EHA&EuroBloodNet Spotlight on Castleman Disease
Session 2: Unicentric Castleman Disease

Eric Oksenhendler

University of Paris

1. Imaging and Pathological features of UCD

2. Recent insights on UCD pathogenesis

3. Clinical management and treatment of UCD

www.castleman.eu

Un Réseau membre de la
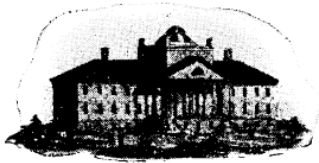Filière de Santé Maladies Rares
MARIH

Consultant for

- EusaPharma

- CSL Behring

CASE RECORDS OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT
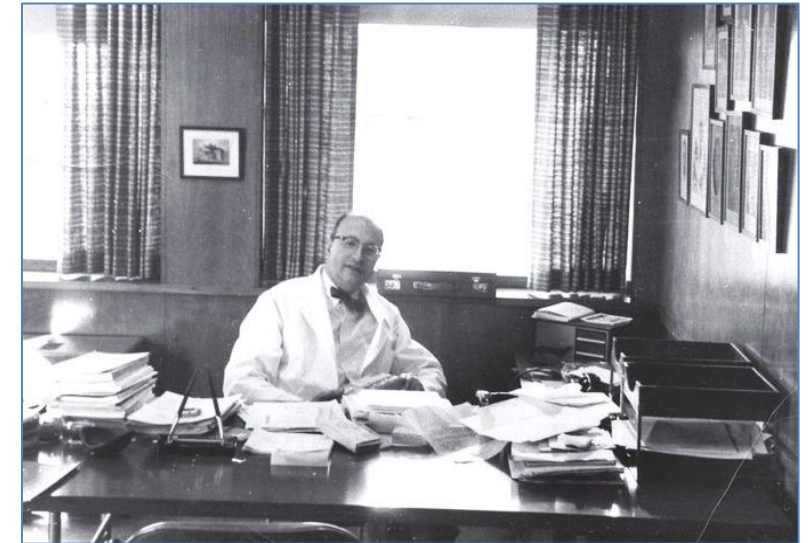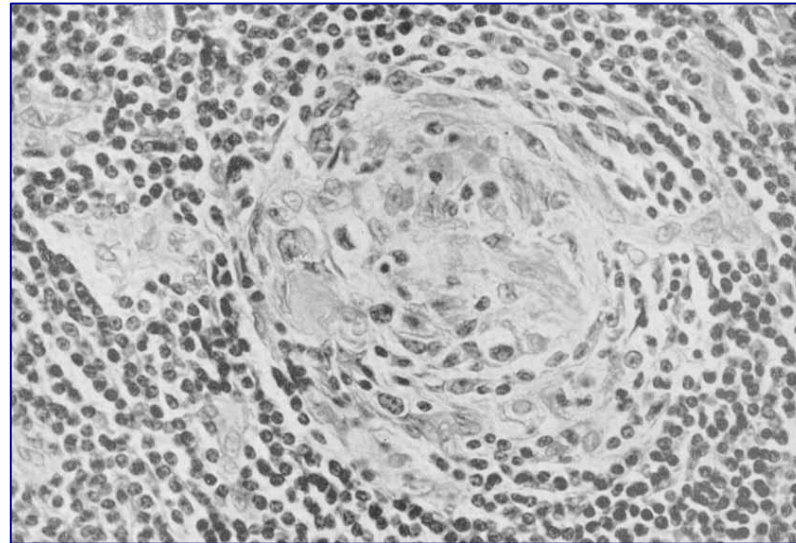
BENJAMIN CASTLEMAN, M.D., *Editor*
VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40011

PRESENTATION OF CASE

A forty-year-old executive was referred to the hospital because a mediastinal mass had been discovered on a survey chest photofluorogram two weeks previously.

Jan 7, 1954

DR. CHAPMAN: This is a new disease syndrome that you are presenting to us!

LOCALIZED MEDIASTINAL LYMPH-NODE HYPERPLASIA
RESEMBLING THYMOMA

BENJAMIN CASTLEMAN, M.D., LALLA IVERSON, M.D., AND V. PARDO MENENDEZ, M.D.

Cancer, 1956

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

- Children or young adults

- Self-examination or incidentally / Imaging

- Chest – Cervix - Abdomen

- Usually asymptomatic

- Compressive symptoms

- Inflammatory symptoms are uncommon

- Complications

Diagnosis

Imaging
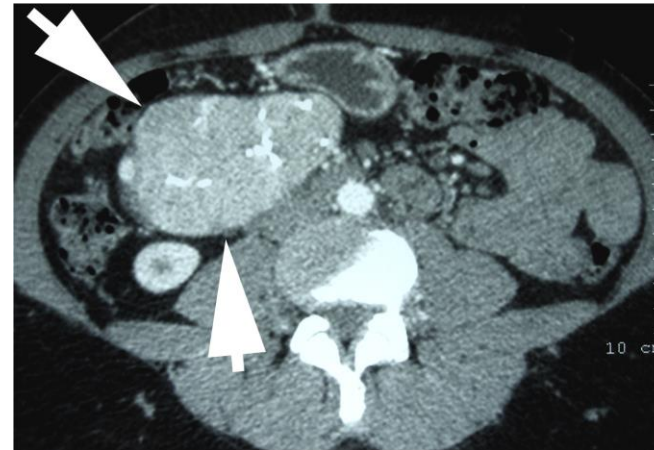
Pathology

Workup

Complications

Pathophysiology

Treatment

- Solitary lesion
- Median ≈ 6 cm
- Clean-cut margins

Non-enhanced CT:

- Uniform density
- Micro-calcifications with central distribution

Contrast-enhanced CT:

- Significant enhancement in the arterial phase
- Continuous enhancement in the portal phase
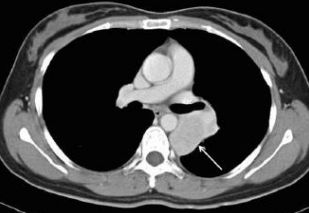
Hypervascular « shining » lesion

UCD

Computed Tomography Classification

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Type	Imaging		Resection	Pathology
I n=5 (8%)	Single mass with smooth margin		Complete 100 %	HV: 100 %
II n=33 (52%)	Single mass with irregular or lobulated margin			
III n=20 (32%)	Single invasive mass with blurred margin		Complete 60 % Partial: 40%	HV: 85 % Mixed: 15 %
IV n=5 (8%)	Multiple fused masses		Partial: 100 %	HV: 80 % PC: 20 %

Adapted from Sun X. et al. Quant Imaging Med Surg, 2021

A Definition based on Histopathology
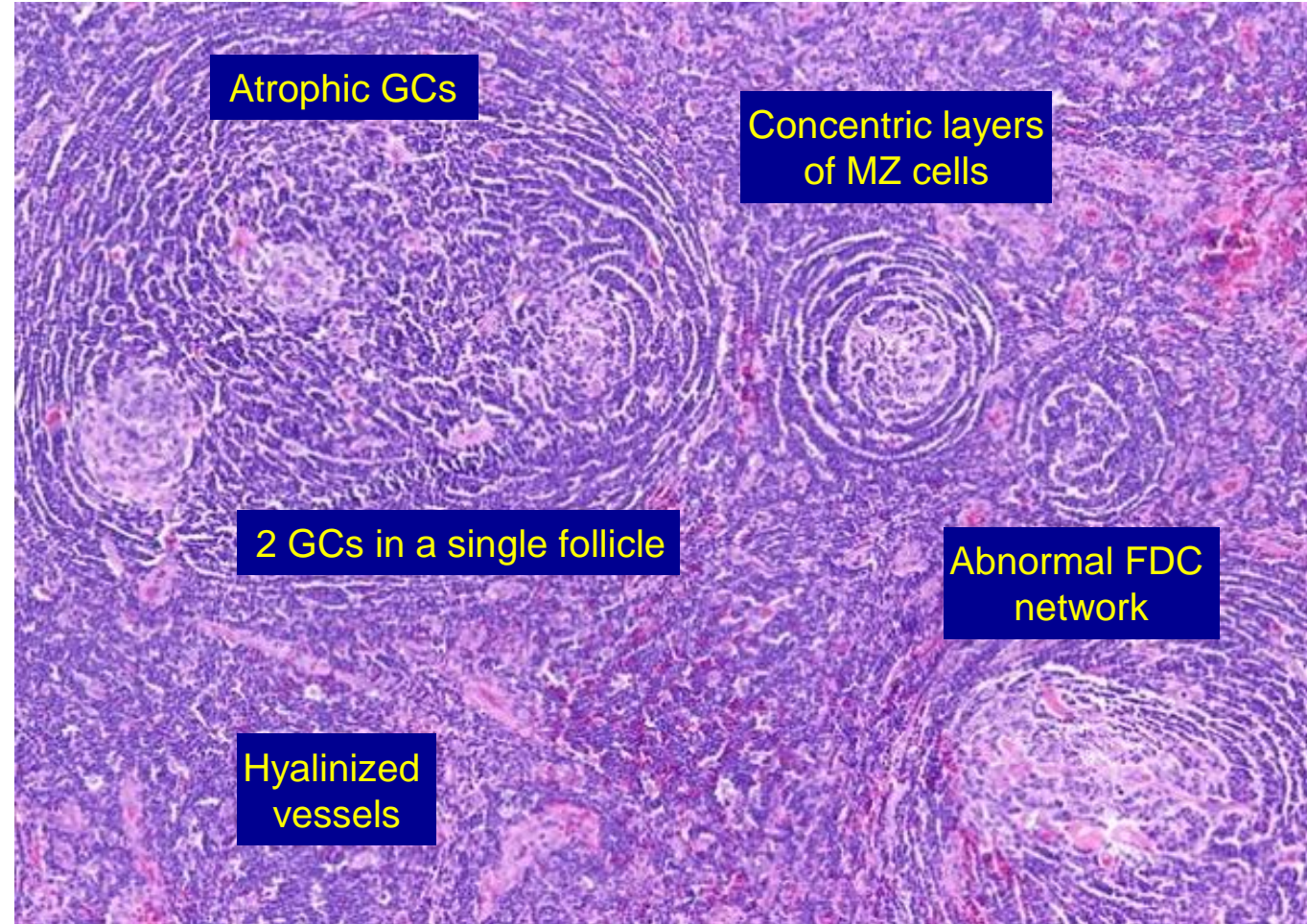
Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Atrophic GCs

Concentric layers of MZ cells

2 GCs in a single follicle

Abnormal FDC network

Hyalinized vessels

@V.Meignin

A Definition based on Histopathology

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

- **Abnormal Germinal Centers**

- Atrophic GCs

- Abnormal FDCs network

- Some follicles contain 2 GCs

  (*Handcuff, Twinning, Budding*)

- Hyalinized penetrating vessels

  (*Lollipop*)

- Interfollicular hypervascularity

- Concentric layers of MZ cells

  (*Onion skin*)

- Variable interfollicular plasmacytosis
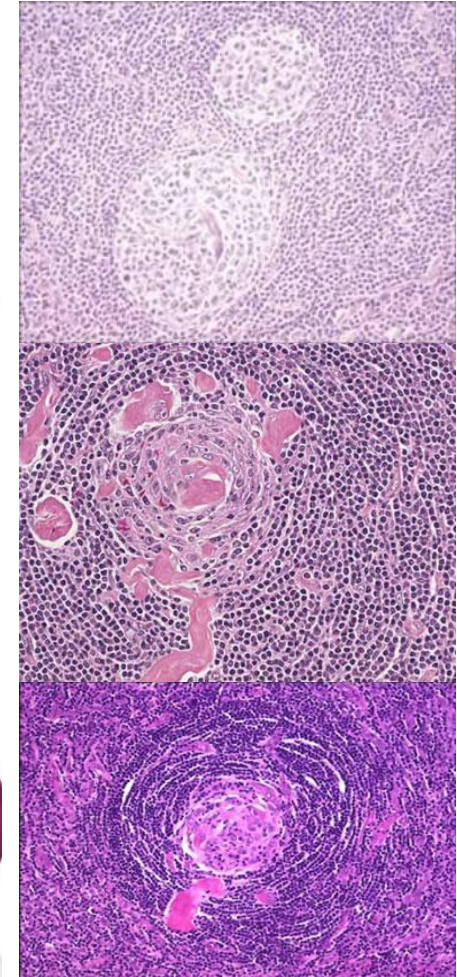
@V.Meignin

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

EHA
EUROPEAN HEMATOLOGY ASSOCIATION

Webinars
EuroBloodNet

1. Review the lymph node pathology

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Hyaline-Vascular Type ≈ 80 %

Plasmacytic Type ≈ 20 %

Atrophic GCs
« Onion-skin » MZ
Hypervascularity
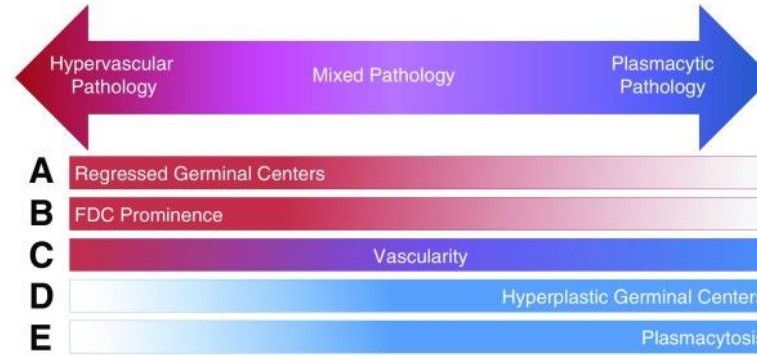
Hyperplastic GCs
Interfollicular plasmacytosis

Fajgenbaum D. et al. Blood 2017

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

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

1. Review the lymph node pathology

Diagnosis

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Pathology

Workup

Complications

Pathophysiology

Treatment

Follicular Dendritic Cell Sarcoma ?

- Proliferation of spindle cells arranged in a fascicular or storiform pattern
- Tumor cells with ovoid vacuolated nuclei and pale eosinophilic cytoplasm

1. Review the lymph node pathology

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Plamacytoma or low-grade lymphoma ?
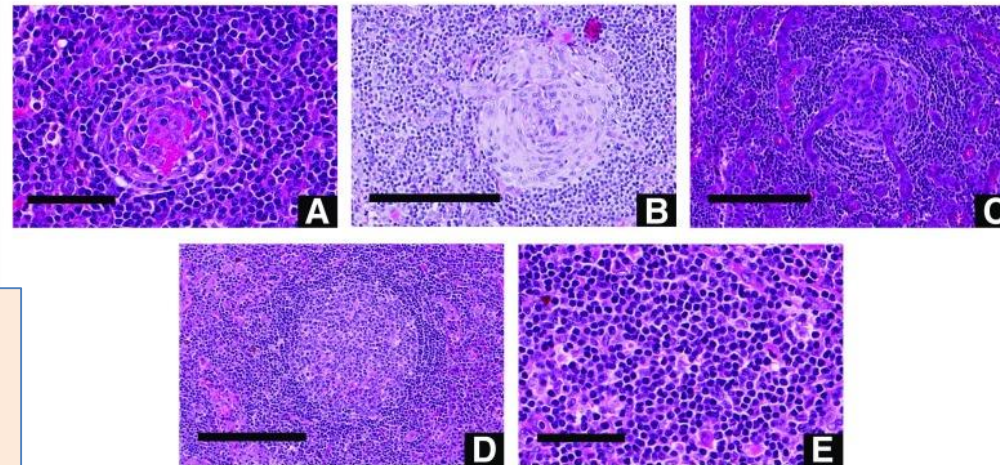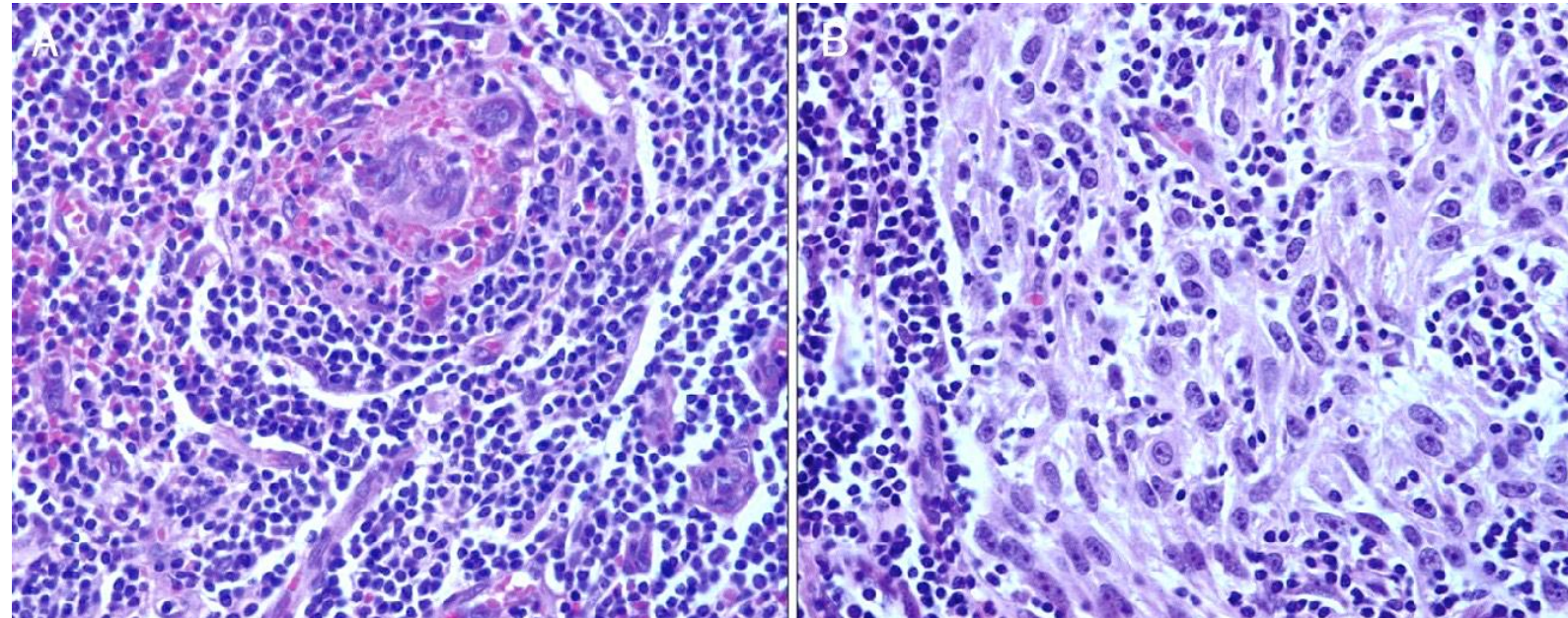

kappa

lambda

IgG

IgA
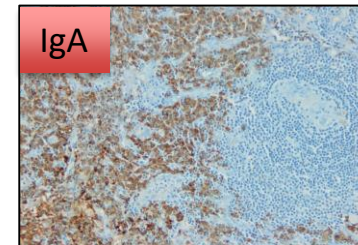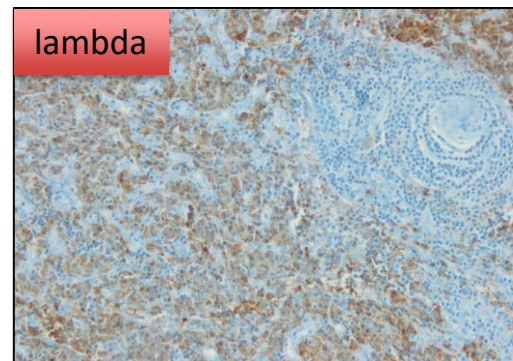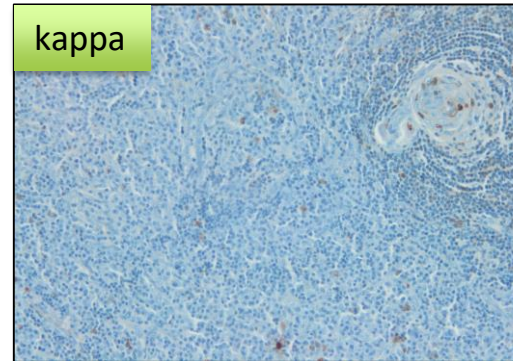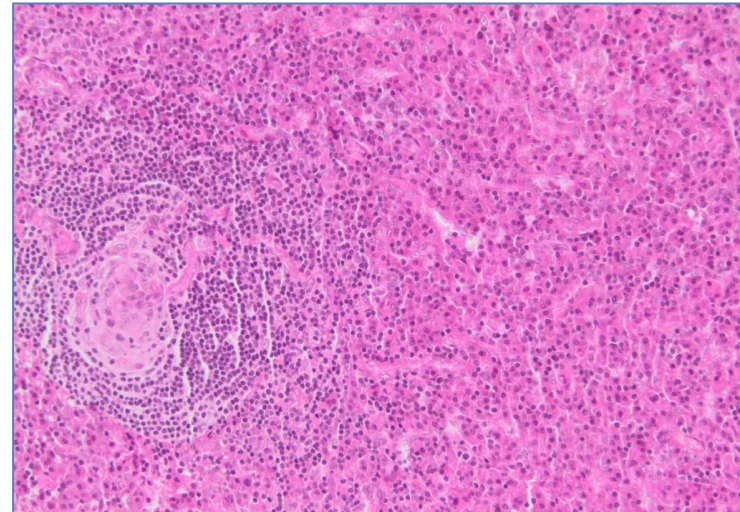
2. Imaging: CT and/or PET-CT

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Unicentric CD
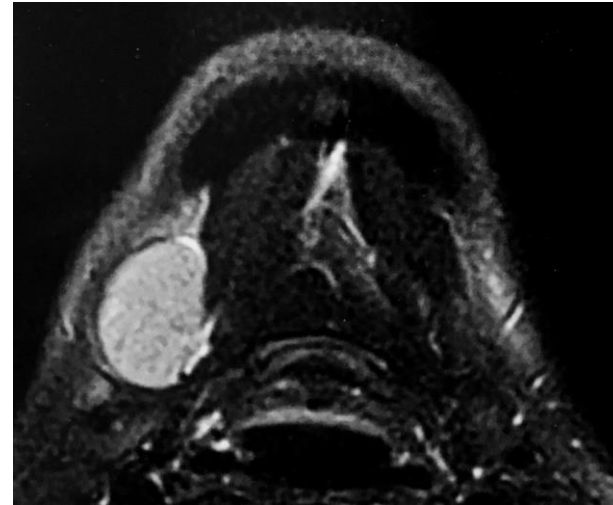
Oligocentric or regional CD

@E.Oksenhendler

One single lesion
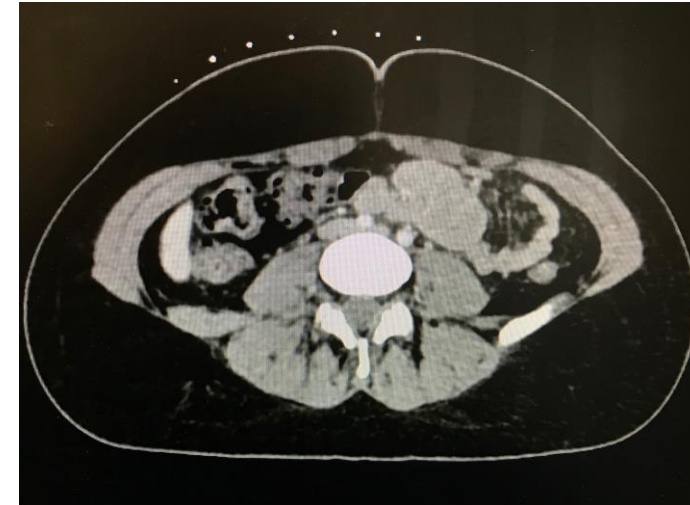
Multiple adjacent lesions in the same lymphoid region

3. **Inflammation ?**

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

- « B » symptoms ?
- Fatigue
- Lymphadenopathy
- Splenomegaly

Usually Absent

- Skin lesions
- Oral lesions
- Respiratory symptoms (PNP)
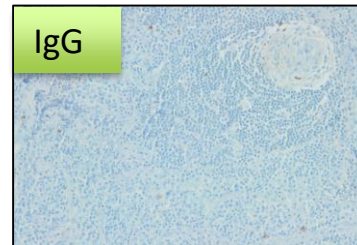
Usually
Normal or Negative

- Blood counts
- Serum CRP
- Serum protein electrophoresis
- Immunofixation

- Liver tests
- Ferritin
- Kidney function & proteinuria

- aDsg1-3
- aAChR & aMuSK

- Serum IgG4
- ANA
- aSSA
- DAT
- VEGF

	Total
number	**118**
Sex M / F	54 / 64
Age (median) years	43,5
Localization	
Mediastinum	34
Abdominal	33
Cervical	30
Axillary	8
Inguinal	6
Extranodal	6
Not specified	1
Fever	6
Complications	
Splenomegaly	2
Edema/Effusion	2
Lung	15
Skin	10
Kidney	2
PNP	8
Polyneuropathy	3
AIHA	1
AITP	3
Hemoglobin (median, g/dL)	13.5
Platelets (median, x10^6/L)	270500
CRP (median, mg/L	2
≥ 10 mg/L	**22 (20,5%)**
Serum albumin (median, g/L)	43.9
Gammaglobulin (median, g/L)	11.8
Follow-up (median, months)	20
Lymphoma during Follow-up	1
Deaths	2

Updated from Boutboul D. et al. Br J Haematol, 2019

« Grey » zones

Several lymph nodes in a single area
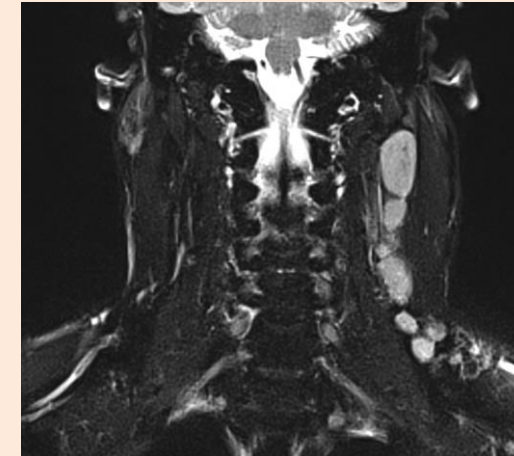
@E.Oksenhendler

Plasma Cell type

Symptomatic disease

- Inflammation
- Failure to thrive
- Autoimmunity

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

UCD

	Regional Oligocentric			Plasmacytic type	
	Single lesion	Single station		HV	PC or mixed
number	**86 (73%)**	**32 (27%)**		**91 (77%)**	**27 (23%)**
Sex M / F	40 / 46	14 / 18		41 / 50	13 / 14
Age (median) years	35	38		32	40
Fever	3	3		4	2
Complications					
Splenomegaly	1	1		0	2
Edema/Effusion	1	1		2	0
Lung	10	5		12	3
Skin	7	3		8	2
Kidney	2	0		1	1
PNP	6	2		7	1
Polyneuropathy	1	2		0	3
AIHA	0	1		0	1
AITP	2	1		2	1
Hemoglobin (g/dL)	13.8	12.8		13.7	12.85
Platelets (x10^6/L)	260500	283500		268000	305000
CRP (median, mg/L	2	5		2	10,5
≥ 10 mg/L	13 (17%)	**9 (31%)**		10 (12%)	**12 (54,5%)**
Serum albumin (g/L)	44	42		44	41.5
Gammaglobulin (g/L)	11.7	11.8		11.5	12.7
Follow-up (months)	16.5	34.5		15	45
Lymphoma during F-up	1	0		0	1
Deaths	0	2 *PNP *BOOP, AML		1 *PNP	1 *BOOP, AML

UCD

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

HV
Single lesion
Asymptomatic

PC
or
Inflammation

Regional
or
Complication

Surgery
straight forward

Consider as
« localized iMCD »

Surgery still an option

Specific
Management

Paraneoplastic Pemphigus (PNP)

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment
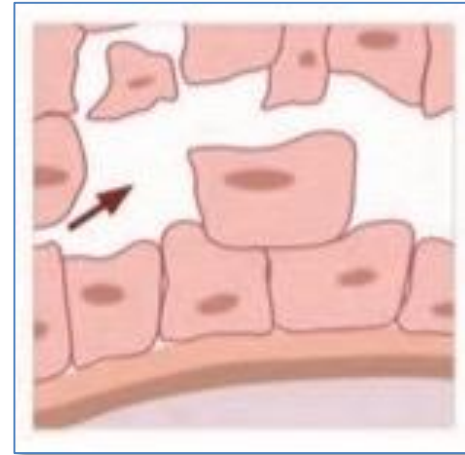
Table 1 Autoantigens of paraneoplastic pemphigus (PNP) and detection methods.

Autoantigen	MW (kD)	Detection method
Plectin	500	IP+IB
Desmoplakin I	250	IP or IB
BP230	230	IP or IB
Desmoplakin II	215	IP or IB
Envoplakin	210	IP or IB
Periplakin	190	IP or IB
Unknown	170	IP
Dsg1	160	ELISA
Dsg3	130	ELISA

MW=molecular weight; IP=immunoprecipitation; IB=immunoblotting; ELISA=enzyme-linked immunosorbant assay; Dsg=desmoglein.
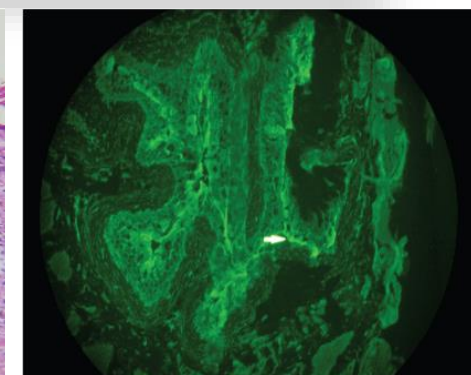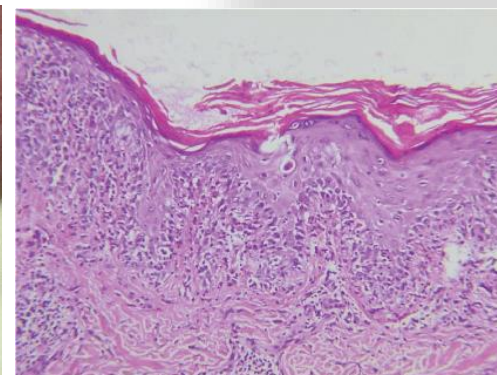
Lee SE. Dermatologica sinica, 2010

Paraneoplastic Pemphigus (PNP)

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

More frequent in China?

- Usually precedes UCD diagnosis
- **Skin and mucous lesions**
- **Severe lung disease (BO)**

- More frequent with « stroma-rich » HV UCD or FDCS

Wang L. et al am J Clin Pathol 2020

- Intensive specific therapy before Surgery

Other complications

- Diagnosis
- Imaging
- Pathology
- Workup
- Complications
- Pathophysiology
- Treatment

- Myasthenia gravis

- Autoimmune cytopenia

- Glomerular Nephropathy / Thrombotic Microangiopathy

A clonal disease ?

- No BCR or TCR rearrangement

- Clonal cytogenetics abnormalities

  in stroma cells cultures

- HUMARA monoclonal pattern
  - 22 /28 HV-UCD
  - 3 /3 PC-CD
  - Correlated with tumor size and stromal proliferation

Pauwels P. et al. Am J Surg Pathol, 2000
Chen WC. et al. Cancer genet Cytogenet, 2006
Chang KC. et al. Mod Pathol, 2014

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Transcriptome analysis

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

A.

Upregulation

- **FDC markers** (CXCL13, clusterin)

- **Angiogenesis factors** (LPL, DLL4)

- **Extracellular matrix remodeling factors** (TGFβ, SKIL, LOXL1, IL-1β, ADAM33, CLEC4A)

- **Complement components** (C3, CR2)

- **GC activation markers** (ZDHHC2, BLK)

total = 679 variables

Bulk analysis on whole lymph node

B.

se

eactive

CD

6

C3   CXCL13   CXCR4   FADS3   SKIL   SOX4   SPPL2B   TGFB3   TSC22D3   ZDHHC2

Wing A. et al. Modern Pathol 2021

Webinars
EuroBloodNet
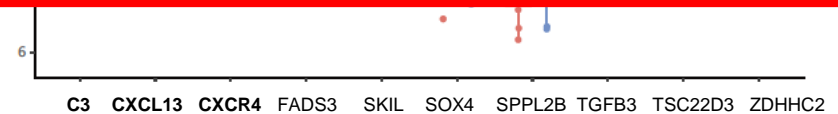
Genetic abnormalities in UCD

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Butzmann A. et al. Biology 2021

Pathways	UCD	iMCD
MAPK pathway	FAS, PDGFRB, FGFR3, NF1, IL6ST, HRAS, KRAS, NRAS, ERBB4, JAK3, BRAF and TGFBR2	PTPRR, ERBB2, FAS, STK3, TGFBR2
Interleukin signaling pathway	PDGFRB, FGFR3, NF1, PIM1, PTPN6, IL6ST, JAK1, HRAS, KRAS, NRAS, JAK2, AKT1, ERBB4, JAK3	ERBB2, JAK2, PTPN6
Chromatin remodeling	none	SETD1A, ASH1L, DOT1L, JAK2, KMT2E, DNMT3A

Somatic mutations in UCD

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment
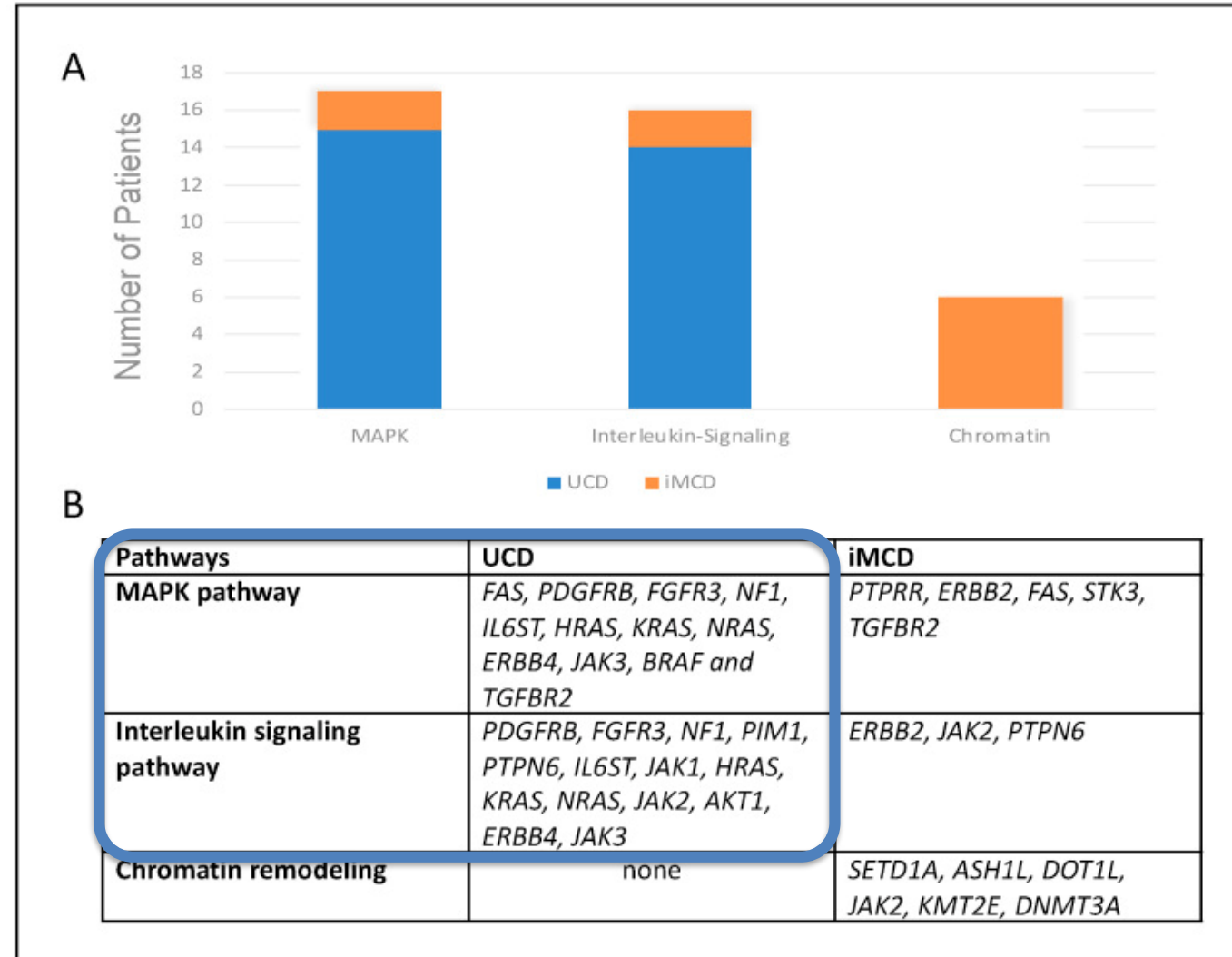
LETTER

Genomics and gene therapy

Recurrent *PDGFRB* mutations in unicentric Castleman disease

Zhaoming Li[1,2] · Xuan Lan[1,2] · Chaoping Li[1,3] · Yanjie Zhang[1,3] · Yingjun Wang[1,3] · Weili Xue[1,3] · Lisha Lu[1,3] · Mengyuan Jin[1,3] · Zhiyuan Zhou[1,3] · Xinhua Wang[1,2] · Ling Li[1,2] · Lei Zhang[1,2] · Xin Li[1,2] · Xiaorui Fu[1,2] · Zhenchang Sun[1,2] · Jingjing Wu[1,2] · Xudong Zhang[1,2] · Hui Yu[1,2] · Feifei Nan[1,2] · Yu Chang[1,2] · Jiaqin Yan[1,2] · Xiaolong Wu[1,2] · Guannan Wang[4] · Dandan Zhang[4] · Yuan Zhang[5] · Ken H. Young[6] · Mingzhi Zhang[1,2]
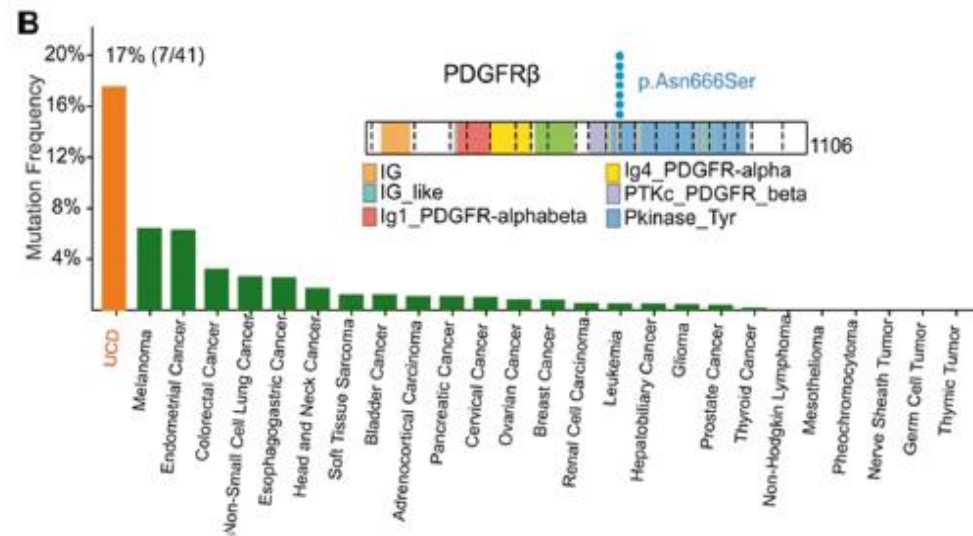
Missense Mutation Asn666Ser

17% of UCD

GOF

Activation of Receptor Kinase Activity

Fibroblasts Transformation

Mutation in CD45neg cells

FDC or FDC precursor ?

EHA
EUROPEAN
HEMATOLOGY
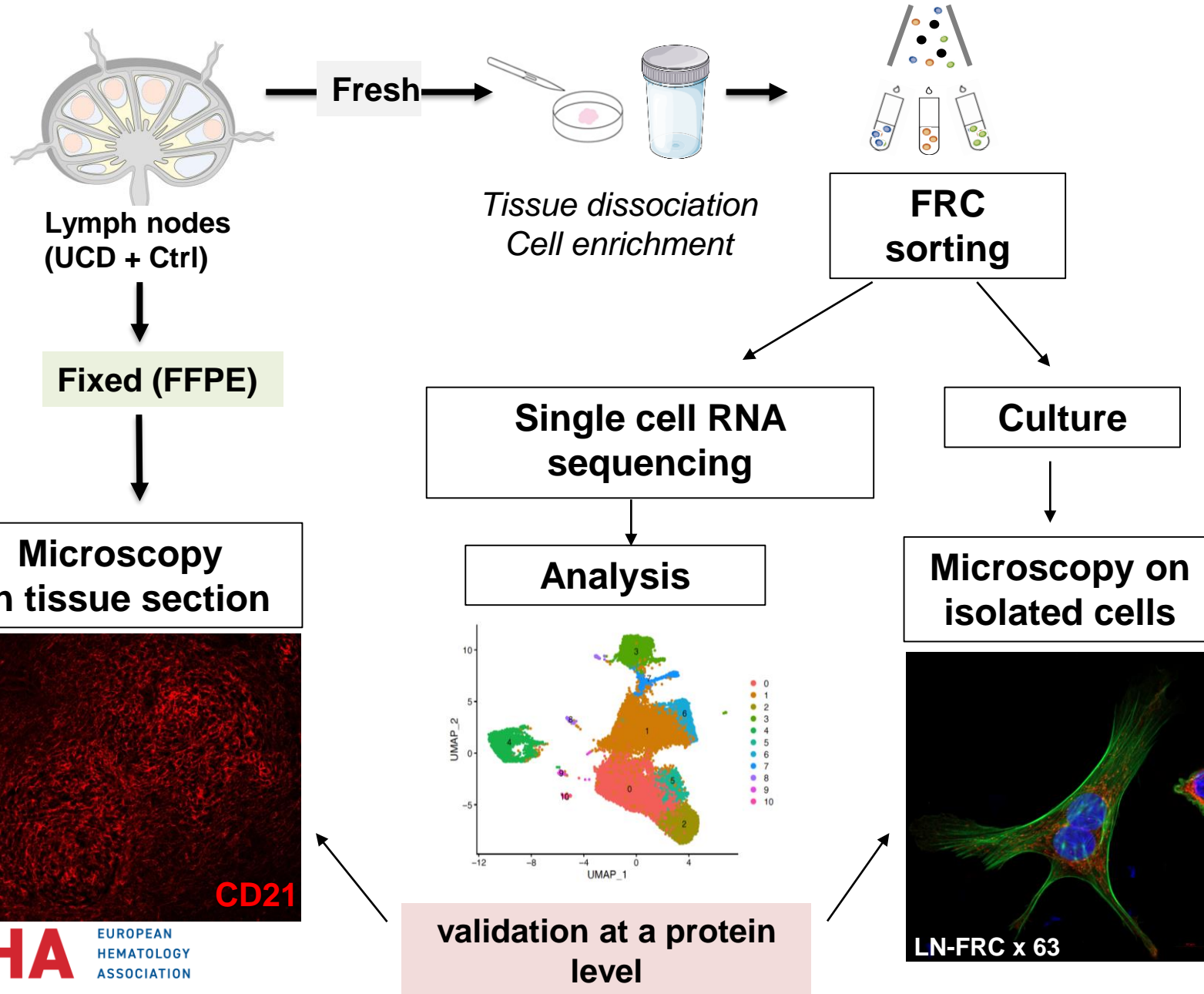ASSOCIATION

Webinars
EuroBloodNet

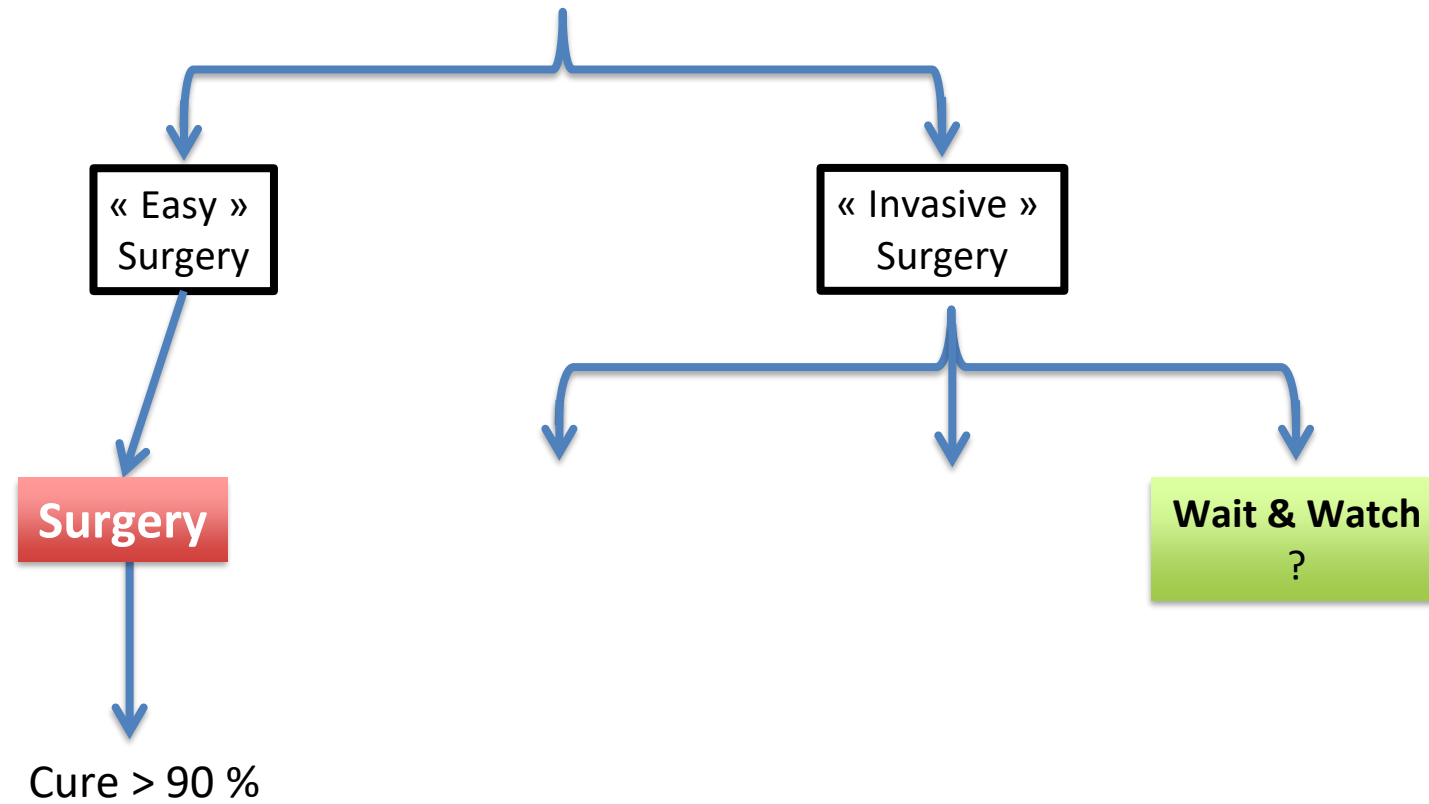# Global strategy for UCD-FRC characterization

U976 HIPI
Justine Poirot
Constance Lahuna
Floriane Noël
David Boutboul

Treatment strategy for UCD

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

« Easy » Surgery

« Invasive » Surgery

Surgery

Cure > 90 %

Wait & Watch ?

Treatment strategy for UCD

Wait & Watch ?

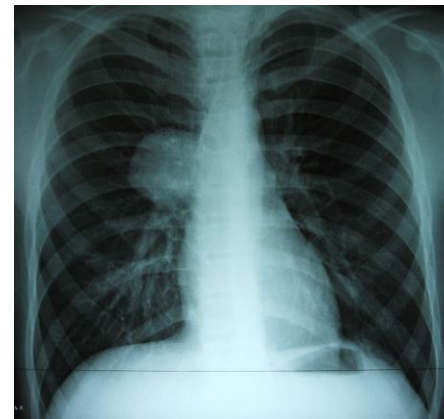Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

2005
13-year-old boy
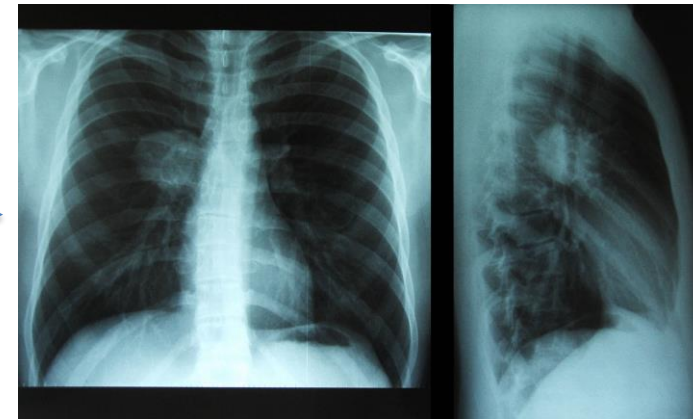« Hunchback »
(Mother thoughted)

No symptoms
Normal blood tests

Biopsy: **CD HV type**

2019
27-year-old man
« Handsome »
(Girlfriend thoughts)
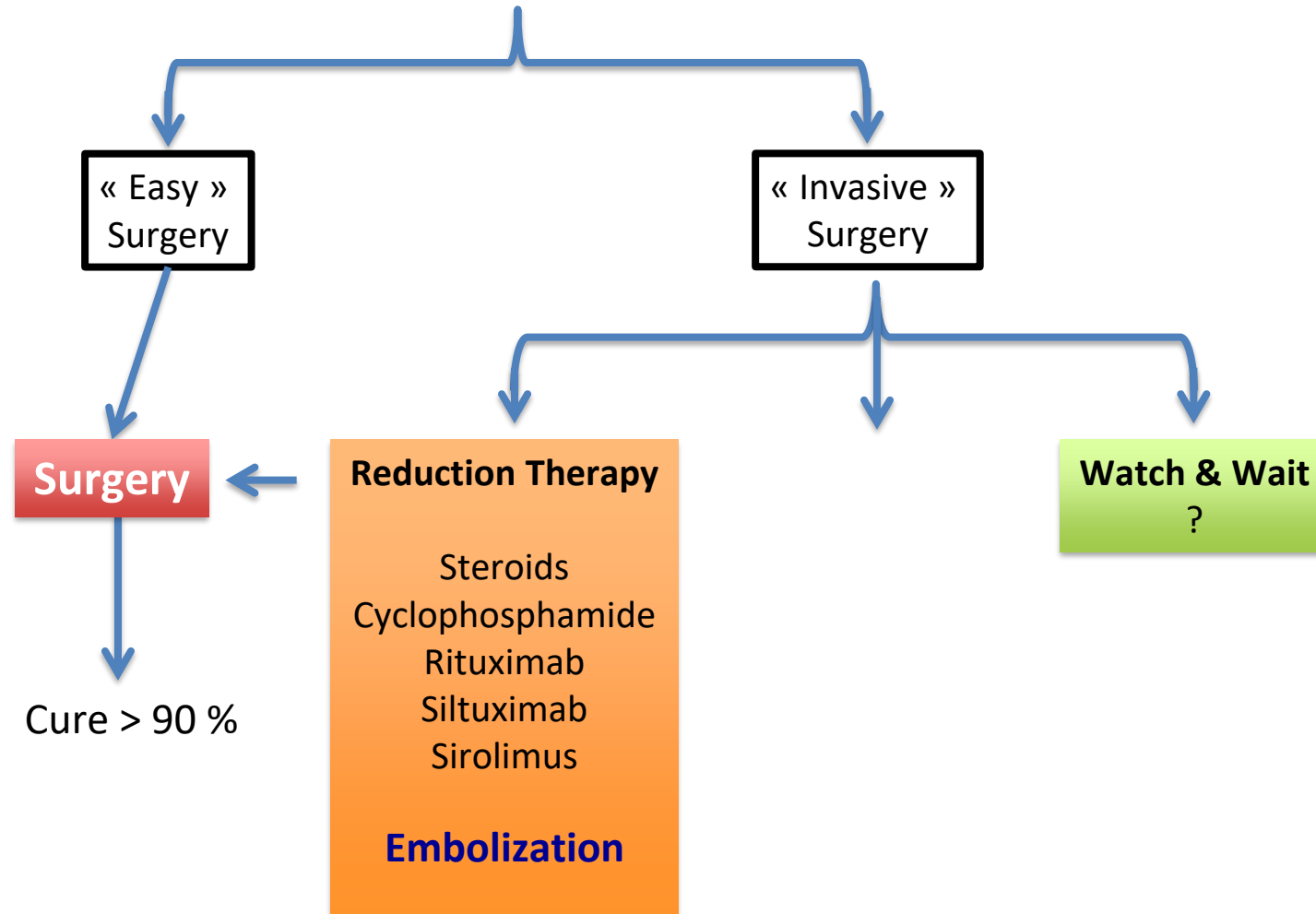

No symptoms
Normal blood tests

No progression

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

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Webinars EuroBloodNet

Treatment strategy for UCD

Diagnosis

Imaging

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Pathophysiology

Treatment

« Easy » Surgery

« Invasive » Surgery

Surgery

Cure > 90 %

Reduction Therapy

Steroids
Cyclophosphamide
Rituximab
Siltuximab
Sirolimus

Embolization

Watch & Wait
?

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Treatment strategy for UCD

Embolization

Diagnosis

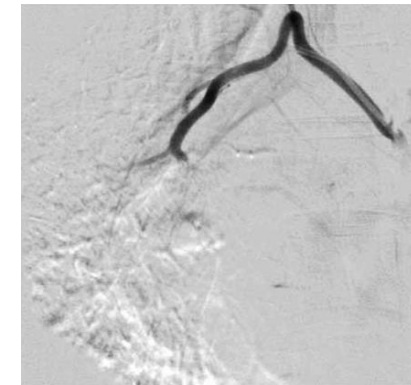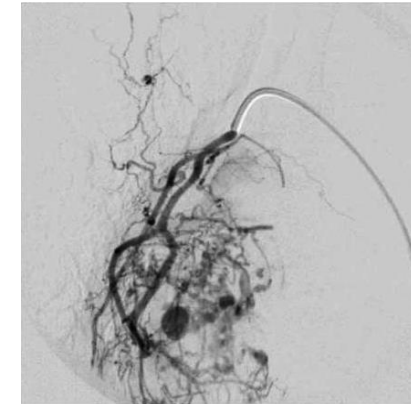**Imaging**

Pathology

Workup

Complications

Pathophysiology

Treatment

UCD is a hyper-vascular tumor

- Vascular blush

- Vascular recruitment of enlarged vessels

- Carefull analysis of all vessels connections before embolization

- Use of small particles to occlude the vessels

- The procedure can be repeated

Treatment strategy for UCD

Embolization

Diagnosis

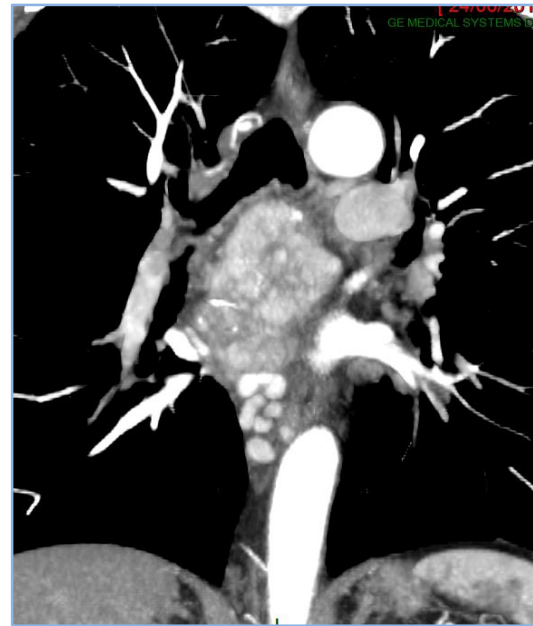Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Occlusion of the vessels that supply the tumor

- PreOp

- Hemostatic

- Therapeutic

Mohan M et al.
Eur J Haematol. 2021
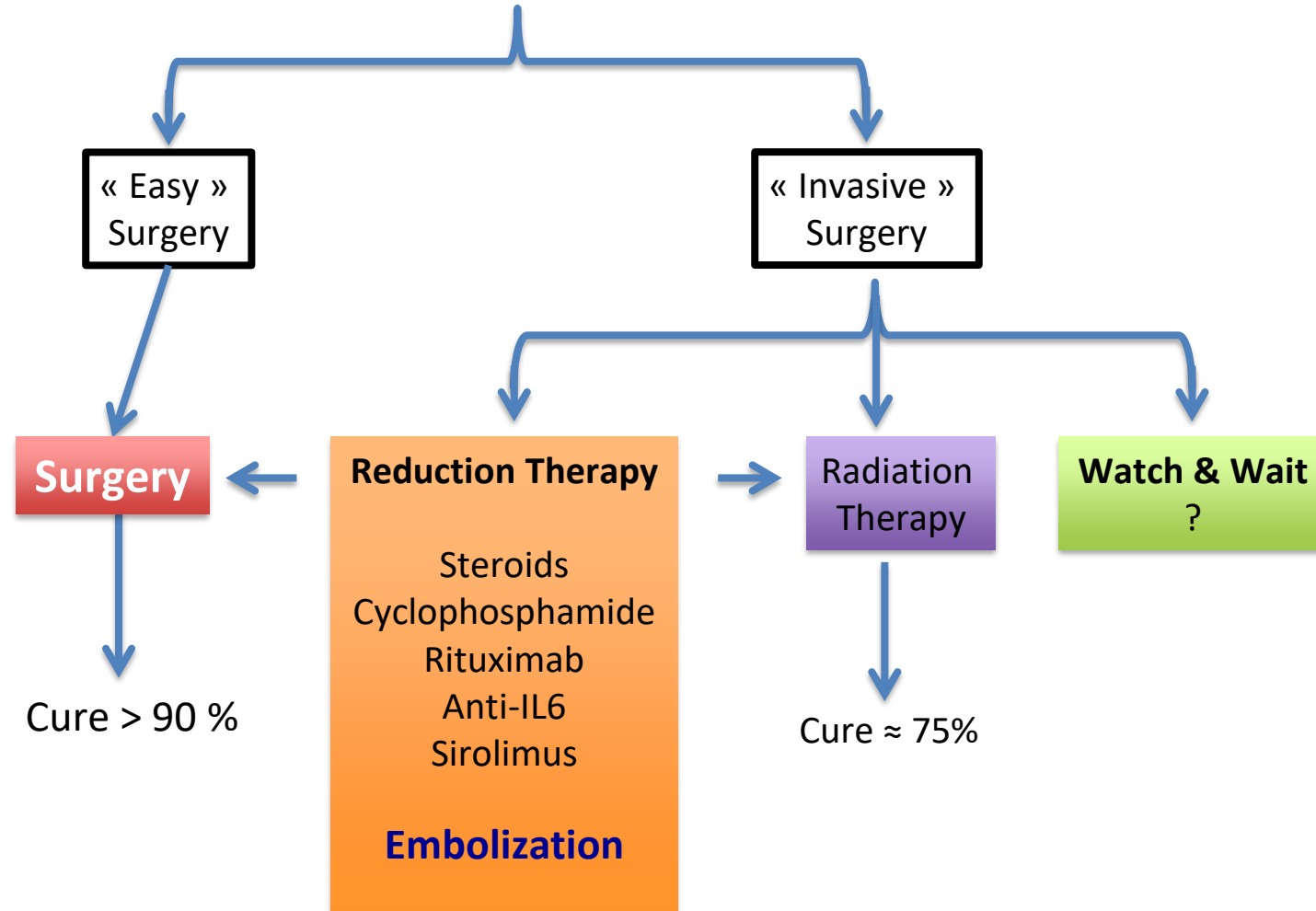

@Antoine Khalil

Treatment strategy for UCD

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

« Easy » Surgery

« Invasive » Surgery

Surgery

Cure > 90 %

Reduction Therapy

Steroids
Cyclophosphamide
Rituximab
Anti-IL6
Sirolimus

Embolization

Radiation Therapy

Cure ≈ 75%

Watch & Wait ?

Treatment of UCD and PNP

Diagnosis

Imaging

Pathology

Workup

Complications

Pathophysiology

Treatment

Risk of severe PNP flare following surgery

Intensive treatment of PNP BEFORE Surgery

Steroids, IVIg, Rituximab

- **Usually asymptomatic** but sometimes compressive single mass,

- **Peculiar signs on imaging** can be suggestive of the diagnosis,

- Should be **systematically looked for after a diagnosis of PNP**,

- **Standard blood tests are usually normal**, but inflammation markers in a subset of patients,

- Surgical biopsy or **complete resection should be prefered** if the diagnosis is suspected,

- **Diagnosis is based on the pathological examination** of the lymph node,

- Possible **clonal disease of FDCs** or FDC precursor,

- **Somatic mutations in PDGFRB gene** or associated pathway (?),

- **Complete resection**, when possible, is the frontline therapy (Cure > 90%),

- **Wait & Watch** is an option in some asymptomatic cases.

David Boutboul

Jehane Fadlallah

Marion Malphettes

Lionel Galicier

Claire Fieschi

Laurence Gérard

Eric Oksenhendler

European Reference Network

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Network
Hematological
Diseases (ERN EuroB_

centre de référence maladies rares

CASTLEMAN