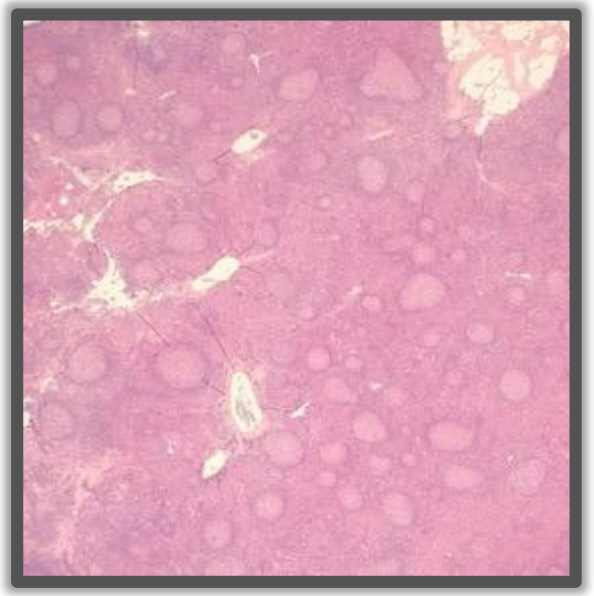
Lymph node biospy

- Vascular plasma cells proliferation and expansion along with focal aspects of follicular regression

- Compatible diagnosis of “HHV-8/HIV negative iMCD, of uncertain histopathological classification”, thus neither clearly attributable to the Hyalino Vascular, nor Plasmacytic nor Mixed subtype.







Ferrero, S. *J Med Case Reports,* 2021

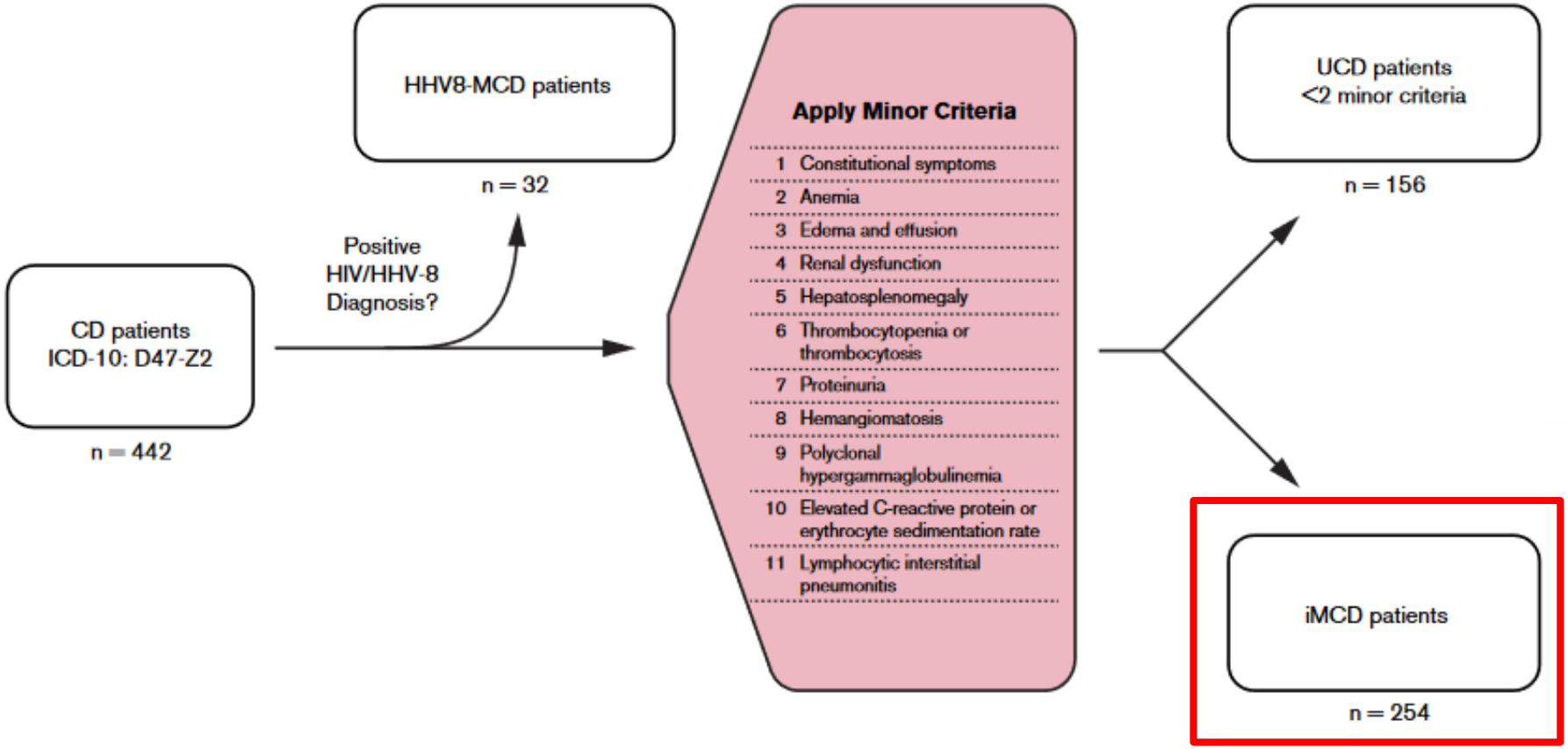
Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy

blood advances

Sudipto Mukherjee,[1] Rabecka Martin,[2] Brenda Sande,[2] Jeremy S. Paige,[3] and David C. Fajgenbaum[4]

[1]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]EUSA Pharma, Burlington, MA; [3]Eversana, LLC, Milwaukee, WI; and [4]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

- The epidemiology of CD and, more specifically, iMCD in the United States and worldwide remains poorly understood.
- After the introduction of a CD-specific ICD and publication of international evidence-based diagnostic criteria, it is more feasible to obtain more accurate population estimates.
- Patients with a CD-specific ICD-10 code between 1 January 2017 and 31 December 2019 were included in this analysis.



Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy

blood advances

Sudipto Mukherjee,[1] Rabecka Martin,[2] Brenda Sande,[2] Jeremy S. Paige,[3] and David C. Fajgenbaum[4]

[1]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]EUSA Pharma, Burlington, MA; [3]Eversana, LLC, Milwaukee, WI; and [4]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

- iMCD **incidence** was estimated to be **3.4 per million** in 2017 and 3.1 (95% CI, 1.2 2 10.0) per million in 2018.
- iMCD **prevalence** was estimated to be **6.9 per million** in 2017 and 9.7 (95% CI, 5.6-17.8) per million in 2018.

Table 3. Annual incidence and prevalence from 2017 to 2018

	All CD		UCD		MCD		HHV-8-MCD		iMCD	
	Cases per million	Total US cases	Cases per million	Total US cases	Cases per million	Total US cases	Cases per million	Total US cases	Cases per million	Total US cases
Incidence										
2017	5.5 (2.8-11.5)	1804 (928-3768)	1.9 (0.7-5.5)	612 (239-1804)	4 (1.71-9.9)	1303 (560-3250)	0.4 (0.1-1.6)	141 (44-514)	3.4 (1.4-9.2)	1111 (440-2996)
2018	5.8 (3.0-12.9)	1904 (994-4216)	2.5 (0.9-7.9)	800 (307-2572)	3.7 (1.57-10.7)	1213 (513-3503)	0.6 (0.1-3.1)	193 (39-1027)	3.1 (1.2-10.0)	1022 (405-3274)
Prevalence										
2017	10.2 (6.2-17.3)	3326 (2034-5671)	2.7 (1.2-6.6)	894 (409-2174)	7.7 (4.3-14.3)	2504 (1407-4675)	0.7 (0.2-3.1)	235 (65-1024)	6.9 (3.7-13.3)	2246 (1223-4348)
2018	16.2 (10.5-25.6)	5282 (3450-8385)	5.1 (2.6-11.2)	1653 (855-3662)	11 (6.6-19.5)	3613.4 (2154-6381)	1.2 (0.4-4.3)	395 (131-1407)	9.7 (5.6-17.8)	3172 (1820-5835)

iMCD clinical presentation

Signs and symptoms

- Lymphadenopathy
- Symptoms B
- Hepatosplenomegaly
- Pleural effusion, anasarca, ascites
- Severe cases with important generalized inflammation status and organ failure
- Skin involvement (cherry hemangioma)

Laboratory abnormalities

- Elevation of inflammatory indices (ESR, PCR, IL-6, VEGF)
- Hypoalbuminemia, hypergammaglobulinemia, proteinuria
- Anemia, thrombocytosis, or thrombocytopenia
- Autoantibodies (anti-erythrocytes, anti-platelets)

iMCD recommended work-up

blood 2018 132: 2115-2124
doi:10.1182/blood-2018-07-862334 originally published online September 4, 2018

Purpose	Tests
Inflammatory response	CBC, renal function, liver function, CRP, ESR, fibrinogen, immunoglobulins & free light chains, albumin, ferritin*
Histopathology	Hypervascular/mixed cellularity/ plasmacytic variant
Virologic status	HIV serology, HHV-8 qPCR (peripheral blood), EBER (lymph node), LANA-1 (lymph node)
Cytokine profile	IL-6, VEGF, sIL-2 receptor†
Imaging	CT-PET or CT neck, chest, abdomen, pelvis
Bone marrow evaluation	MGUS, myeloma, reticulin fibrosis
Immunology	ANA, rheumatoid factor
Organ function	ECHO, pulmonary function

iMCD histological presentation

1. Three types of histological model:
    1. Hypervascular
    2. Plasmacytic
    3. Mixed

2. Other features include:
    1. The expanded mantle surrounding the CGs with "onion skin" appearance;
    2. Vessels penetrating GCs with a "lollipop" appearance;
    3. "budding" follicles

3. Subtypes may alternate in subsequent biopsies or may be present at the same time at different sites in the same patient.

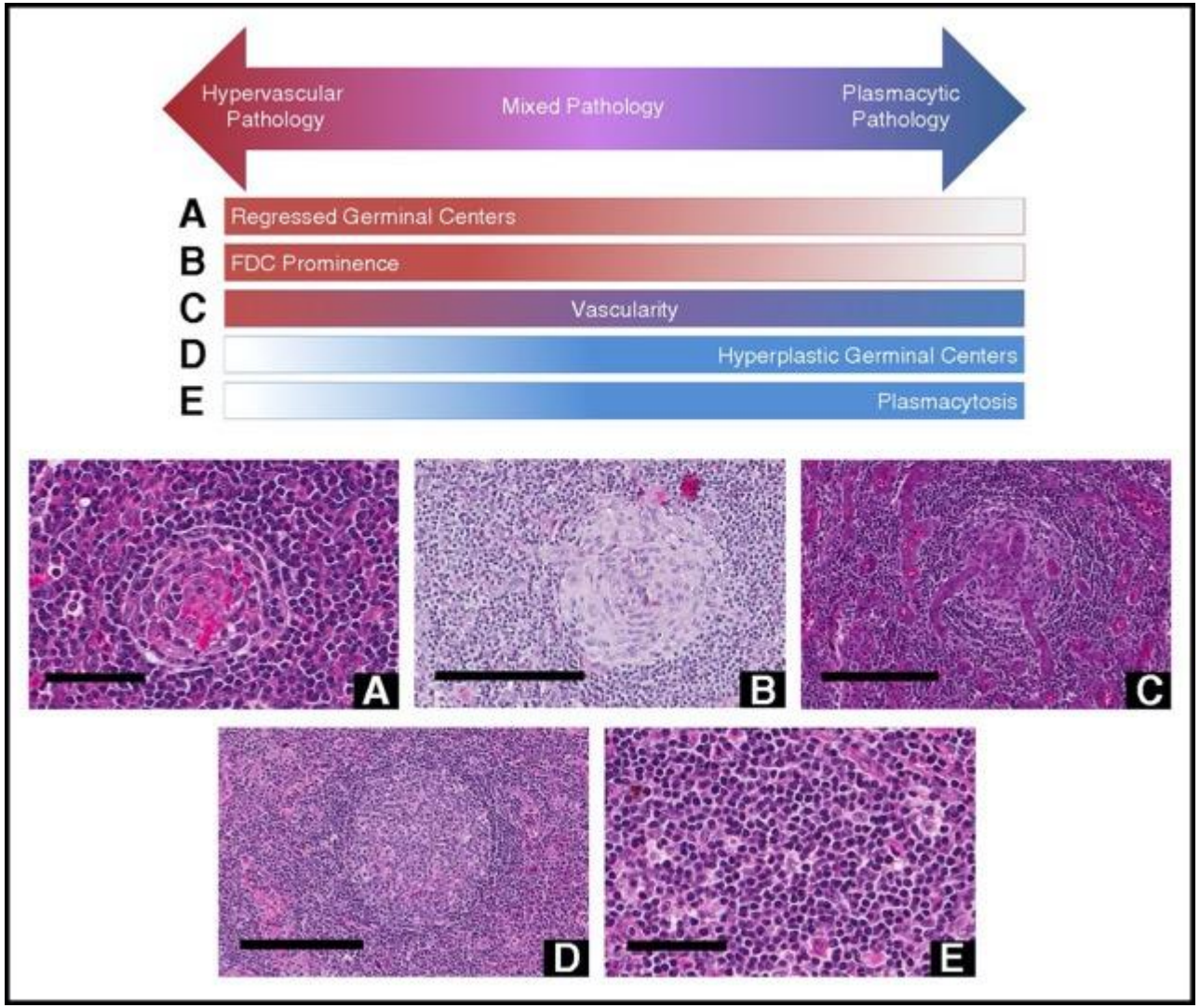


Figure from Fajgenbaum, D. C. et al, Blood, 2017

iMCD diagnostic criteria

CLINICAL TRIALS AND OBSERVATIONS | MARCH 23, 2017

International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease

Clinical Trials & Observations

David C. Fajgenbaum, Thomas S. Uldrick, Adam Bagg, Dale Frank, David Wu, Gordan Srkalovic, David Simpson, Amy Y. Liu, David Menke, Shanmuganathan Chandrakasan, Mary Jo Lechowicz, Raymond S. M. Wong, Sheila Pierson, Michele Paessler, Jean-François Rossi, Makoto Ide, Jason Ruth, Michael Croglio, Alexander Suarez, Vera Krymskaya, Amy Chadburn, Gisele Colleoni, Sunita Nasta, Raj Jayanthan, Christopher S. Nabel, Corey Casper, Angela Dispenzieri, Alexander Fosså, Dermot Kelleher, Razelle Kurzrock, Peter Voorhees, Ahmet Dogan, Kazuyuki Yoshizaki, Frits van Rhee, Eric Oksenhendler, Elaine S. Jaffe, Kojo S. J. Elenitoba-Johnson, Megan S. Lim

Inclusion diagnostic criteria for iMCD
I. Major Criteria (need both):
1. Histopathologic lymph node features consistent with the iMCD spectrum
2. Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)
Laboratory*
1. Elevated CRP (>10 mg/L) or ESR (>15 mm/h)
2. Anemia (hemoglobin < 12.5 g/dL for males, hemoglobin < 11.5 g/dL for females)
3. Thrombocytopenia (platelet count < 150 k/mL) or thrombocytosis (platelet count > 400 k/mL)
4. Hypoalbuminemia (albumin < 3.5 g/dL)
5. Renal dysfunction (eGFR < 60 mL/min/1.73m2) or proteinuria (> 150 mg/2 h or > 10 mg/100 ml)
6. Polyclonal hypergammaglobulinemia (total g globulin or immunoglobulin G > 1700 mg/dL)
Clinical
1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis
Select additional features supportive of, but not required for diagnosis
Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M
Diagnosis of other disorders that have been associated with iMCD
Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)

✓ Both major criteria and at least 2 out of 11 minor criteria (including at least 1 laboratory abnormality) must be met

✓ All diseases reported in the exclusion criteria must be excluded

Exclusion diagnostic criteria for iMCD
Infection-related disorders
Autoimmune/autoinflammatory diseases
Malignant/lymphoproliferative disorders
Malignant/lymphoproliferative disorders

Diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease (iMCD). Adapted from Fajgenbaum, D. C. et al, Boold, 2018

Webinars
EuroBloodNet

iMCD severity

- To be defined as a "severe" MCI, at least 2 of the 5 established criteria must be present

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

Frits van Rhee, International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018

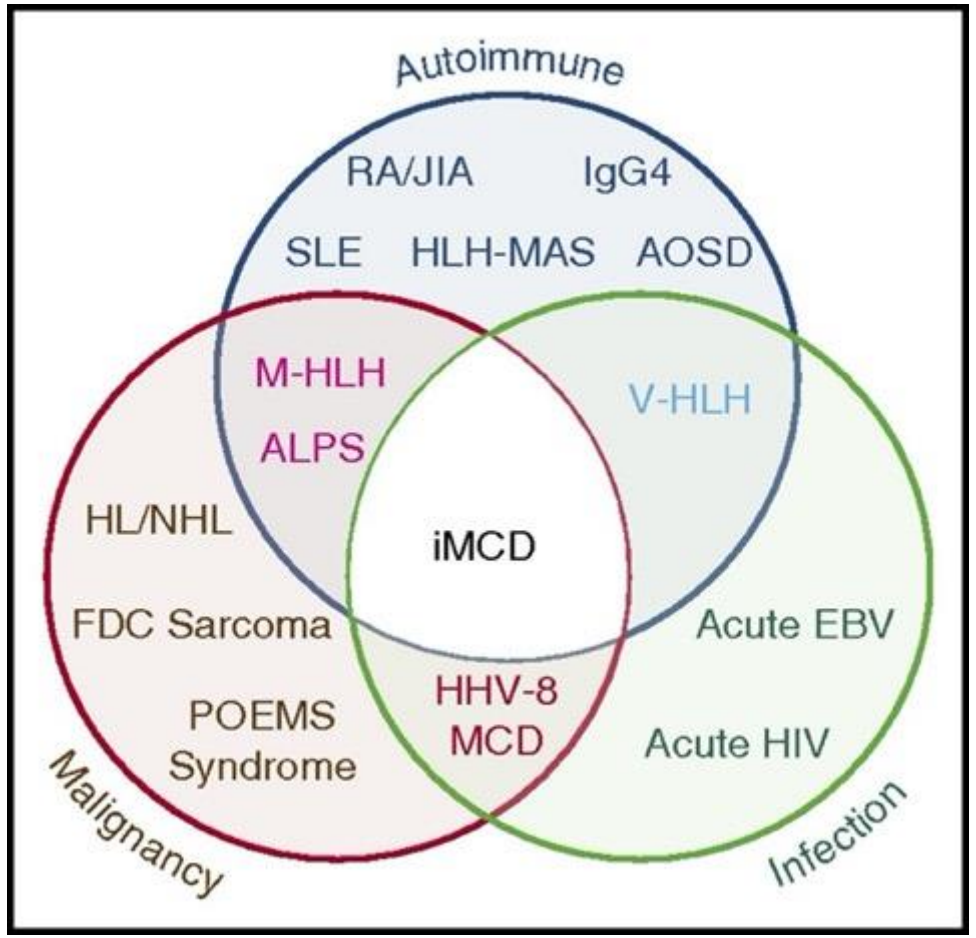
iMCD correlated diseases

1. Patients with MCI have a prevalence of neoplasms three times higher than healthy controls. However, the relationship between MCI and neoplasms remains unclear.

2. TAFRO syndrome may or may not be associated with MCI

3. IgG4-related disease is frequently seen in patients with idiopathic Castleman disease (ICM) but is not a criterion for exclusion.

4. POEMS syndrome is often observed in association with MCI, it can be considered the result of cytokine storm triggered by neoplastic plasma cells.



David C. Fajgenbaum, International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease. *Blood* 2017

TAFRO syndrome vs iMCD

- 57 years old male
- **Medical history:** diabetes type 2, hypertension, cholecystectomy after previous cholecystits
- **Hospitalization** for abdominal pain, vomit, fever, dyspnea, and declivous oedemas:

Thrombocytopenia + **A**scites + Reticulin **F**ibrosis + **R**enal dysfunction + **O**rganomegaly

TAFRO Syndrome diagnosis

Blood tests
- leukocytos
thrombocyto
60k/mm^3)
- Anormal co
(aPTT 33 se
- elevation o
(1.9 mg/dl), ALP (491 U/L), GGT (255 mg/dl) and CRP (200 mg/l)
- Hypoalbuminemia 2,5 g/L
- Blood coltures: negative

- mild increase of size of abdominal lymh nodes
- Bilateral pleural effusion
- Mediastinal adenopathies (max 2.4 cm)

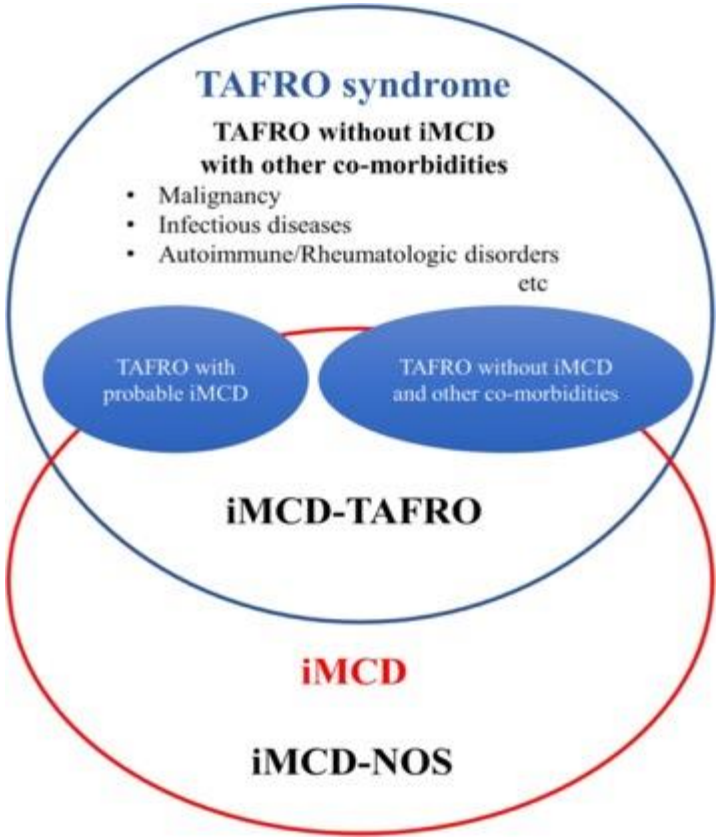
and invasive ventilation (P/F ratio 140)

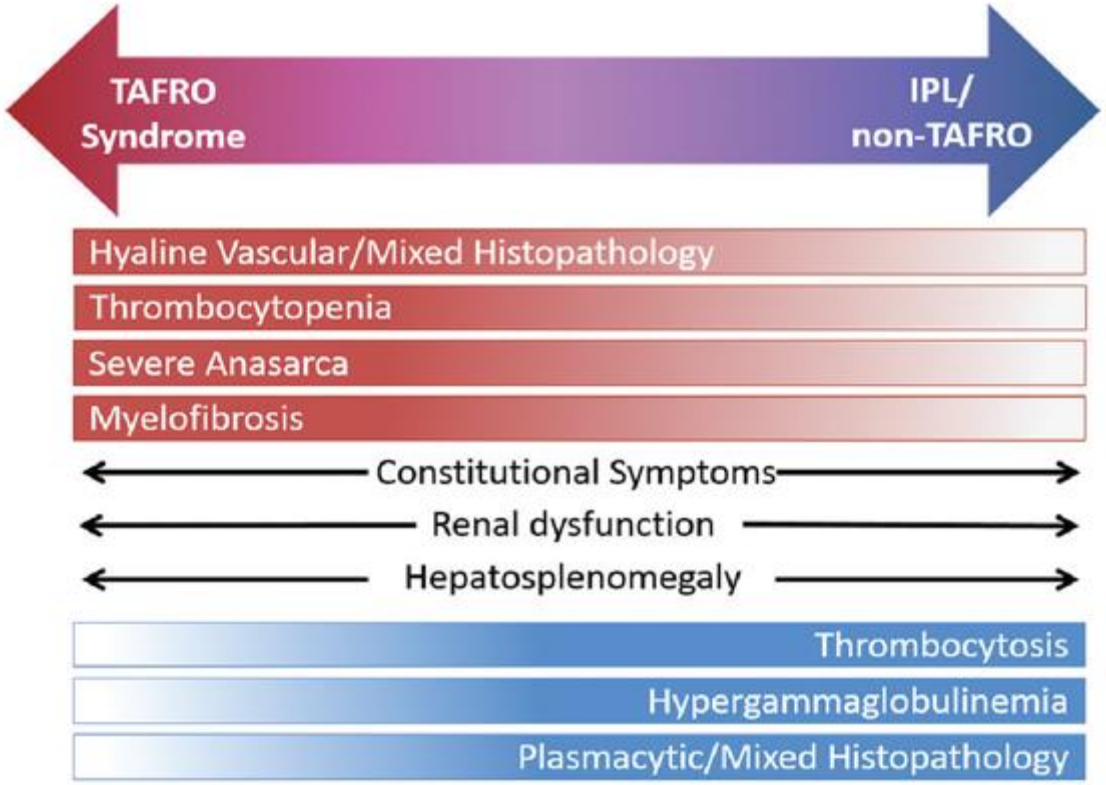
Fever → Extended spectrum antibiotic and antimycotic drugs (microbiologic tests negative)

marrow
y:
ulin fibrosis and megakaryocytic line expansion

TAFRO syndrome

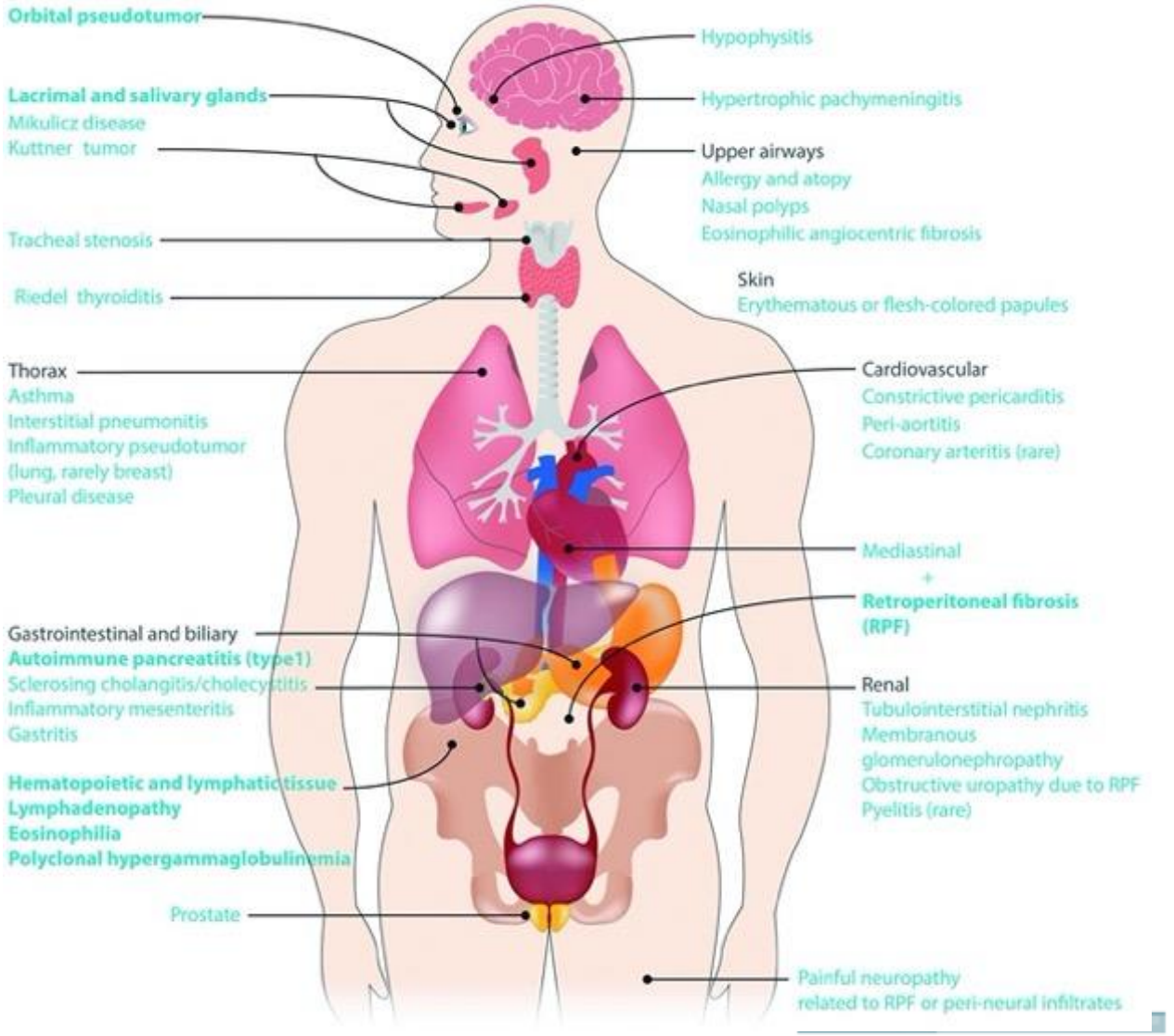
- **T**hrombocytopenia
- **A**scites
- Reticulin **F**ibrosis
- **R**enal dysfunction
- **O**rganomegaly





IgG4 related-disease

- "Fibro-inflammatory" disease with tumefactive (puffy) inflammatory infiltrates and fibrosis mainly of for glandular tissue
- Classical presentation with autoimmune pancreatitis, orbital disease and major salivary gland involvement
- Multicentric Castleman disease-like morphologic subtype (preserved nodal architecture with patent sinusoids and hyperplastic follicles; abundant mature plasma cells in interfollicular areas with some eosinophils).



Luke Y.C. Chen, IgG4-related disease: what a hematologist needs to know. Haematologica 2019

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)
EHA EUROPEAN HEMATOLOGY ASSOCIATION
EuroBloodNet

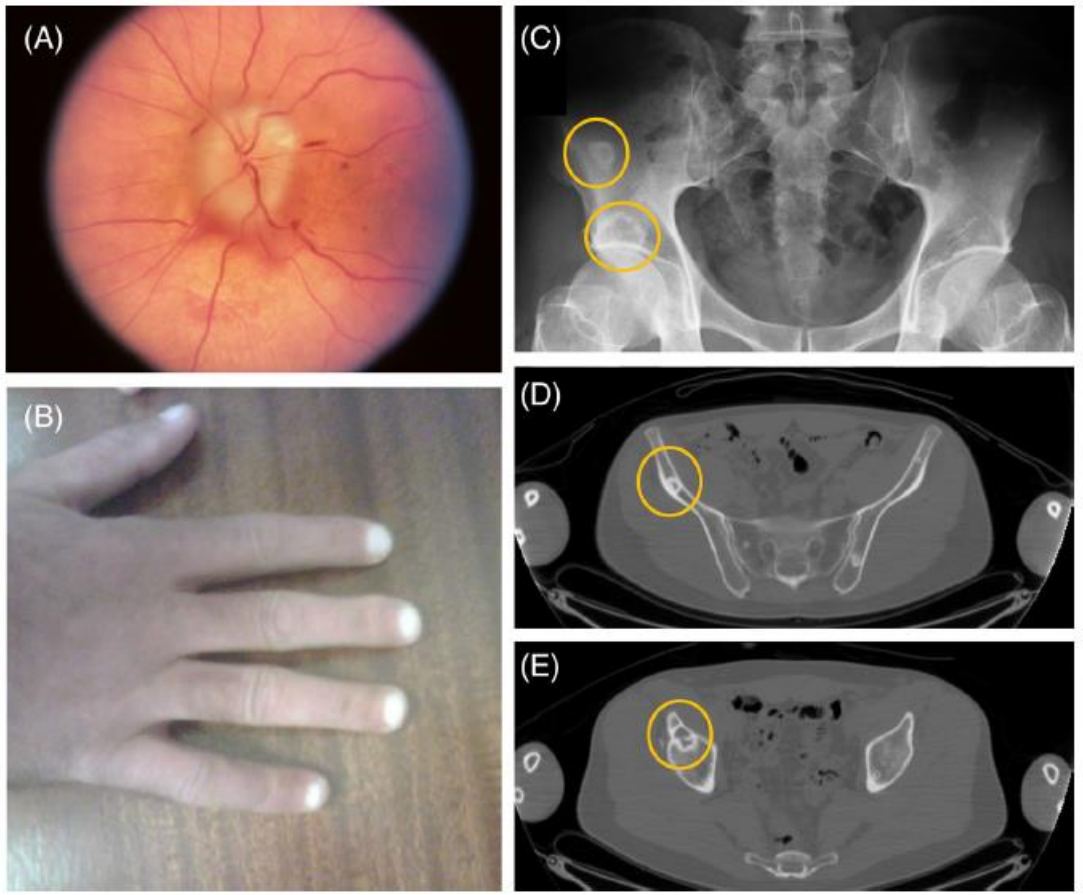
POEMS syndrome

- Paraneoplastic syndrome

- Clinical presentation:
  - **P**olyneuropathy
  - **O**rganomegaly
  - **E**ndocrinopathy
  - **M**onoclonal immunoglobulin spike
  - **S**kin changes

- MCD can co-occur with POEMS

- Castleman disease is a major criterion in the diagnosis of POEMS syndrome.



Dispenzieri A. POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management. Am J Hematol. 2019.

POEMS syndrome

The diagnosis of POEMS syndrome in a patient with MCD requires both polyneuropathy and monoclonal plasma cell proliferative disorder along with at least one of (Dispenzieri A,Am J Hematol. 2019):

- Organomegaly
- Extravascular volume overload
- Endocrinopathy
- Skin changes
- Papilledema
- Thrombocytosis or polycythemia

POEMS-MCD	iMCD-TAFRO	iMCD-NOS
Multiple lymph nodes and tissues	Multiple lymph nodes and tissues	Multiple lymph nodes and tissues
Multiple lymphadenopathies (peripheral and central); monoclonal plasma cell disorder; anaemia	Multiple lymphadenopathies (peripheral and central, often of small volume); thrombocytopenia; anaemia	Multiple lymphadenopathies; thrombocytosis; anaemia
Fever; night sweats; anasarca; weight loss	Fever; night sweats; anasarca; weight loss	Fever; night sweats; anasarca; weight loss
Hepatomegaly; splenomegaly	Hepatomegaly; splenomegaly	Hepatomegaly; splenomegaly
Polyneuropathy; endocrinopathy; skin changes	Renal dysfunction; liver dysfunction	Renal dysfunction; liver dysfunction
Plasma cell type: interfollicular mature plasmacytosis; hyaline vascular type: rich intraperi-follicular vascularity	Plasma cell type: interfollicular mature plasmacytosis; hyaline vascular type: rich intraperi-follicular vascularity	Plasma cell type: interfollicular mature plasmacytosis; hyaline vascular type: rich intraperi-follicular vascularity

Table retrieved and adapted from Carbone A, Nat Rev Dis Primers. 2021

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Pathogenic Significance of Interleukin-6 (IL-6/BSF-2) in Castleman's Disease

By Kazuyuki Yoshizaki, Tadashi Matsuda, Norihiro Nishimoto, Taro Kuritani, Lee Taeho, Katsuyuki Aozasa, Tatsutoshi Nakahata, Hiroshi Kawai, Hiromi Tagoh, Toshihisa Komori, Susumu Kishimoto, Toshio Hirano, and Tadamitsu Kishimoto

blood
1989 74: 1360-1367

- In 1986, the authors examined **2 patients with plasma cell variant Castleman disease**
- IL-6 was quantified in the culture supernatants of lymph node blocks taken from each of the 2 patients as well as in swollen lymph node blocks taken from noninflammatory controls: **IL-6 levels were elevated in both patients compared with the controls**
- **After resecting the enlarged lymph node** from each patient, all abnormal findings in **patient 1** disappeared with a marked **reduction in serum IL-6 levels**.
- On the other hand, in **patient 2**, symptoms and elevated serum IL-6 levels, **persisted** after surgical removal of the enlarged lymph node

Table 1
Clinical and laboratory findings before and after resection of a hyperplastic lymph node

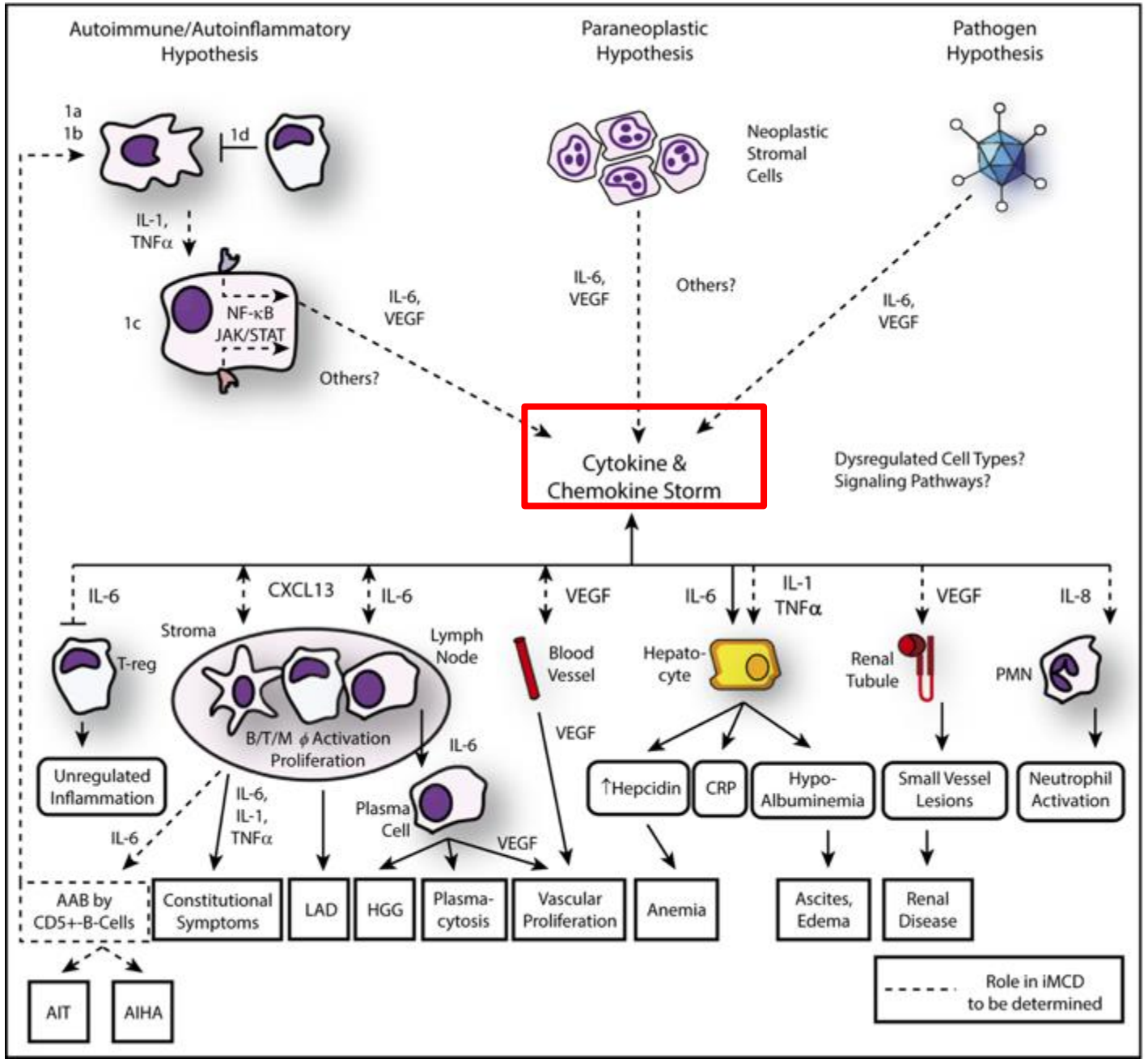
Patient (Age, Sex)	Before and After Surgery	Affected Lymph Nodes	Clinical Symptoms	Hb (g/dL)	ESR (mm/h)	Immunoglobulins IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)	IgE (U/mL)	CRP (mg/dL)	IL-6 (pg/mL)
1 (14, F)	Before	Solitary	(+)	9.1	157	4350	468	332	12	20.70	110
	After (2 wk)	No	(−)	11.6	22	2471	190	253	9	0.05	ND
	After (4 mo)	No	(−)	12.9	6	1813	165	246	ND	0.04	30
2 (52, F)	Before	Multiple	(+)	10.1	138	4650	1040	180	19,900	5.80	70
	After (1 mo)	Multiple	(+)	9.0	144	5320	941	179	ND	5.70	ND
	After (4 mo)	Multiple	(+)	8.2	144	4280	832	163	13,200	12.40	68

Table retrieved from Yoshizaki K, The Role of Interleukin-6 in Castleman Disease, Hematology/Oncology Clinics of North America, 2018

iMCD pathogenesis

The cytokine and chemokine storm

Regardless of the etiology, the cytokine and chemokine storm **is the common pathway** that results in the subsequent clinical and histopathological features of iMCD.



HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy

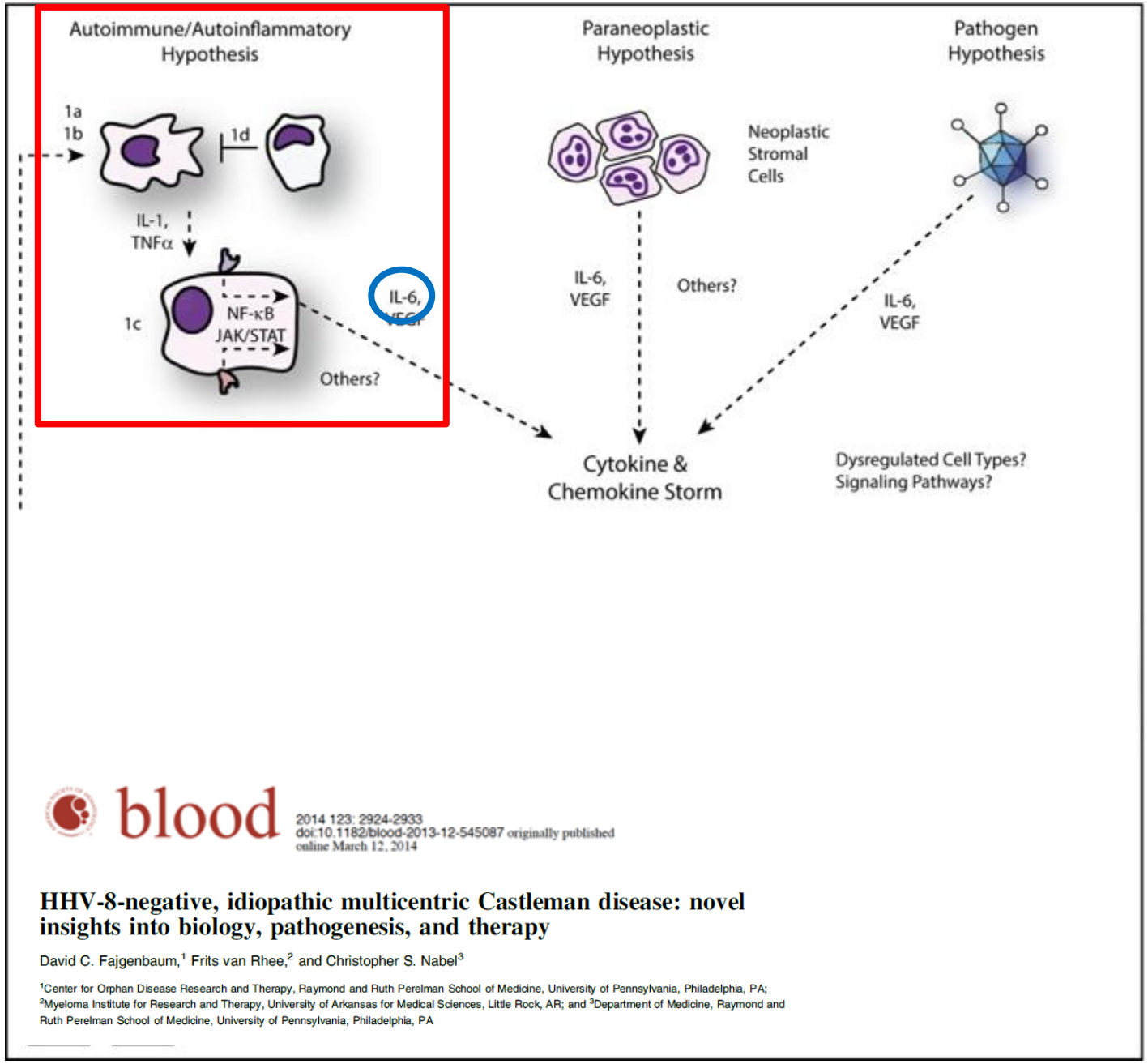
David C. Fajgenbaum,[1] Frits van Rhee,[2] and Christopher S. Nabel[3]

[1]Center for Orphan Disease Research and Therapy, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; and [3]Department of Medicine, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

iMCD pathogenesis

The autoimmune and autoinflammatory hypotheses

- **Auto-antibodies** triggering proinflammatory **cytokine release by antigen-presenting cells** that induce the as-yet-unknown hypercytokine-secreting cell to release IL-6
- **Dysregulated signaling in an antigen presenting cell** releasing IL-6 or other pathologic cytokines
- **A defect in the regulation of activated inflammatory cells.** The cytokine and chemokine storm is perpetuated by positive feedback of IL-6, other pathologic cytokines, and/or possibly further auto-antibody stimulation.



blood 2014 123: 2924-2933
doi:10.1182/blood-2013-12-545087 originally published online March 12, 2014

HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy

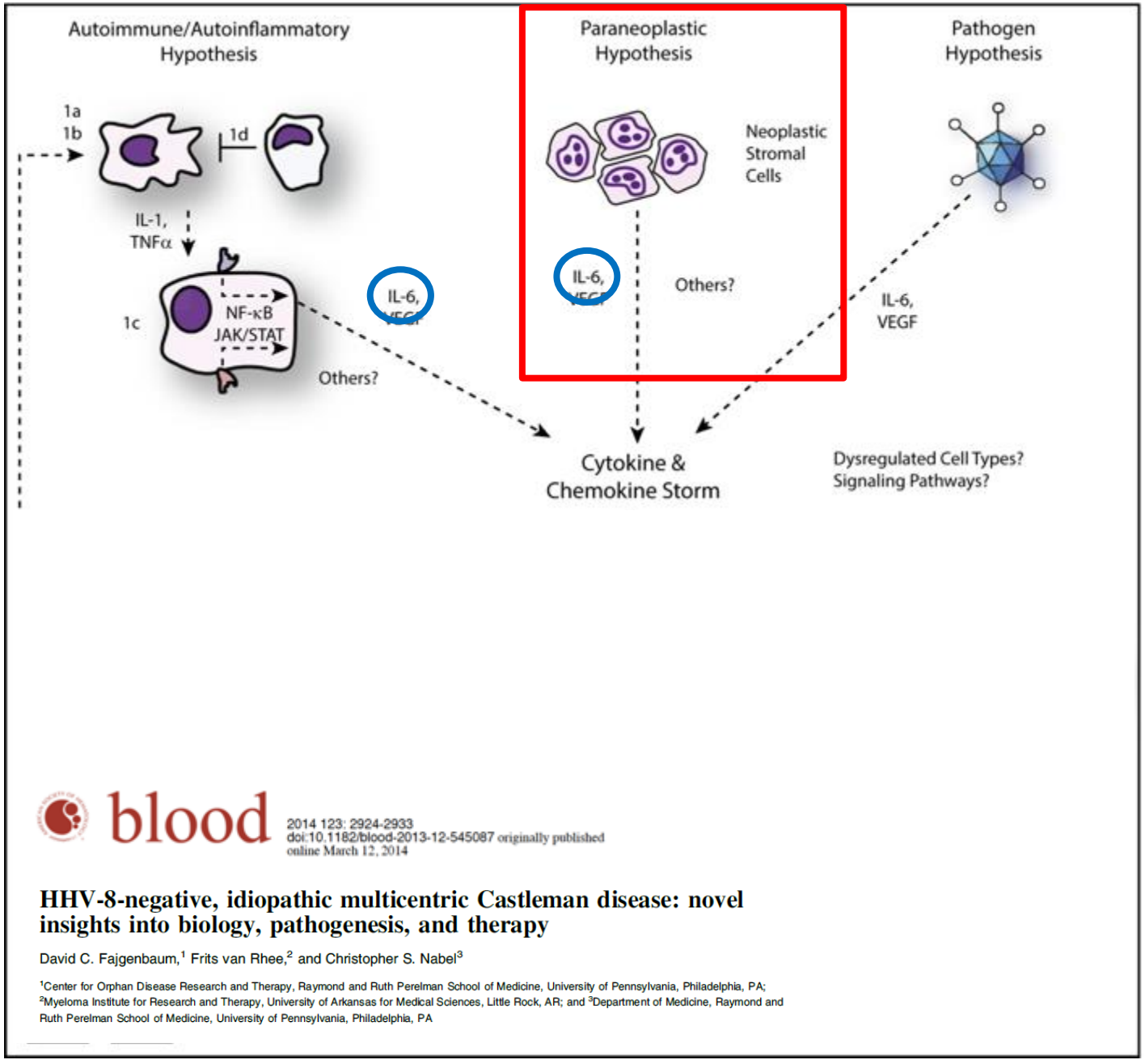
David C. Fajgenbaum,[1] Frits van Rhee,[2] and Christopher S. Nabel[3]

[1]Center for Orphan Disease Research and Therapy, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; and [3]Department of Medicine, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

iMCD pathogenesis

The paraneoplastic syndrome hypothesis

- A **somatic mutation in benign or malignant cells** inside or outside of the lymph node causes constitutive cytokine release.
- Preliminary data suggest these may be **lymph node stromal cells**.



blood
2014 123: 2924-2933
doi:10.1182/blood-2013-12-545087 originally published online March 12, 2014

HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy

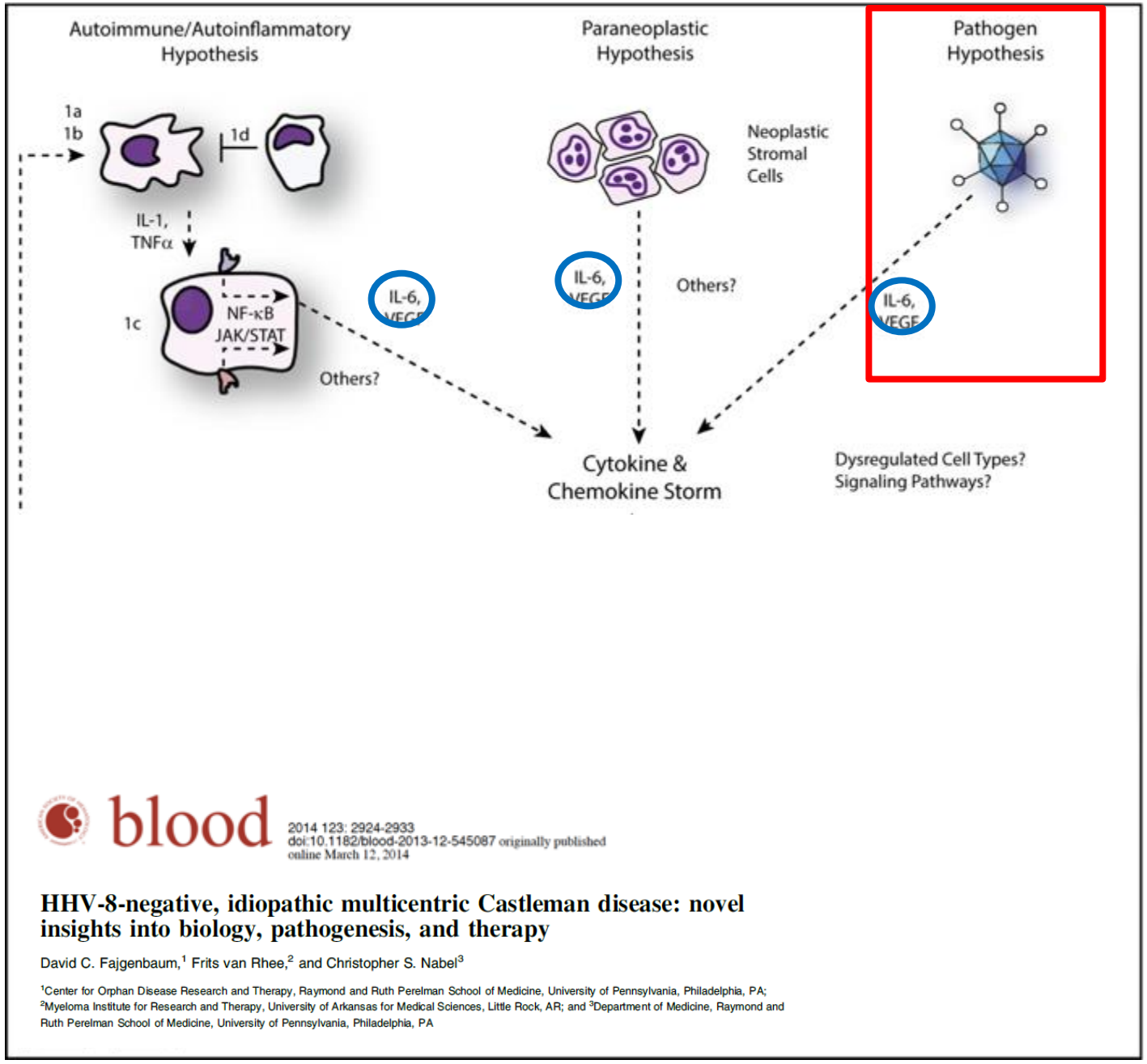
David C. Fajgenbaum,[1] Frits van Rhee,[2] and Christopher S. Nabel[3]

[1]Center for Orphan Disease Research and Therapy, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; and [3]Department of Medicine, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

iMCD pathogenesis

The pathogen hypothesis

- Involves either infection with **HHV-8 that is clinically undetectable, a novel virus, or another pathogen** signaling proinflammatory cytokines.
- An active infection by a single virus is less likely based on preliminary data generated from pathogen discovery studies.



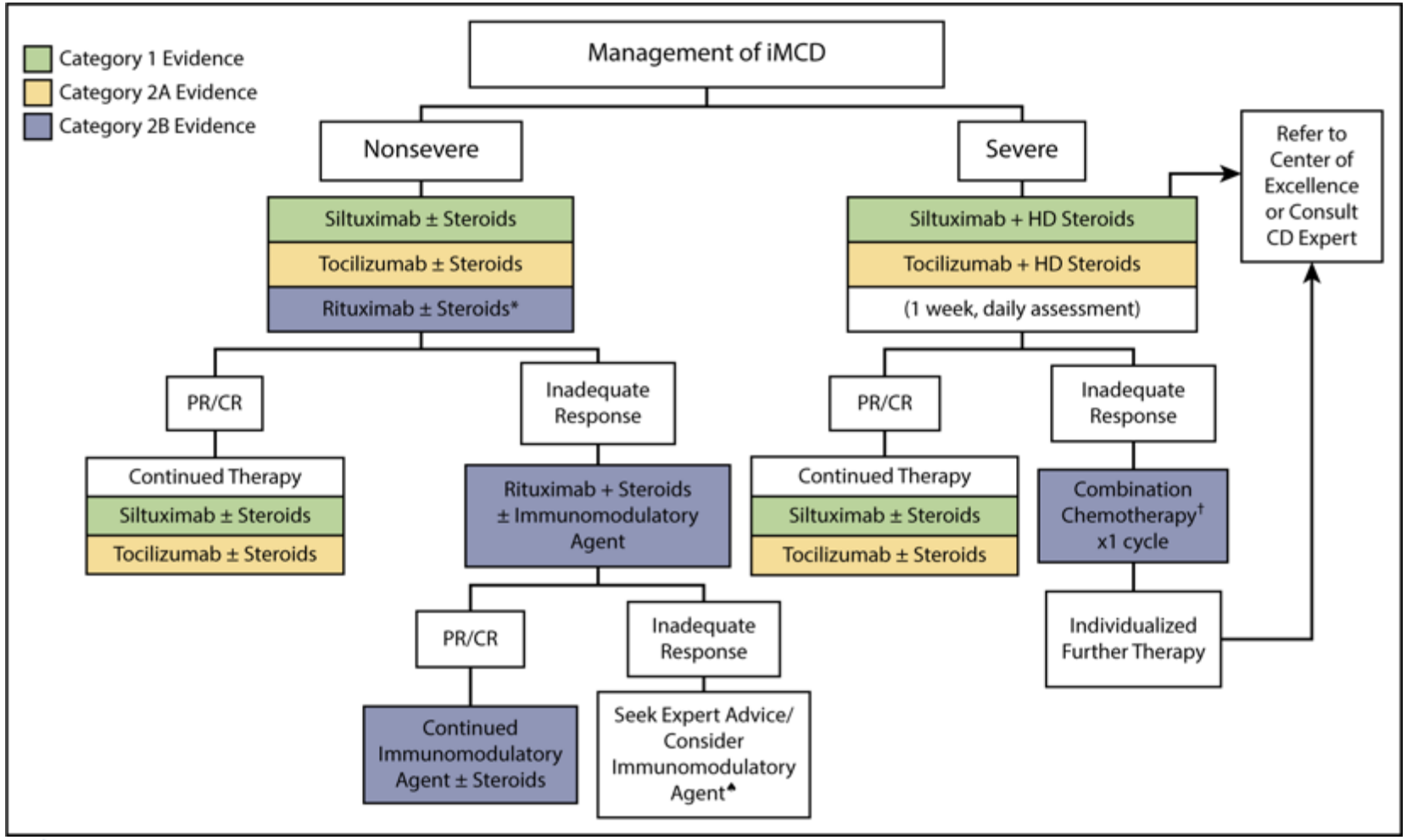
blood
2014 123: 2924-2933
doi:10.1182/blood-2013-12-545087 originally published online March 12, 2014

HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy

David C. Fajgenbaum,[1] Frits van Rhee,[2] and Christopher S. Nabel[3]

[1]Center for Orphan Disease Research and Therapy, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; and [3]Department of Medicine, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

iMCD treatment



Frits van Rhee, International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease, Blood, 2018.

iMCD treatment

IL-6 blockade

- Inhibiting IL-6 → **Siltuximab**

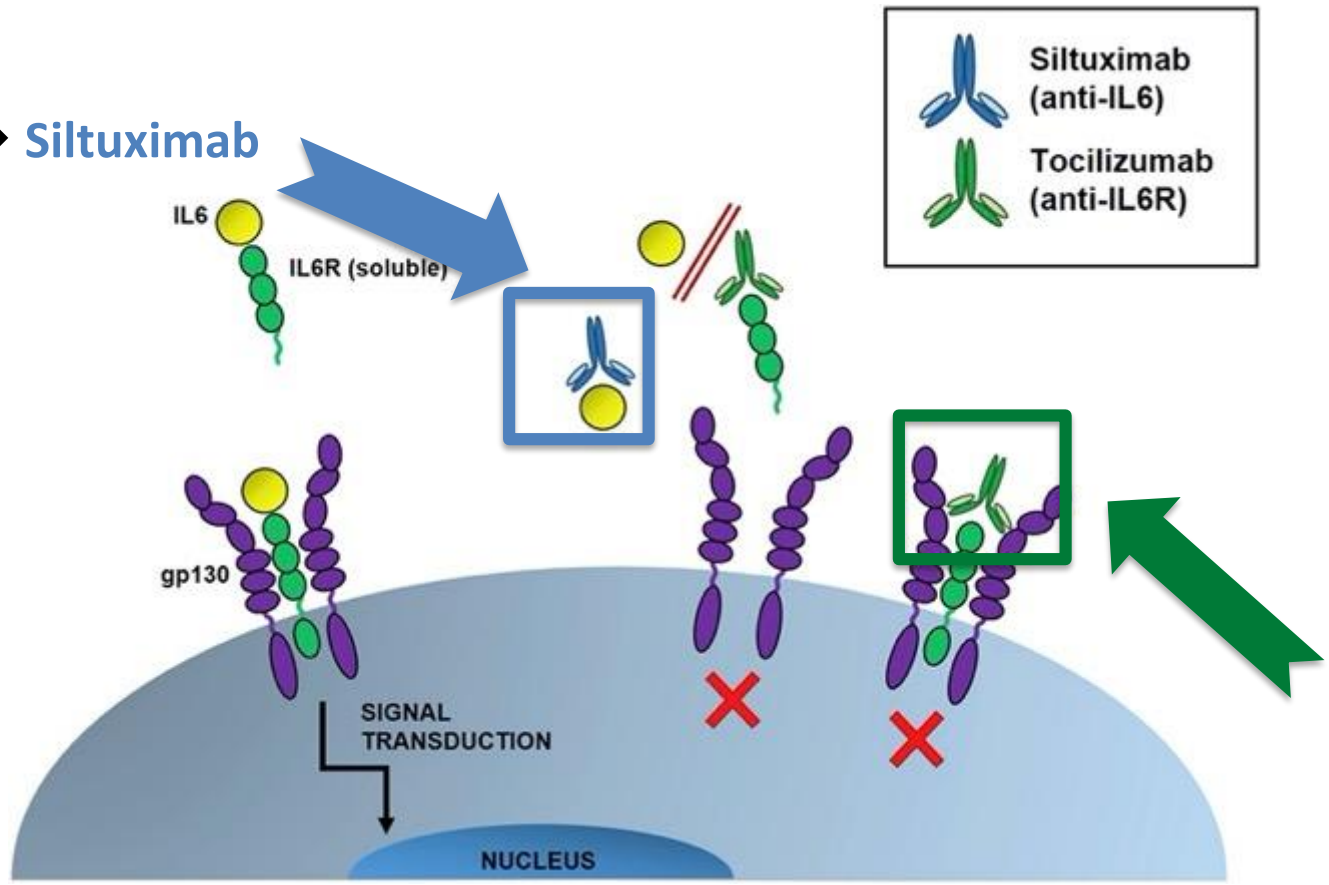


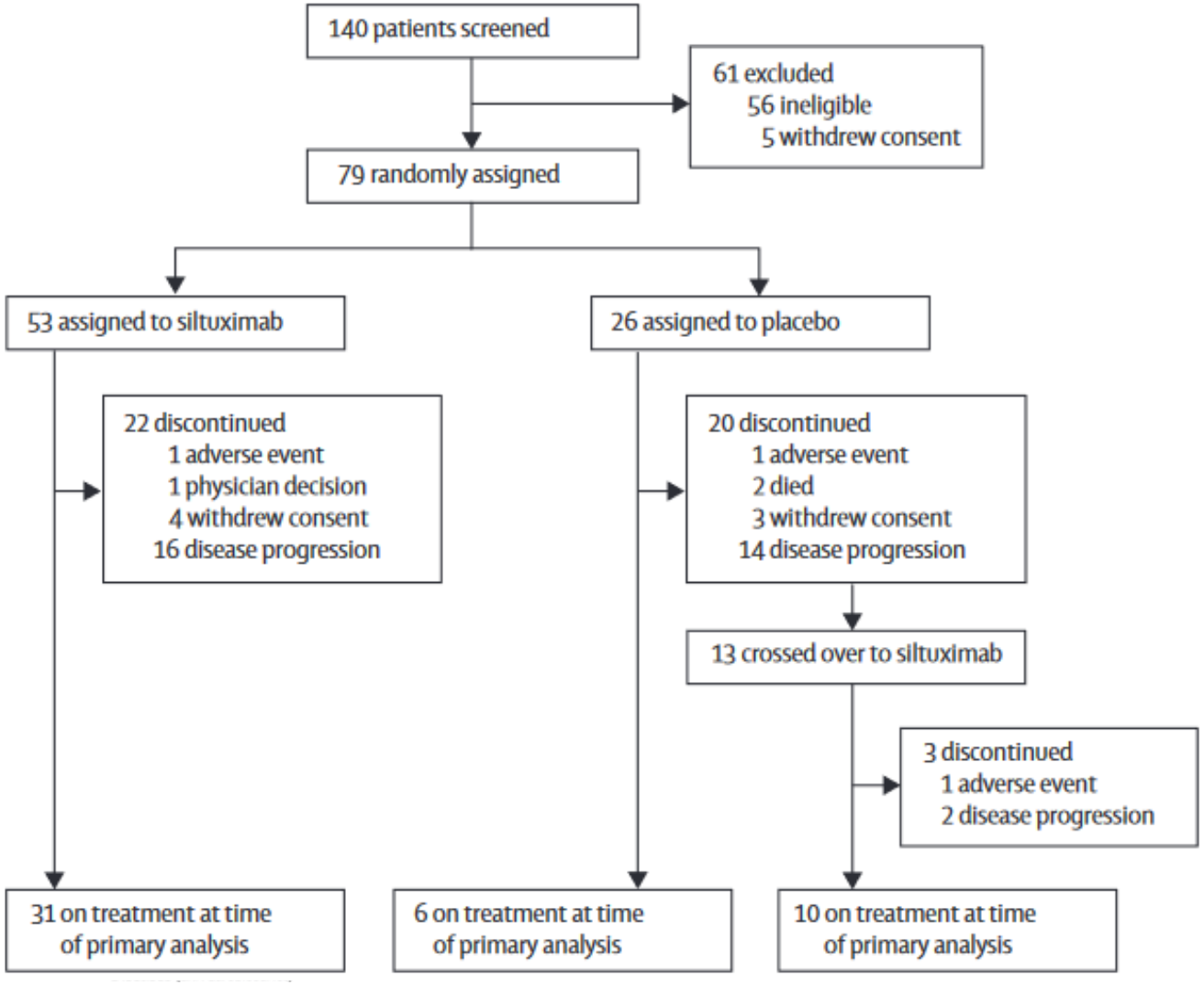
Figure from Treatment of Idiopathic Castleman Disease,
Frits van Rhee, Hematology/Oncology Clinics, 2018

- Inhibiting IL-6 binding on IL-6 receptor → **Tocilizumab**

Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial

THE LANCET Oncology
Lancet Oncol 2014; 15: 966–74

Frits van Rhee, Raymond S Wong, Nikhil Munshi, Jean-Francois Rossi, Xiao-Yan Ke, Alexander Fosså, David Simpson, Marcelo Capra, Ting Liu, Ruey Kuen Hsieh, Yeow Tee Goh, Jun Zhu, Seok-Goo Cho, Hanyun Ren, James Cavet, Rajesh Bandekar, Margaret Rothman, Thomas A Puchalski, Manjula Reddy, Helgi van de Velde, Jessica Vermeulen, Corey Casper

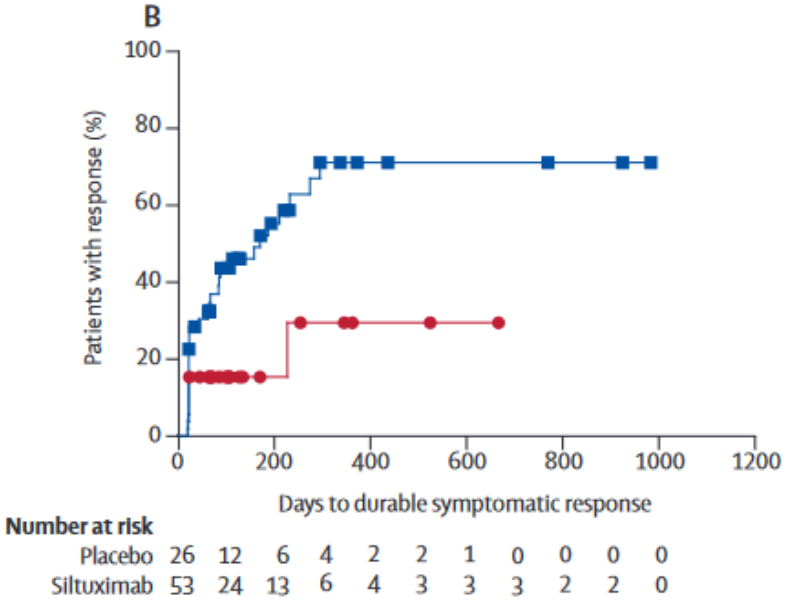


- Double-blind, placebo-controlled study
- Enrolled iMCD patients
- Patients were randomly assigned (2:1) to siltuximab (11 mg/kg intravenous infusion every 3 weeks) or placebo.
- Patients continued treatment until treatment failure.
- The primary endpoint was durable tumour and symptomatic response for at least 18 weeks for the intention-to-treat population

Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial

THE LANCET Oncology
Lancet Oncol 2014; 15: 966–74

Frits van Rhee, Raymond S Wong, Nikhil Munshi, Jean-Francois Rossi, Xiao-Yan Ke, Alexander Fosså, David Simpson, Marcelo Capra, Ting Liu, Ruey Kuen Hsieh, Yeow Tee Goh, Jun Zhu, Seok-Goo Cho, Hanyun Ren, James Cavet, Rajesh Bandekar, Margaret Rothman, Thomas A Puchalski, Manjula Reddy, Helgi van de Velde, Jessica Vermeulen, Corey Casper



Kaplan-Meier plot of time to durable symptomatic response

Kaplan-Meier plot of time to next treatment in the intention-to-treat population during the masked treatment period

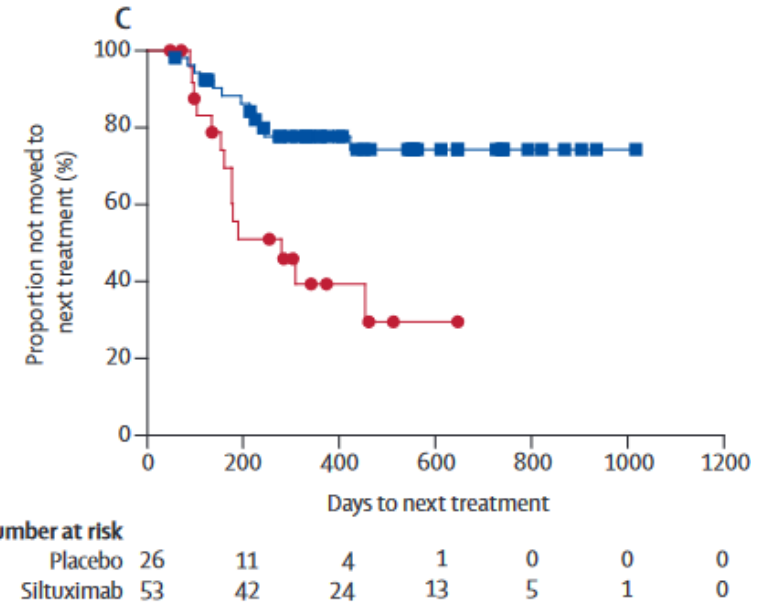


Table of adverse events

	Siltuximab group (n=53)		Placebo group (n=26)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with ≥1 adverse event	53 (100%)	25 (47%)	25 (96%)	14 (54%)
Pruritus	22 (42%)	0 (0%)	3 (12%)	0 (0%)
Upper respiratory tract infection	19 (36%)	0 (0%)	4 (15%)	1 (4%)
Fatigue	18 (34%)	5 (9%)	10 (38%)	1 (4%)
Maculopapular rash	18 (34%)	0 (0%)	3 (12%)	0 (0%)
Peripheral oedema	17 (32%)	1 (2%)	6 (23%)	0 (0%)
Malaise	15 (28%)	0 (0%)	5 (19%)	0 (0%)
Dyspnoea	13 (25%)	1 (2%)	9 (35%)	1 (4%)
Peripheral sensory neuropathy	13 (25%)	0 (0%)	5 (19%)	1 (4%)
Diarrhoea	12 (23%)	0 (0%)	5 (19%)	1 (4%)
Localised oedema	11 (21%)	2 (4%)	1 (4%)	0 (0%)
Weight gain	11 (21%)	2 (4%)	0 (0%)	0 (0%)
Hyperhidrosis	10 (19%)	2 (4%)	4 (15%)	0 (0%)
Decreased appetite	9 (17%)	1 (2%)	4 (15%)	0 (0%)
Night sweats	9 (17%)	4 (8%)	3 (12%)	1 (4%)
Cough	8 (15%)	0 (0%)	6 (23%)	0 (0%)
Abdominal pain	8 (15%)	0 (0%)	1 (4%)	1 (4%)
Thrombocytopenia	8 (15%)	2 (4%)	1 (4%)	1 (4%)
Nasopharyngitis	8 (15%)	0 (0%)	1 (4%)	0 (0%)
Hyperuricaemia	7 (13%)	2 (4%)	0 (0%)	0 (0%)
Neutropenia	7 (13%)	2 (4%)	2 (8%)	1 (4%)
Nausea	5 (9%)	1 (2%)	5 (19%)	0 (0%)
Anaemia	5 (9%)	1 (2%)	4 (15%)	3 (12%)
Weight loss	4 (8%)	0 (0%)	4 (15%)	0 (0%)
Tumour pain	4 (8%)	0 (0%)	4 (15%)	0 (0%)
Hypertension	4 (8%)	2 (4%)	1 (4%)	0 (0%)
Hyperkalemia	2 (4%)	2 (4%)	0 (0%)	0 (0%)

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

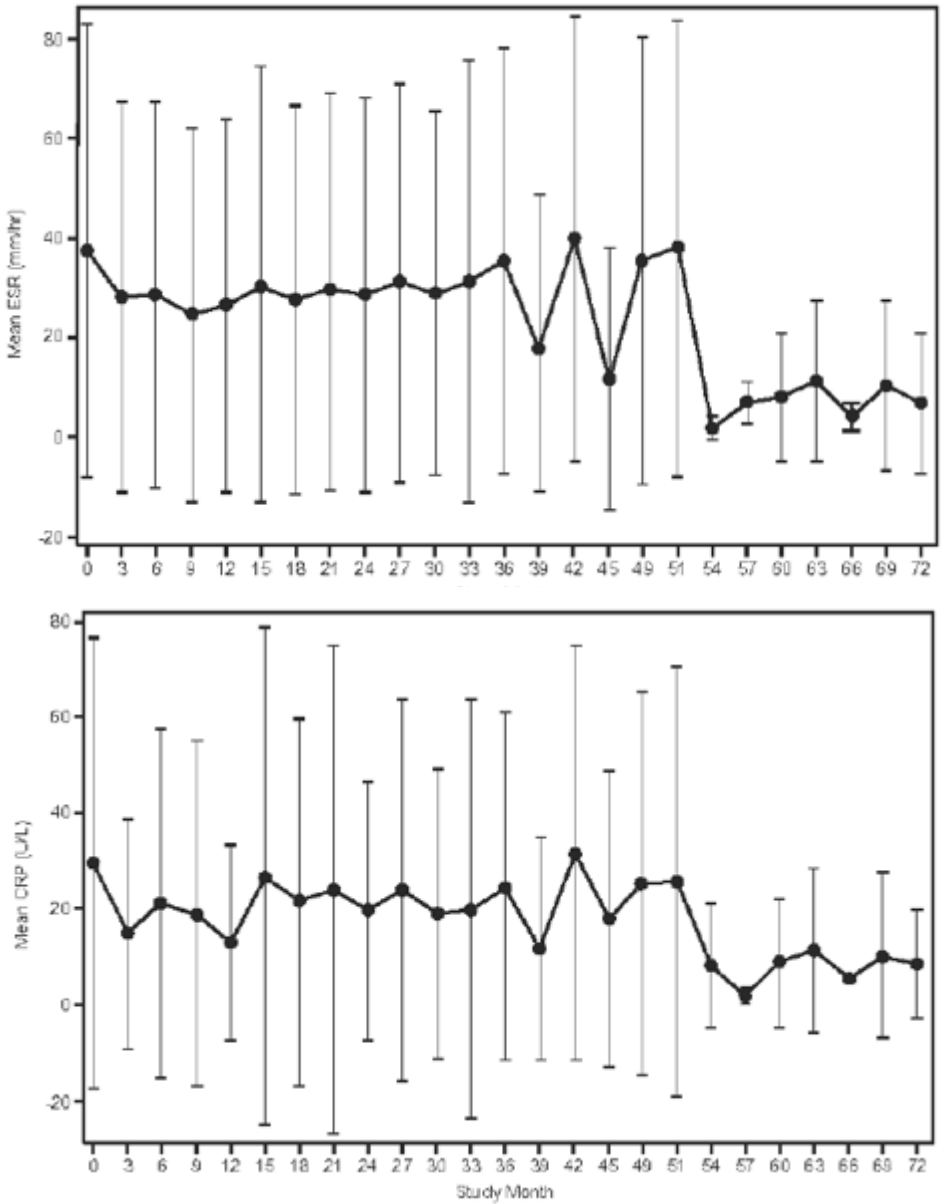
Long-term safety of siltuximab in patients with idiopathic multicentric Castleman disease: a prespecified, open-label, extension analysis of two trials

THE LANCET Haematology

Frits van Rhee, Corey Casper, Peter M Voorhees, Luis E Fayad, Damilola Gibson, Karan Kanhai, Razelle Kurzrock

www.thelancet.com/haematology **Published online February 3, 2020**

- **Siltuximab treatment might falsely increase IL-6 concentrations** for many months after the last dose
- siltuximab/IL-6 complexes interfere with current immunological IL-6 quantification methods
- Serum IL-6 concentrations **should not be used to assess response to treatment.**
- **C-reactive protein** has been identified as **a surrogate biomarker** for IL-6 activity, because its production by hepatocytes is fully dependent on IL-6 in vivo



iMCD treatment

Anti CD20 drugs

Rituximab

- Rituximab (375 mg/m2 x 4-8 doses) recommend as a first-line alternative to anti IL-6 mAb therapy for patients with nonsevere iMCD who do not have marked cytokine-driven symptomatology (Frits van Rhee, Blood, 2018).

- Rituximab recommendation based on limited data set, because rituximab has not been subjected to systematic study in iMCD and data are confined to case reports or small series

- Most papers report the use of rituximab along with conventional chemotherapies.

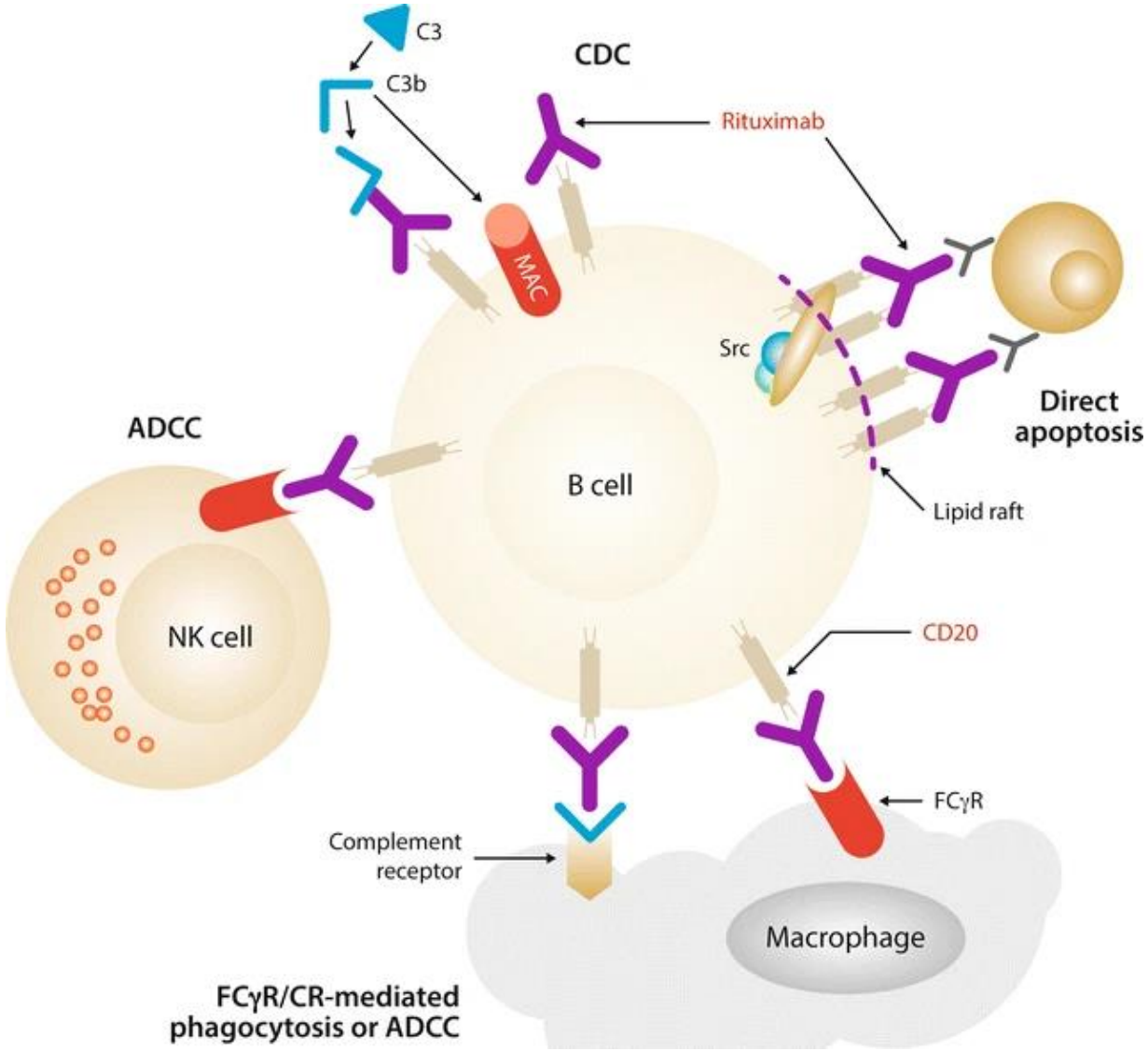
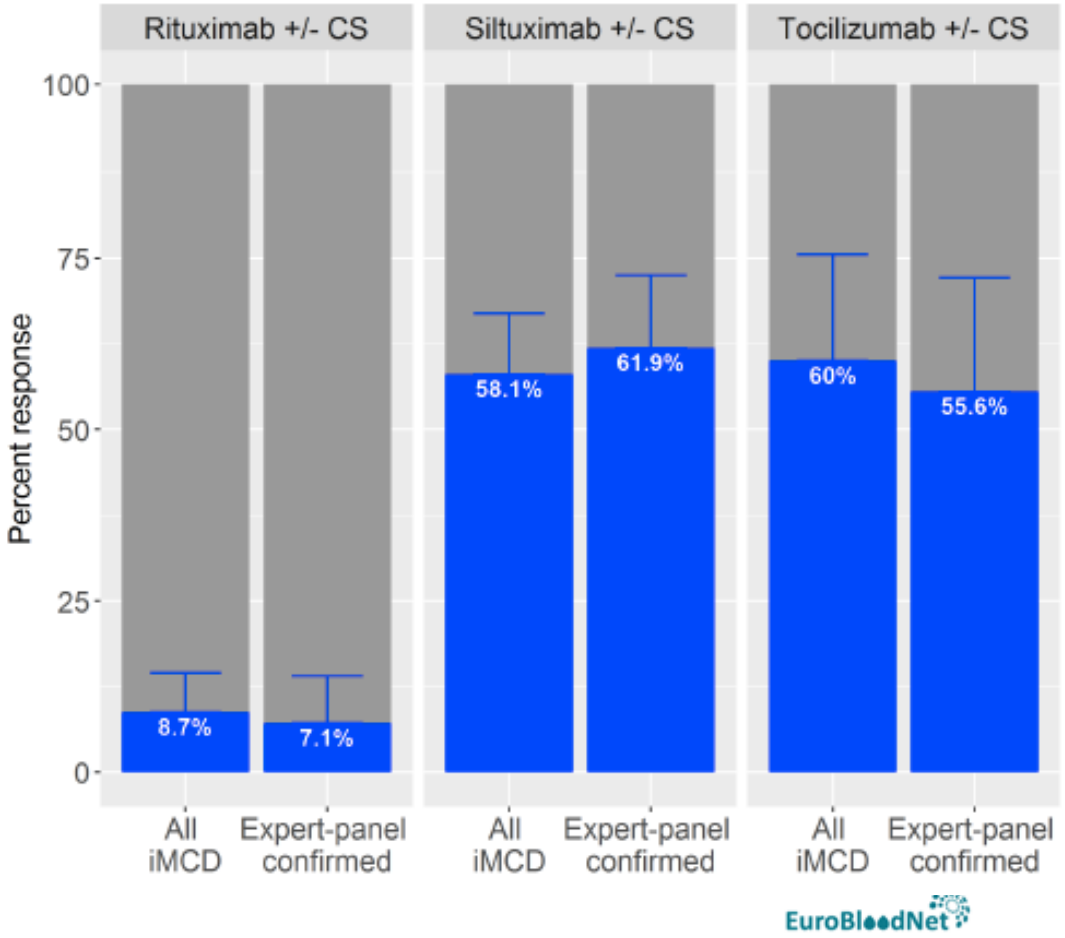


Figure retrieved from Salles G, Adv Ther. 2017

Natural History Study of Idiopathic Multicentric Castleman Disease Identifies Effective Treatments for a Large Proportion of Patients but Treatment-Refractory Patients Remain

Sheila K Pierson, MS, Yue Ren, Johnson Khor, Eric Haljasmaa, Jasira Ziglar, Katherine Floess, Erin NaPier, Faizaan Akhter, Amy Y Liu, Damilola Gibson, Karan Kanhai, MD PhD, Rabecka Martin, PhD, Amy Chadburn, MD, Gordan Srkalovic, MD PhD, Megan S. Lim, MD PhD, Corey Casper, MD MPH, Thomas S. Uldrick, MD MS, Elaine S. Jaffe, MD, Frits van Rhee, MD PhD, Hongzhe Lee, PhD, David C Fajgenbaum, MDMBA,MSc

- Among 37 expert-confirmed iMCD patients, we found:
  - 58% response (11/19) to regimens inclusive of siltuximab,
  - 47% (8/17) to those inclusive of tocilizumab,
  - 27% (7/26) to those inclusive of rituximab.
- Further, in these patients:
  - siltuximab±CS induced response in 11/16 (69%),
  - tocilizumab±CS induced response in 3/6 (50%),
  - rituximab±CS induced response in 1/6 (17%) patients.
- In this cohort **Siltuximab and Tocilizumab demonstrated similar response**.



European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

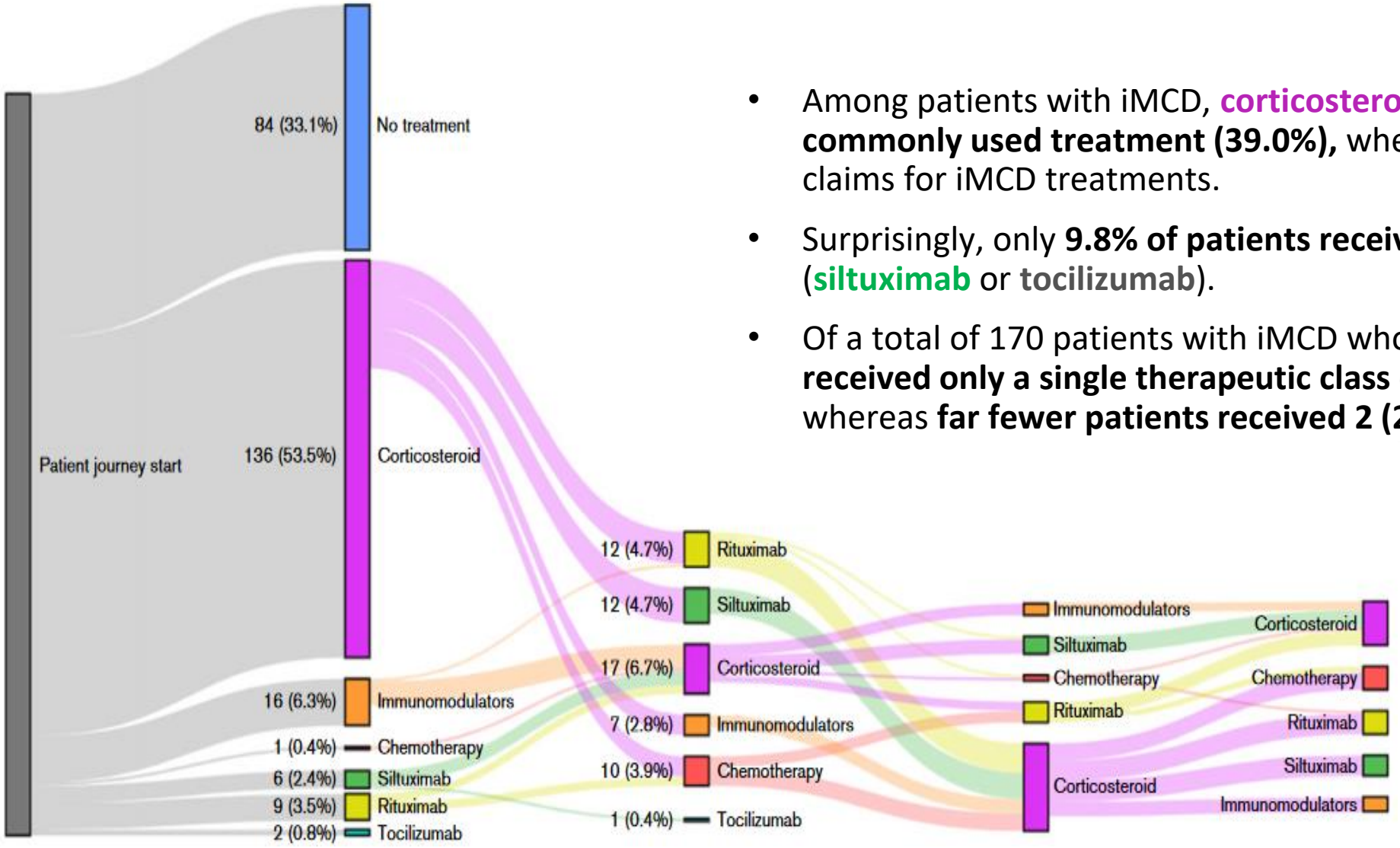
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6–directed therapy

blood advances

Sudipto Mukherjee,[1] Rabecka Martin,[2] Brenda Sande,[2] Jeremy S. Paige,[3] and David C. Fajgenbaum[4]

[1]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]EUSA Pharma, Burlington, MA; [3]Eversana, LLC, Milwaukee, WI; and [4]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA



- Among patients with iMCD, **corticosteroid monotherapy was the most commonly used treatment (39.0%),** whereas 33.1% of patients had no claims for iMCD treatments.
- Surprisingly, only **9.8% of patients received an IL-6–targeted therapy** (**siltuximab** or **tocilizumab**).
- Of a total of 170 patients with iMCD who received any therapy, **65.3% received only a single therapeutic class** during the study period, whereas **far fewer patients received 2 (24.4%) or 3 classes (9.5%).**

iMCD – Other treatments

blood

CLINICAL TRIALS AND OBSERVATIONS | APRIL 18, 2019

Phase 2 study using oral thalidomide-cyclophosphamide-prednisone for idiopathic multicentric Castleman disease

Clinical Trials & Observations

Lu Zhang, Ai-lin Zhao, Ming-hui Duan, Zhi-yuan Li, Xin-xin Cao, Jun Feng, Dao-bin Zhou, Ding-rong Zhong, David C. Fajgenbaum, Jian Li

The TCP regimen administered for 2 years or until treatment failure.

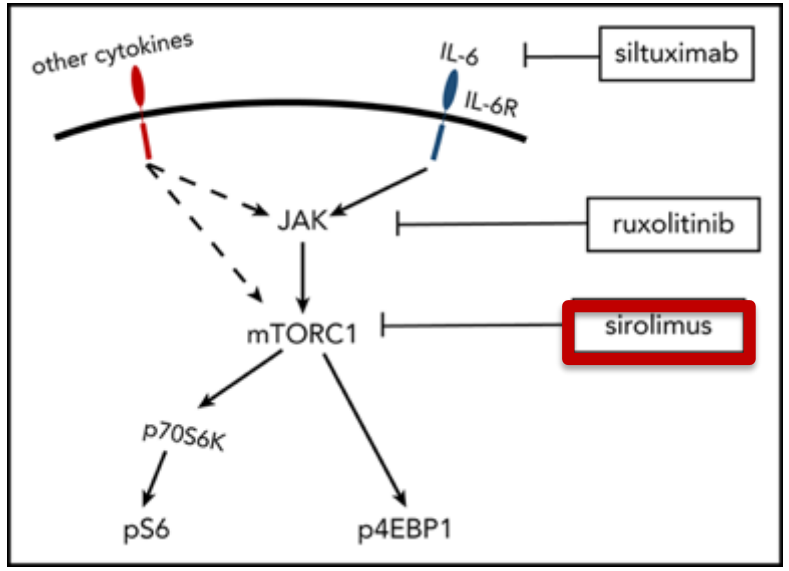
- Thalidomide 100 mg daily for year 1 and year 2;
- Oral cyclophosphamide 300 mg/m2 of a 4-week cycle for year 1;
- Prednisone 1 mg/kg twice a week of a 4-week cycle for year 1

blood

LYMPHOID NEOPLASIA | MAY 7, 2020

Increased mTOR activation in idiopathic multicentric Castleman disease

Daniel J. Arenas, Katherine Floess, Dale Kobrin, Ruth-Anne Langan Pai, Maya B. Srkalovic, Mark-Avery Tamakloe, Rozena Rasheed, Jasira Ziglar, Johnson Khor, Sophia A. T. Parente, Sheila K. Pierson, Daniel Martinez, Gerald B. Wertheim, Taku Kambayashi, Joseph Baur, David T. Teachey, David C. Fajgenbaum



Sirolimus in Previously Treated Idiopathic Multicentric Castleman Disease

ClinicalTrials.gov Identifier: NCT03933904

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Recruitment Status : Recruiting
First Posted : May 1, 2019
Last Update Posted : November 18, 2021

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

iMCD case presentation

Case diagnosis and treatment

- According to consensus diagnostic criteria, iMCD diagnosis was established.
- iMCD was classified as “nonsevere” (absence of compromised performance status, renal dysfunction, anasarca, severe anemia or pulmonary involvement).
- Siltuximab (11 mg/kg every 3 weeks) was started, with rapid improvement of systemic symptoms and laboratory parameters.
- Computed tomography (CT) scan after 6 months of anti-IL-6 therapy → complete regression of all previously reported adenopathies.
- As we report, patient is still receiving Siltuximab every 3 weeks maintaining a good clinical response.

The reported 50-years-old Caucasian male presented at diagnosis:	
iMCD Diagnosis	Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue
	Elevated CRP (>10 mg/L) or ESR (>15 mm/h)
	Histopathologic lymph node features consistent with the iMCD spectrum
	Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations
	HIV and HHV8 negative
	Elevated IL-6
	ECOG < 2
iMCD Severity	No renal dysfunction
	Neither anasarca or ascites or pleural/pericardial effusion
	No severe anemia
	No pulmonary involvement

Diagnosis of non severe iMCD HHV8/HIV negative

POEMS syndrome vs iMCD

- 72 years old male
- **Medical history:** Obstructive sleep apnea treated with CPAP, secondary polycytemia treat with phlebotomy,
- **Hospitalization (2021)** for suspected lymphoproliferative disorder

Blood test + IF on PB: CD5- CD10- CD23- B lymphocytosis (non-LLC phenotype).

Evidence of lower limbs neuropathic pain

Electroneurography: sensory-moto polyneuropathy (Negative for antibodies anti MAG, GD1A, GD1B, GQ1B, GM1, GM2)

2016 **2017** **2019** **2020**

Clinical status: No symptoms

CT- and PET- scan: multiple lateral cervical, axillary and mediastinal lymphadenopathies (maximum size 3 cm, maximum SUV 11,6)

Lymph node biopsy: presence of atrophic follicles, regressing germinal centres, predominantly composed of follicular-dendritic cells, expansion of mantle zone; prominent vascular proliferation and numerous mature polyclonal plasma cells. Conclusions: compatible with Castelman's disease with hyaline-vascular variant.

Blood test:
- No cytopenia, lymphocytosis
- Normal albumin, CRP, ESR
- IgG 1361 mg/dL
- Serum monoclonal protein IgG kappa and IgG lambda (0,5 g/dL)
- HIV and HHV8 negative

- iMCD major criteria fulfilled
- No minor criteria are fulfilled

POEMS syndrome vs iMCD

- 72 years old male
- **Medical history:** Obstructive sleep apnea treated with CPAP, secondary polycytemia treat with phlebotomy,
- **Hospitalization (2021)** for suspected lymphoproliferative disorder

Diagnosis of POEMS syndrome

Treatment:
6 cycles of lenalidomide + dexamethasone

Clinical response
ENG and clinical improvement of neuropathic symptoms

2021

CT- and PET- scan:
Enlargement (max 5 cm) but stable FDG uptake of lateral cervical and mediastinal lymph nodes

Lymph node biopsy:
- Confirmed histological features of Castelman disease with hyaline-vascular variant
- Marginal lymphoma diagnosis

Blood test:
- Stable values of blood test
- VEGF 6356 pg/ml (normal value < 1500)

Bone marrow biopsy and aspirate
- 20% infiltration of CD20+ CD5- CD10- lymphocytes

iMCD or not iMCD ?

- **Medical history:** breast fibroadenoma, recurrent Herpes simplex infections
- **Hem**
  ade
  cm
- **Axi**
  hyp
  con
  Cas
- **Blo**
  5170/mm^3, normal serum albumin, IgG 1175 mg/dL, CRP and ESR negative, no proteinuria, most common viral infections (including HIV) negative, normal IL-6 levels

Both major criteria without any minor criteria fulfilled

Diagnosis of iMCD is not possible

Table 1. Diagnostic criteria for idiopathic multicentric Castleman disease (iMCD)

Inclusion diagnostic criteria for iMCD	
I. Major Criteria (need both):	
1. Histopathologic lymph node features consistent with the iMCD spectrum	✔
2. Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations	✔
II. Minor Criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion)	
*Laboratory**	
	X
es)	X
unt > 400 k/mL)	X
	X
or > 10 mg/100 ml)	X
1700 mg/dL)	X
	X
	X
	X
4. Eruptive cherry hemangiomatosis or violaceous papules	X
5. Lymphocytic interstitial pneumonitis	X
Select additional features supportive of, but not required for diagnosis	
Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M	X
Diagnosis of other disorders that have been associated with iMCD	X
Reticulin fibrosis of bone marrow (particularly in patients with TAFRO syndrome)	X

iMCD case

- **Medical history:** Obesity, AF, glaucoma
- **Her**
  vas
  sup
  (de
- **Hep**
  rea
  cell
  neg
  dia
- **Blo**
  WB
  mg/
  fun
  con

Both major criteria plus 4 minor criteria fulfilled

↓

Diagnosis of iMCD

↓

Initial clinical improvement with prednisone 12.5 mg/die but new vasculitis relapse after steroids discontinuation

↓

Patient started Siltuximab 11 mg/kg administration every 3 weeks due to recurrent vasculitis

Table 1. Diagnostic criteria for idiopathic multicentric Castleman disease (iMCD)

Inclusion diagnostic criteria for iMCD	
I. Major Criteria (need both):	
1. Histopathologic lymph node features consistent with the iMCD spectrum	✔
2. Enlarged lymph nodes (≥ 1 cm in short-axis diameter) in ≥ 2 lymph node stations	✔
	✔
	✔
> 400 k/mL)	X
	X
> 10 mg/100 ml)	X
0 mg/dL)	X
	✔
	X
	X
	✔
	X
	X
	X
	X

Castleman disease network

AMICA
ASSOCIAZIONE MALATI ITALIANI CASTLEMAN-ODV

CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

Euro Castleman

centre de référence maladies rares
CASTLEMAN

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA
EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet

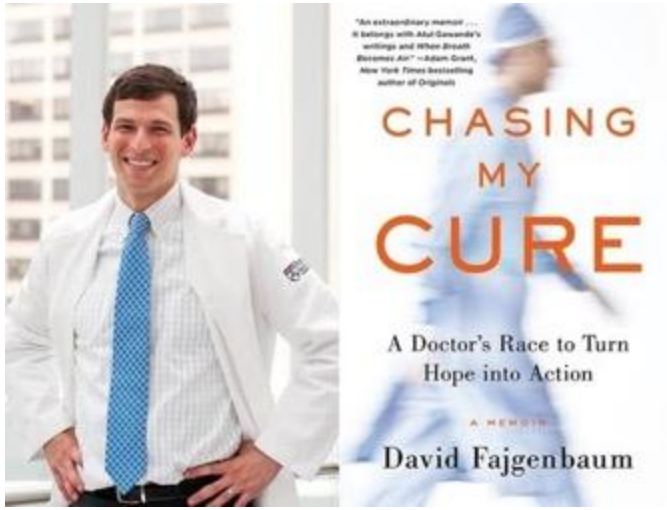
Thanks to….

my Castleman patients

Dr. Simone Ragaini for his precious assistance

AMICA
ASSOCIAZIONE MALATI ITALIANI CASTLEMAN-ODV

CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK



European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet