Maladies de Castleman

David BOUTBOUL
Département d'Immunologie Clinique
CNR Maladies de Castleman
U976 HIPI
Hôpital Saint Louis, Paris
david.boutboul@aphp.fr

Université de Paris

CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

Benjamin Castleman (1906-1982)

- Masse médiastinale unique
- « Hyperplasie folliculaire »
- Follicules à centre clair
- Déplétés en cellules centrofolliculaires
- Distribution irrégulière au sein d'une nappe cellulaire polymorphe **richement vascularisée**

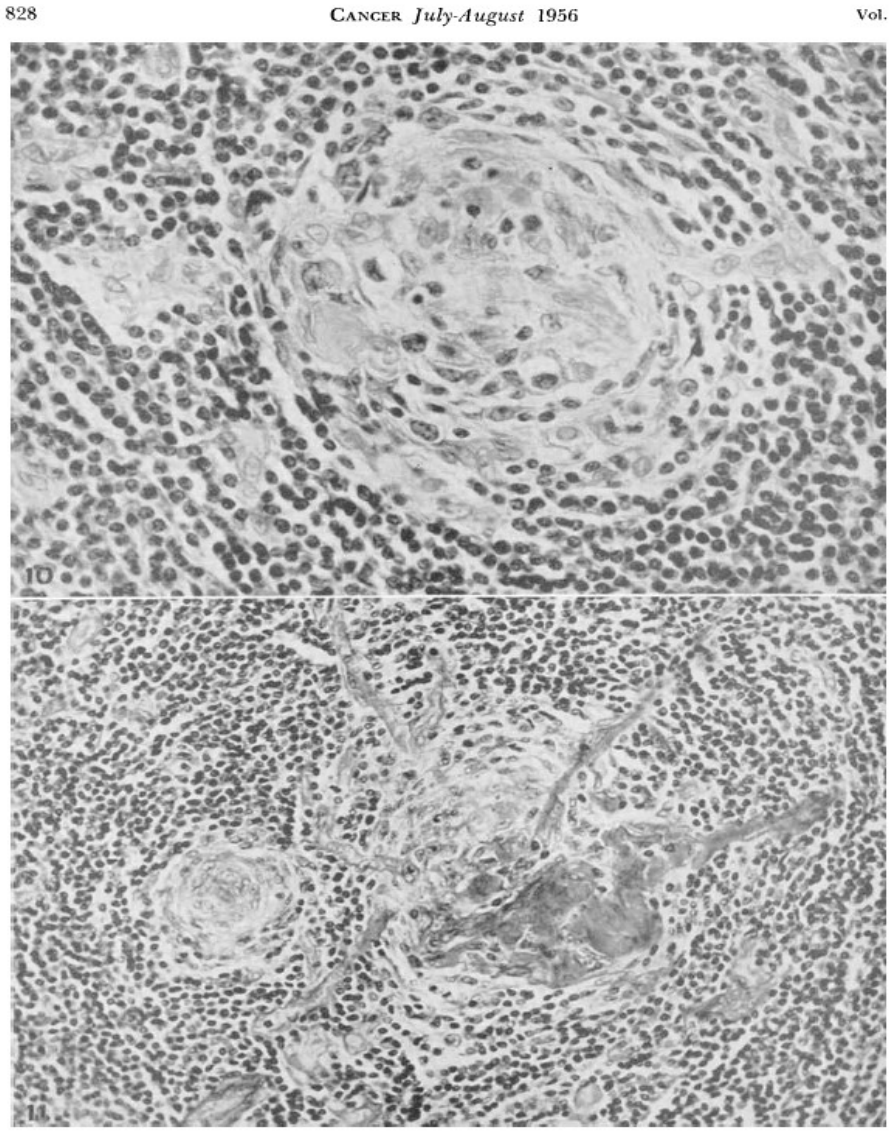
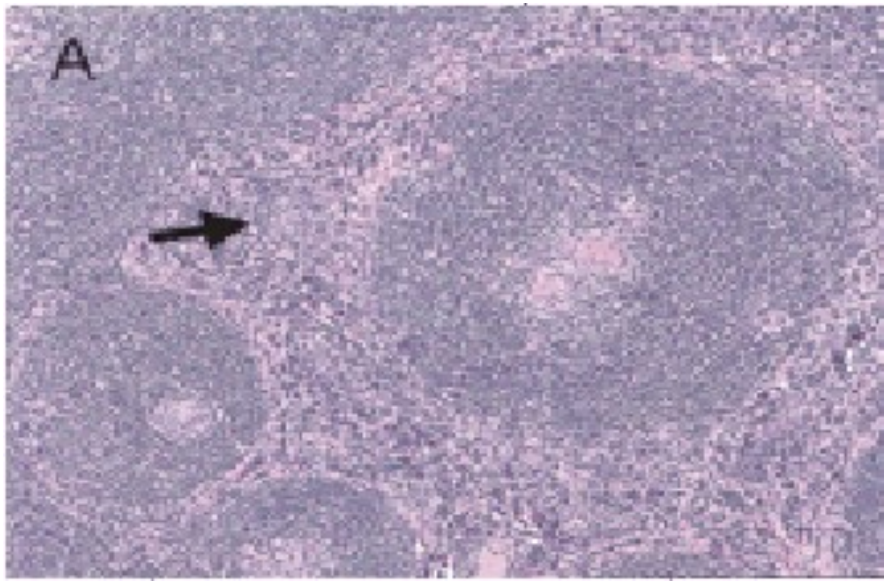


FIG. 10. High magnification showing hyalinization and vascularity of follicle. (×320.)
FIG. 11. High magnification of hyalinized follicle shown in lower right of Fig. 8. The sprouting vessels are well seen. (×325.)

Castleman hyalino-vasculaire - histologie

Centre Germinatif

- Déplétion lymphoïde
- Atrophie des centres germinatifs
- Hyperplasie vasculaire
- FDC en organisation circulaire

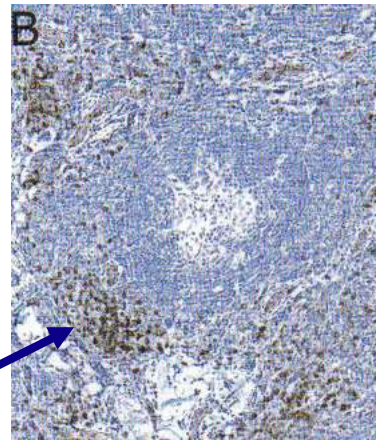


Zone du manteau

- Hyperplasie concentrique lymphocytaire (B)
- Image en « bulbe d'oignon »

Zone inter-folliculaire

- Ly (T) >> Plasmocytes
- Hyperplasie vasculaire avec hyalinisation des parois
- Foyer $\not\subset$ dendritiques plasmacytoides



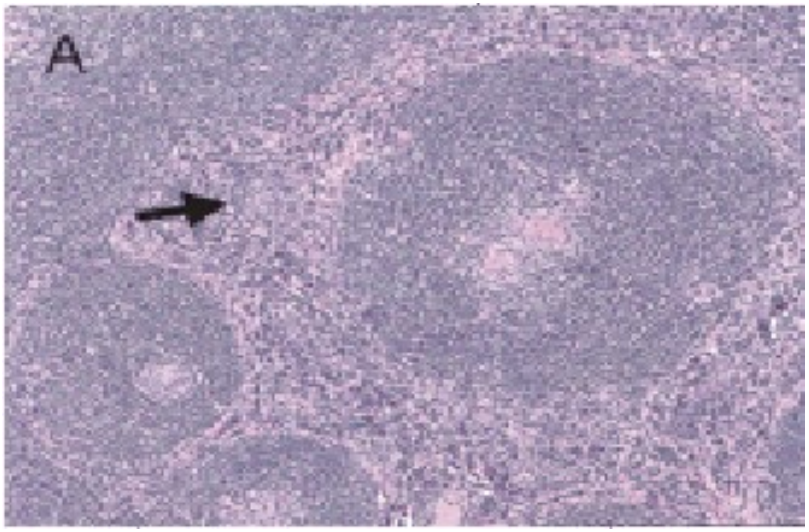
Steven, *ASH* 2004

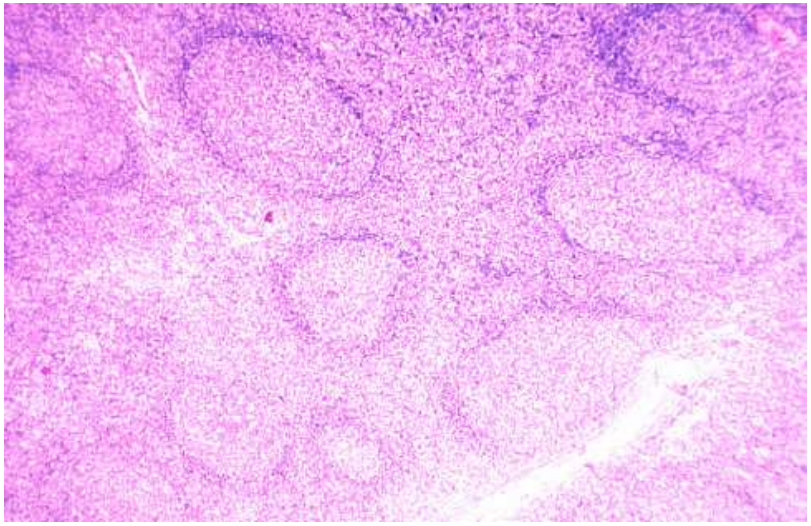
Castleman hyalino-vasculaire

•Majorité des formes localisées

	Total	Single lesion HV	Oligocentric single station HV
Number	71	40	15
Sex Male/Female	32/39	20/20	4/11
Age (median) years	35	35	32
Ethnicity			
Caucasian	52	34	10
Northern Africa	10	2	4
Sub Saharian Africa	7	3	1
Asian	1	1	0
Other	1	0	0
HIV positive	1	1	0
Localisation			
Mediastinum	21	10	8
Abdominal	19	12	1
Cervical	21	11	5
Axillary	3	1	1
Inguinal	3	2	0
Extranodal	4	4	0
Fever	3	0	2

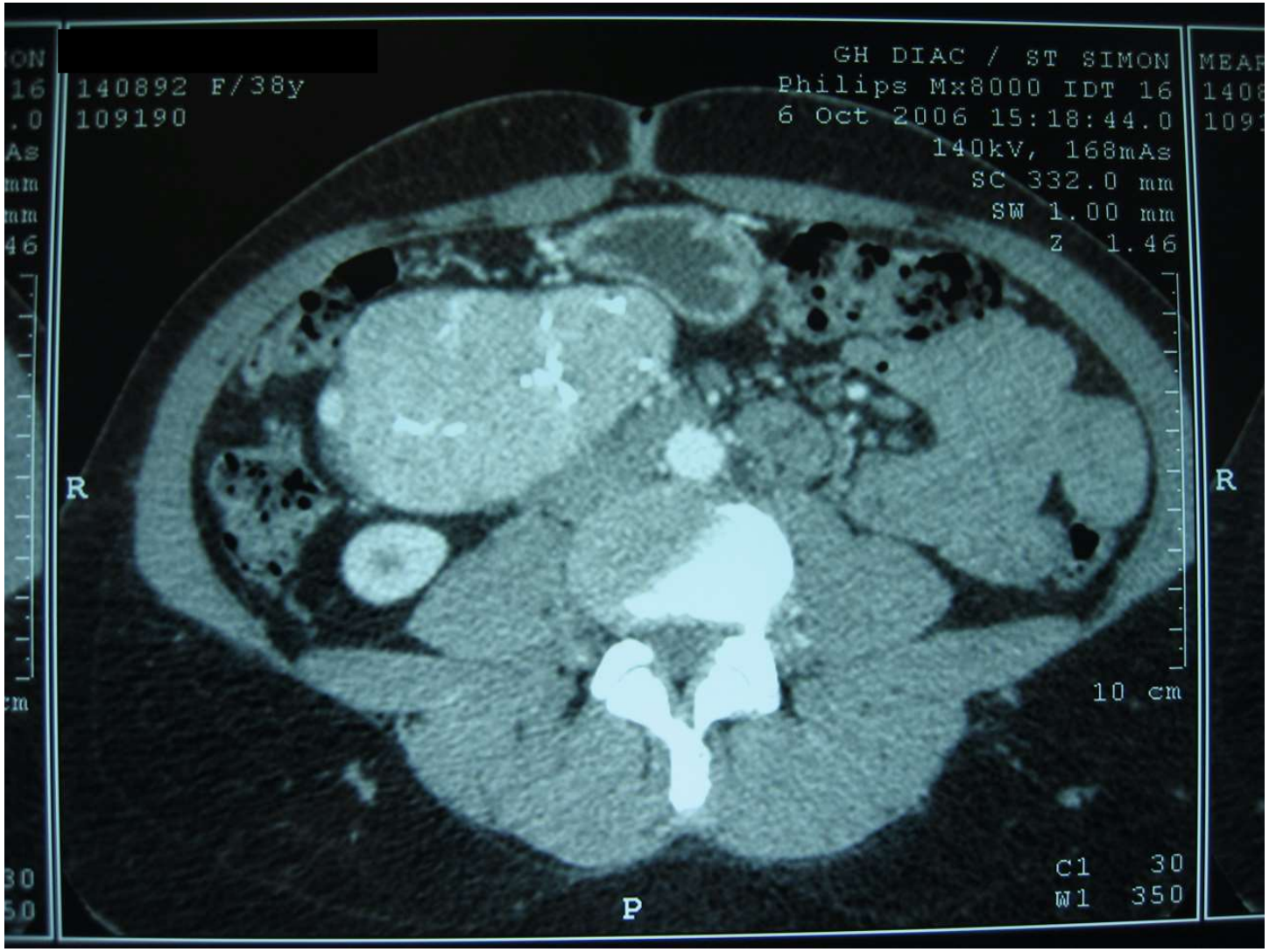
BJH, 2019



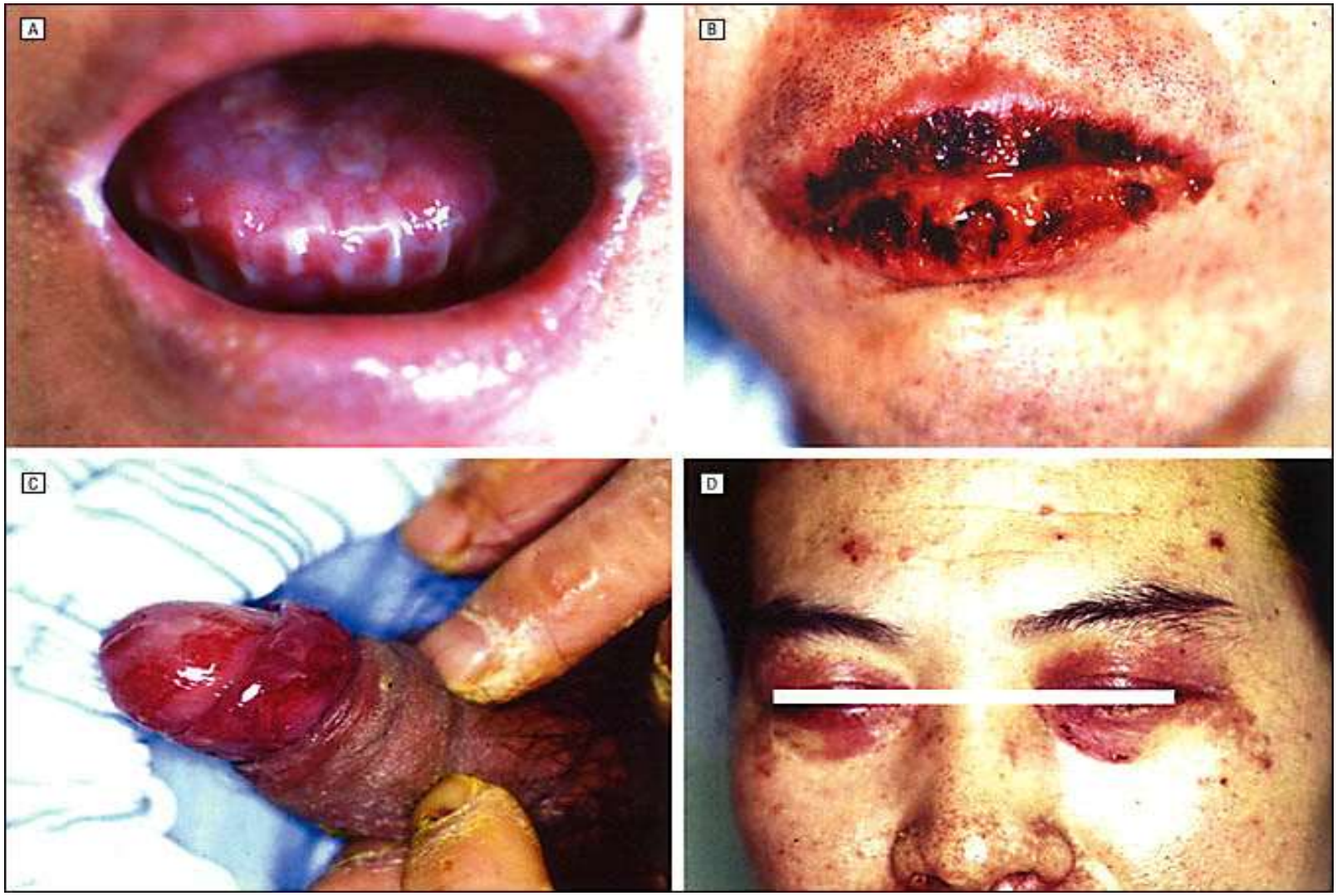


- Peu/pas inflammatoires
- Complications =38% (pemphigus)
- Association à tumeur à cellules folliculaires dendritiques

Castleman hyalino-vasculaire

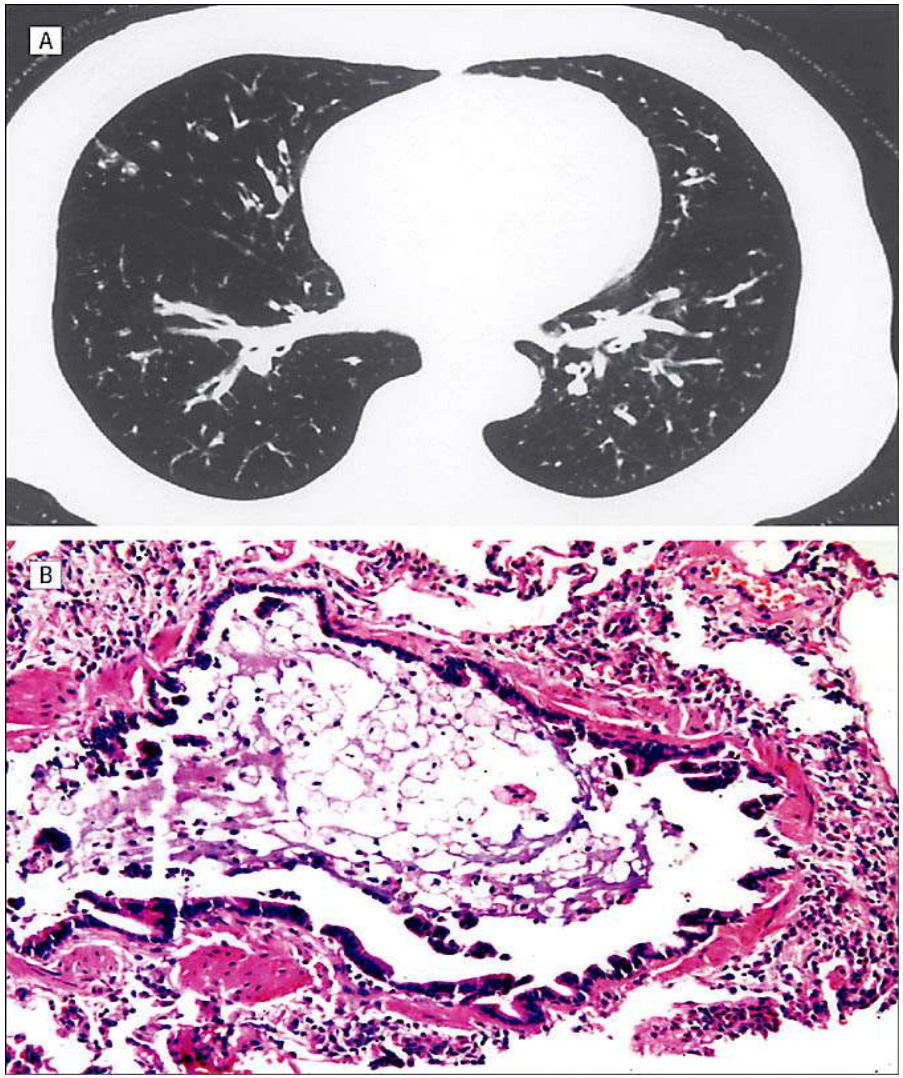


Une complication : le pemphigus paranéoplasique (PNP)



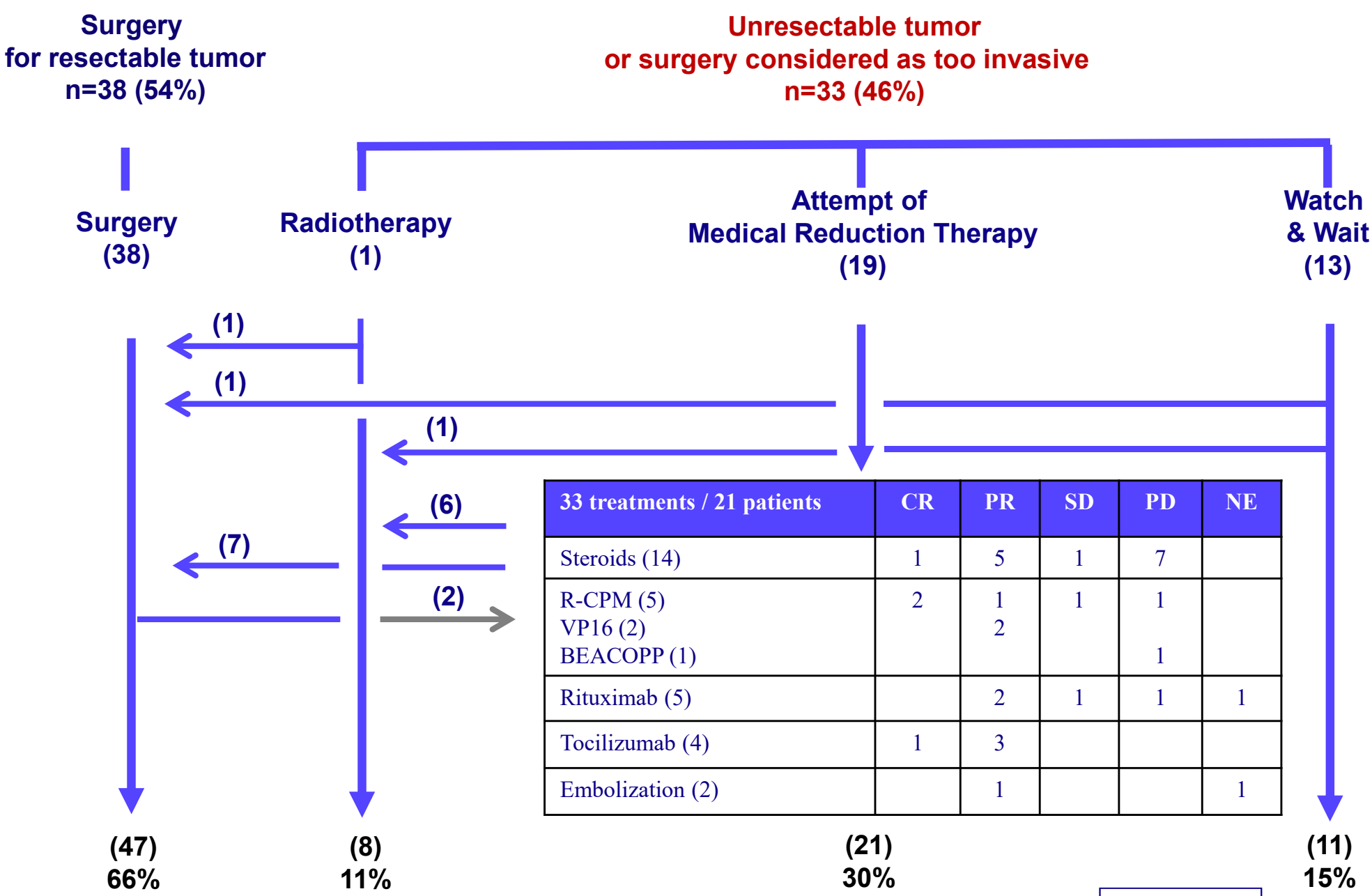
Wang, J. et al. Arch Dermatol 2005;141:1285-1293.

Bronchiolite liée au PNP



Wang, J. et al. Arch Dermatol 2005;141:1285-1293.

Prise en charge thérapeutique

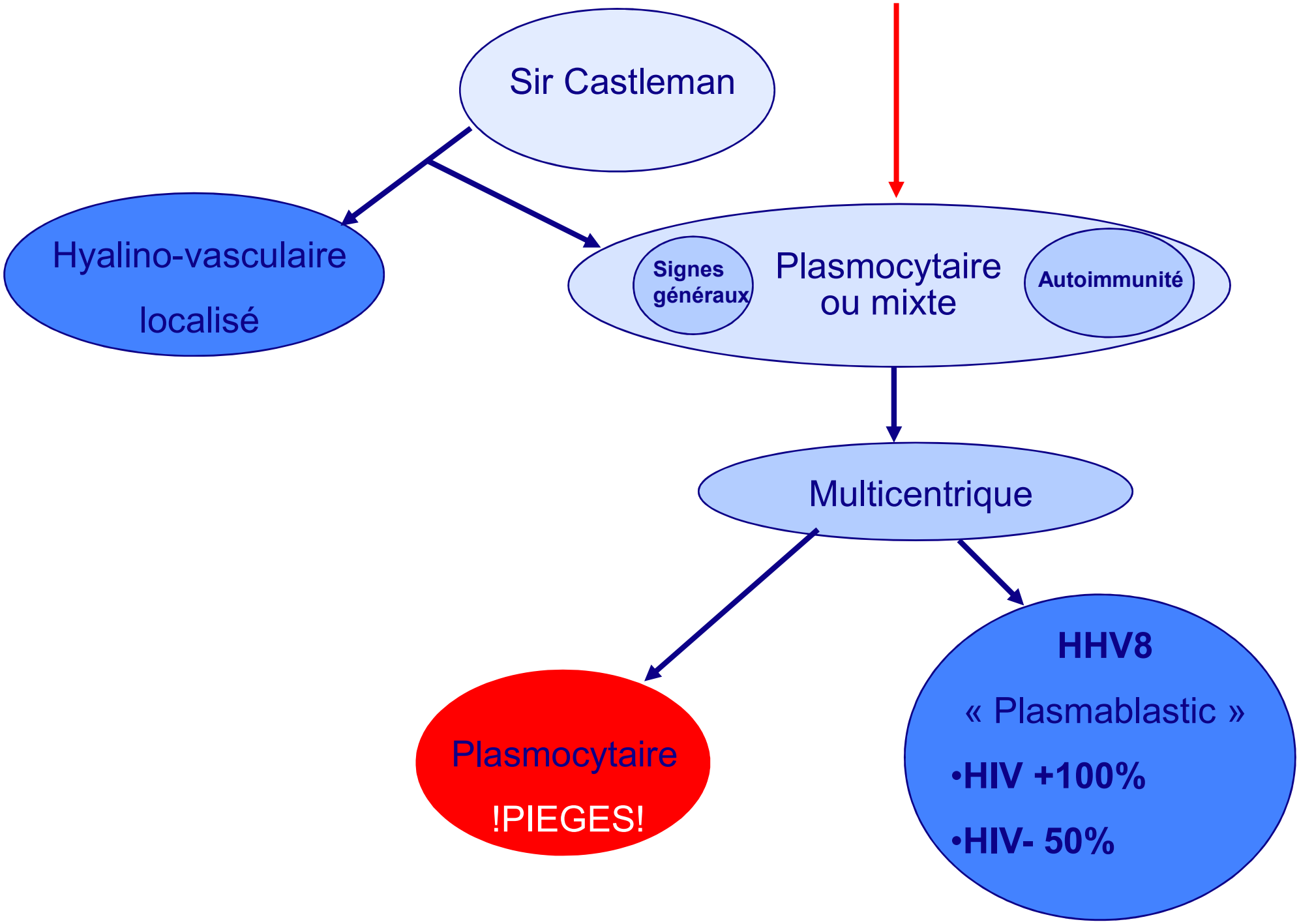


33 treatments / 21 patients	CR	PR	SD	PD	NE
Steroids (14)	1	5	1	7	
R-CPM (5) VP16 (2) BEACOPP (1)	2	1 2	1	1 1	
Rituximab (5)		2	1	1	1
Tocilizumab (4)	1	3			
Embolization (2)		1			1

BJH, 2019

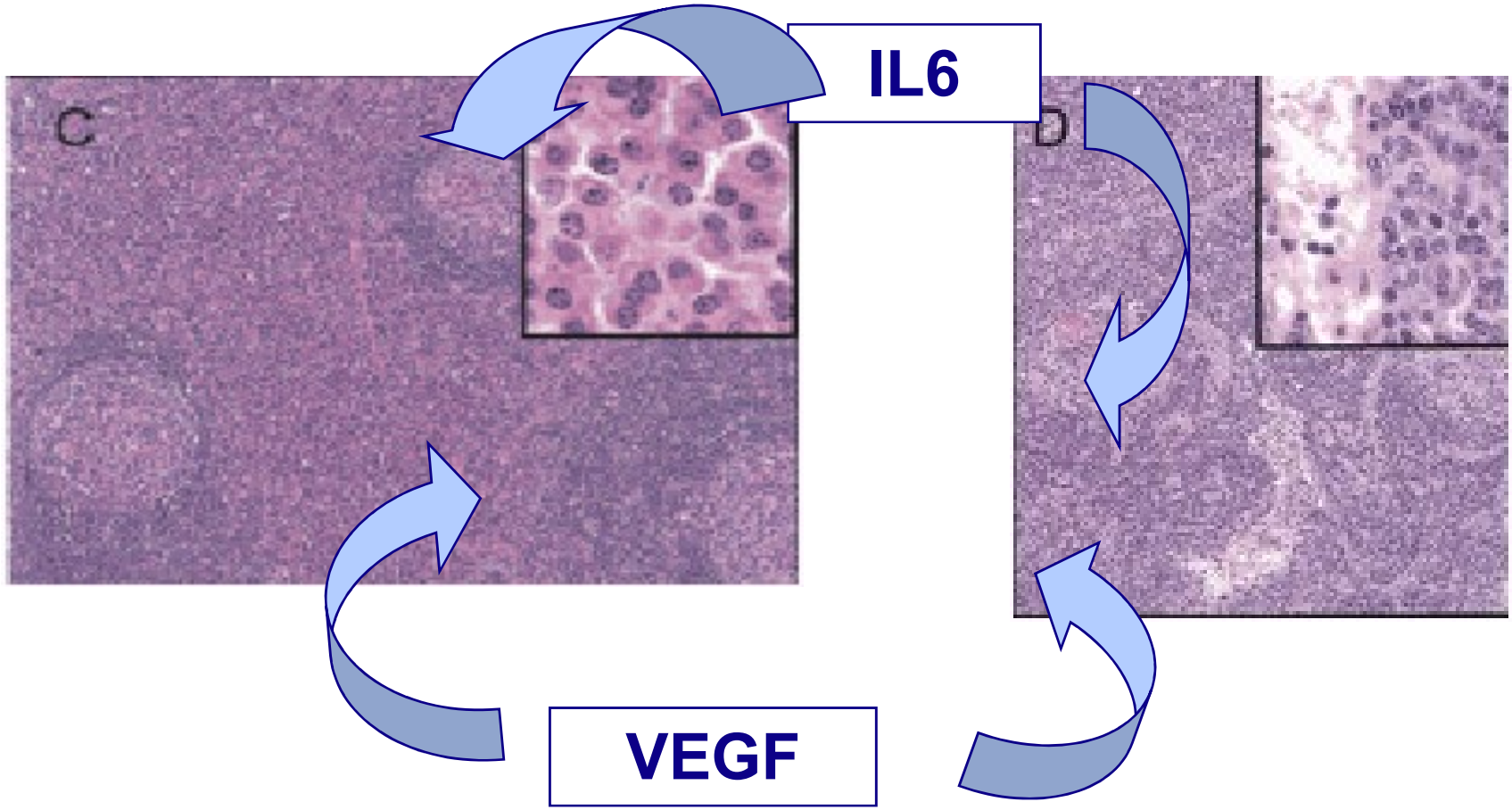
Castleman-HV - Traitement

- **Risque d’exacerbation post op de PNP**
- **Dépister et traiter les complications avant la chirurgie!**
- **Place des ITK?**


Sir Castleman
Hyalino-vasculaire
localisé
Signes généraux
Plasmocytaire
ou mixte
Autoimmunité
Multicentrique
Plasmocytaire
!PIEGES!
HHV8
« Plasmablastic »
•HIV +100%
•HIV- 50%

Castleman plasmocytaire - Histologie

Plasmocytose interfolliculaire intense
Peu/pas d'atrophie des centres germinatifs
Hypervascularisation marquée



Steven, *ASH* 2004

Castleman plasmocytaire

DICHOTOMIE HHV8-/HHV8+

PCR HHV8/Marquage LNA

- **Formes multicentriques**
- **Signes généraux 16-90%**
- **Retard de croissance**

- **Anémie, hyperleucocytose**
- **CRP**
- **Hypergammaglobulinémie**
- **Hypoalbuminémie**
- **Coombs, FR, AAN, APL**

Complications

- **Autoimmunité spécifique**
- **Myalgies, arthrites**
- **Syndrome Raynaud, sicca syndrome**
- **Sérites, œdèmes**
- **Neuro**

Maladie de Castleman HHV8+

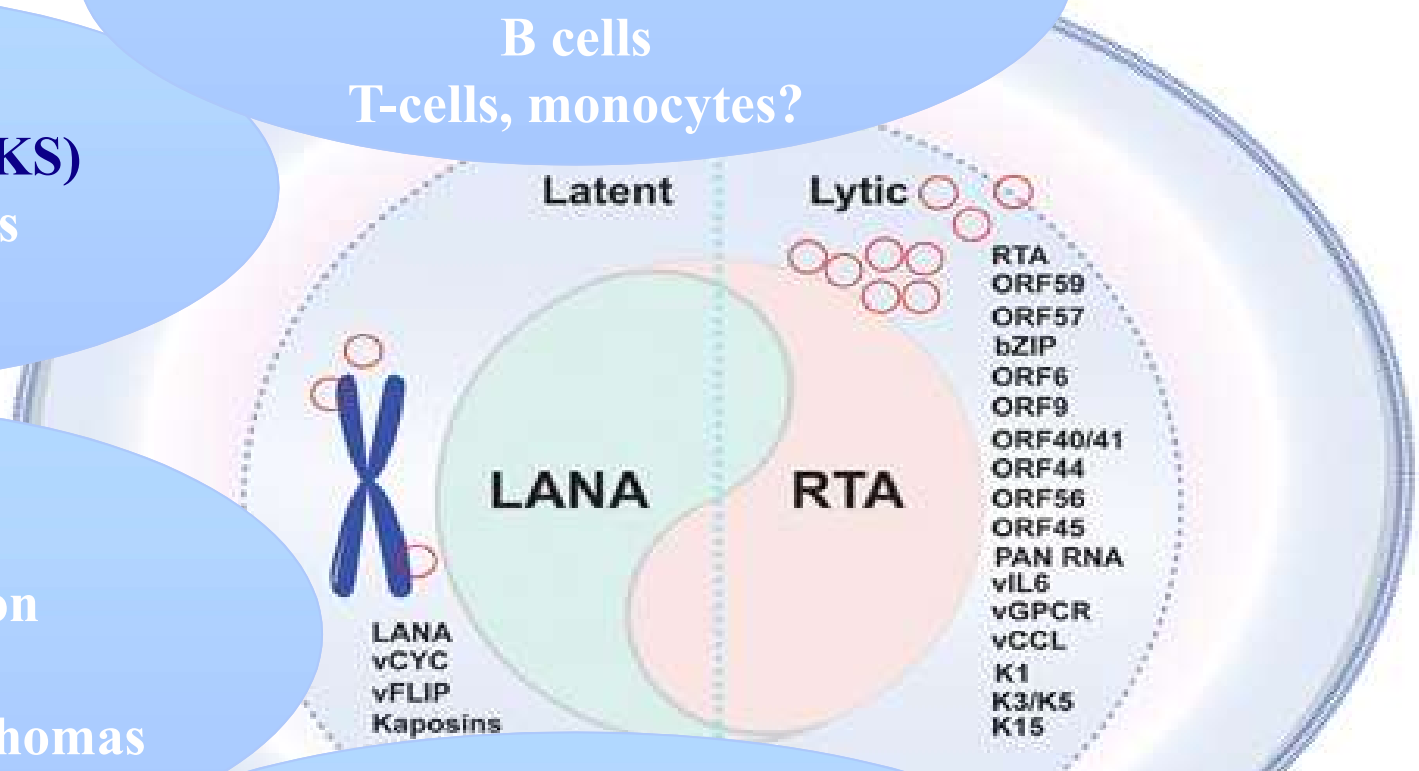
Castleman « plasmablastique »

HHV8-associated diseases

Secondary (HIV, post-transplant) > primary ID setting

HHV-8 primary infection
Eptihelial cells
Endothelial cells
B cells
T-cells, monocytes?

Kaposi Sarcoma (KS)
Endothelial cells

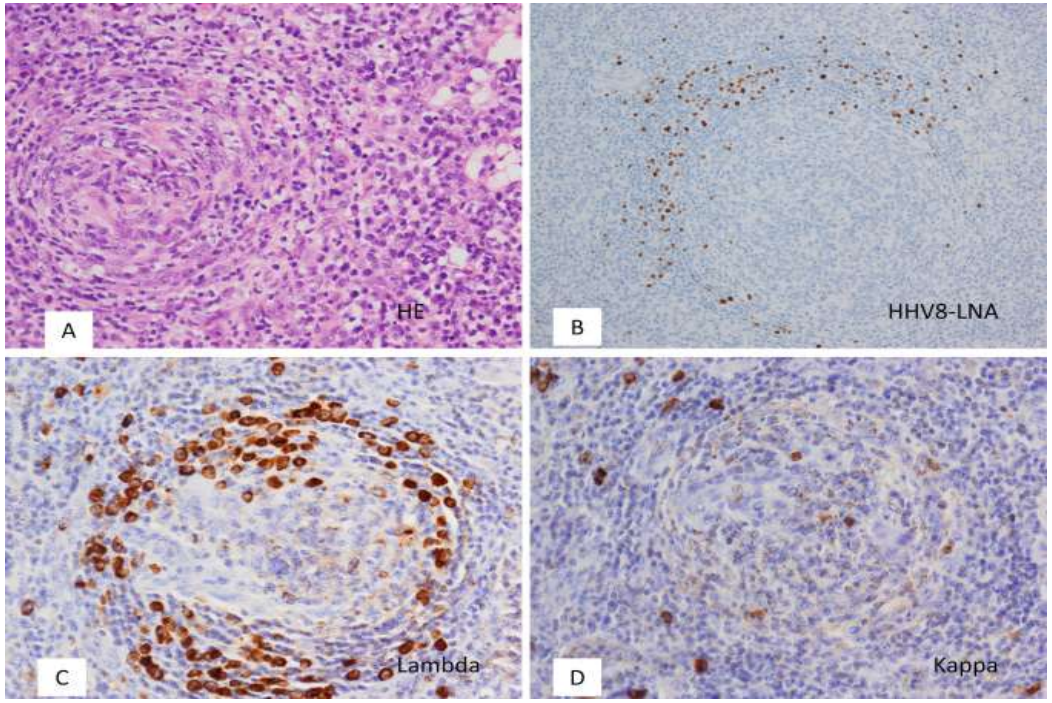


Lymphomas
Primary effusion lymphomas
Plasmablastic lymphomas

HHV-8 Multicentric Castleman Disease
B cells
T-cells, monocytes?

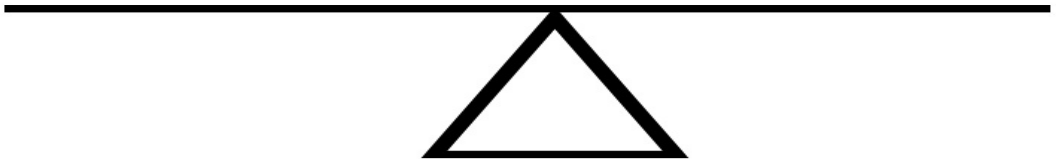
What is HHV8+ MCD?

Plasma-cell type MCD
Evidence of HHV8 *in situ* infection (LNA staining/qPCR)



B-cell side
What drives HHV8+ plasmablast emergence?

T-cell side
Which T-cell defects allow HHV8+ MCD?

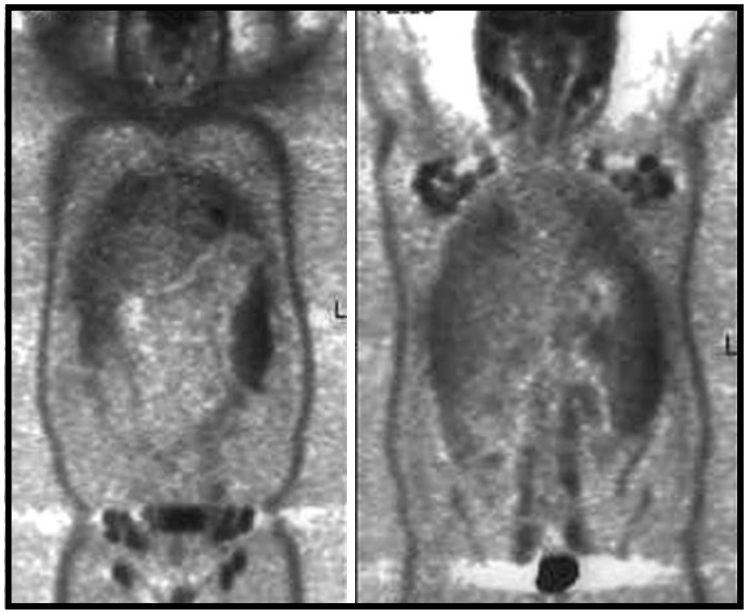


MC HHV8+: diagnostic

Symptômes

* Symptômes "B"
* Polyadénopathie
* Splénomégalie
* Symptômes Respiratoires
* Œdèmes
* Sd sec
* Coma
* Rash

* **Kaposi**



Biologie

* Cytopénies
* CRP très élevée
* Gammaglobuline > 20g/l
* Albumine < 30g/l
* Cholestase
* TP allongé
* Test de Coombs Direct +
* **Hémophagocytose**

* **Rémission spontanée possible**

* **DNA-HHV8 / PBMCs +++**

Oksenhendler, *AIDS* 1996

MCM: Physiopathologie

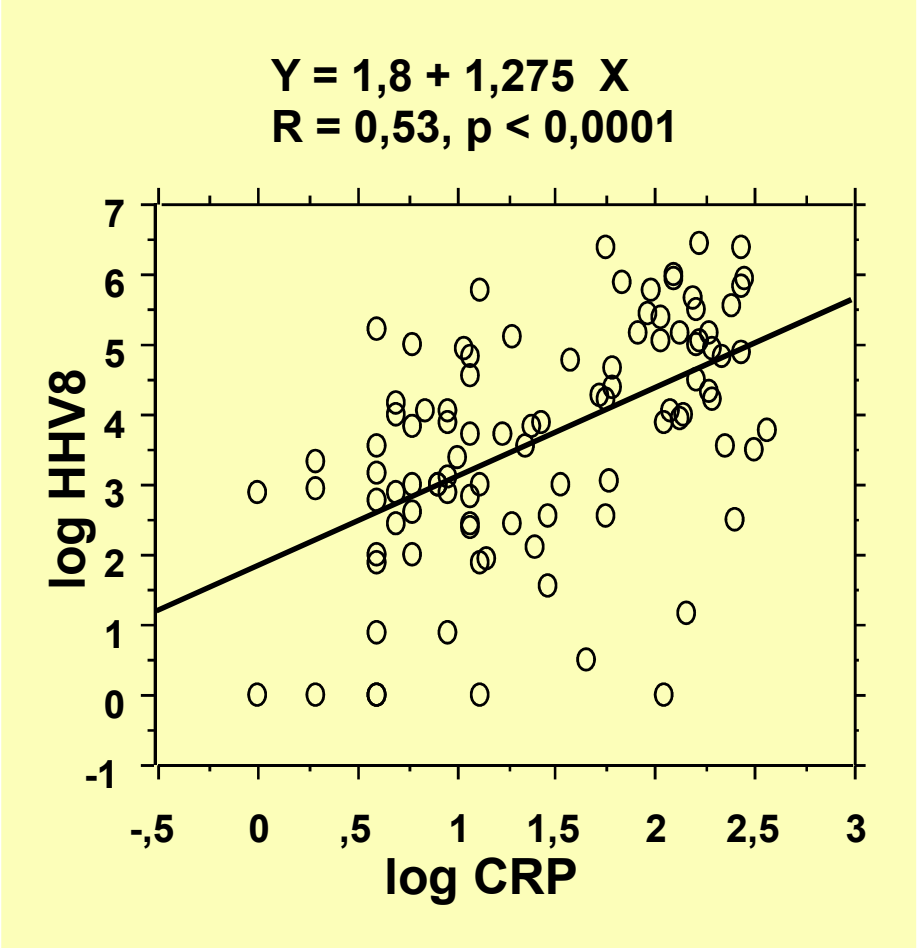
Les« poussées » s'accompagnent d'une charge virale élevée

« Poussées »

- CRP élevée
- « Charge virale » HHV8 élevée dans les PBMCs
  med: 4.8 log copies / µg DNA

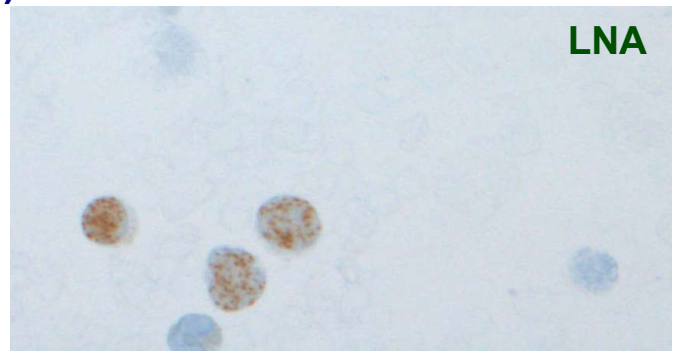
Rémission

- CRP normale
- Faible « charge virale » HHV8 dans les PBMCs
  med: 2.9 log copies / µg DNA



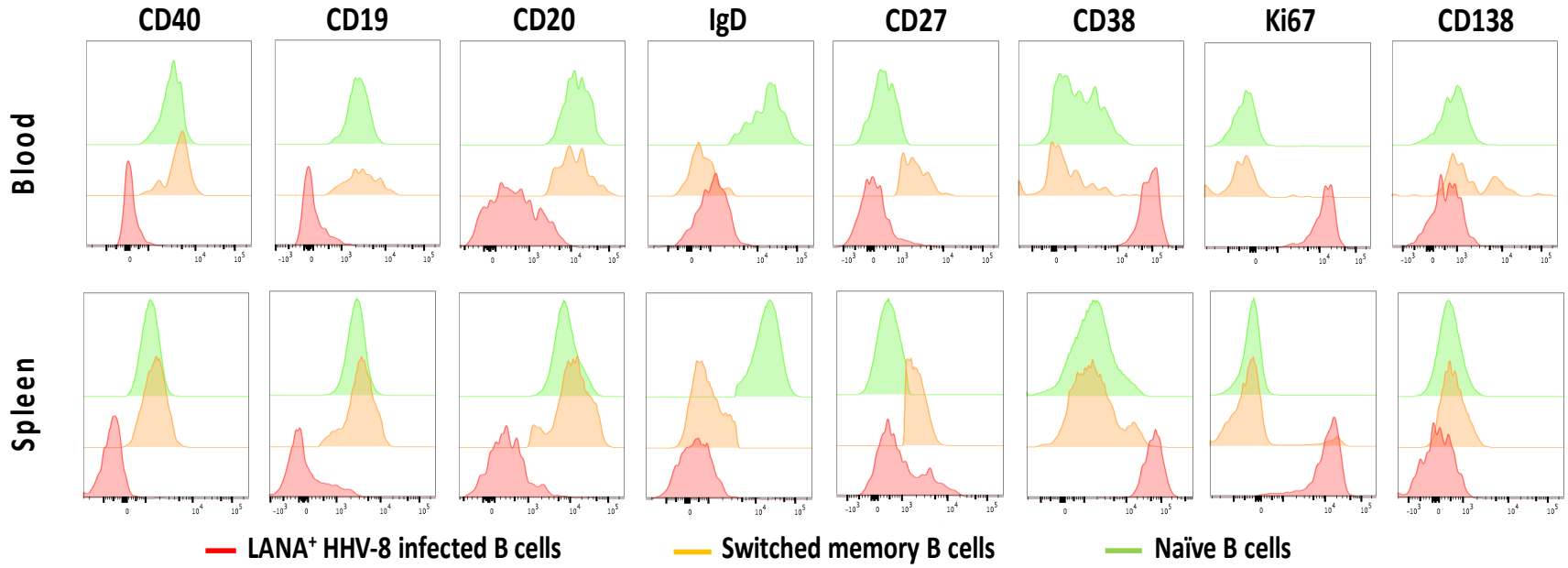
Flow cytometric phenotyping of LNA+ cells

LNA+ λ+ plasmablast-like cells are detectable in the blood of patients with active MCD and HHV-8 PCR>3 log (0.02-6% of PBMC)



LNA staining, blood smear, V. Meignin

Their phenotype is similar to lymph node and splenic LNA+ cells
This could be a quick diagnostic tool for MCD and should be tested in KICS



A; Vanjak, Z. Sbihi, unpublished data

MCM HHV8: Traitement

Chimiothérapie

- ✓ Etoposide (VP16) 150-200 mg PO/IV

Antiviraux

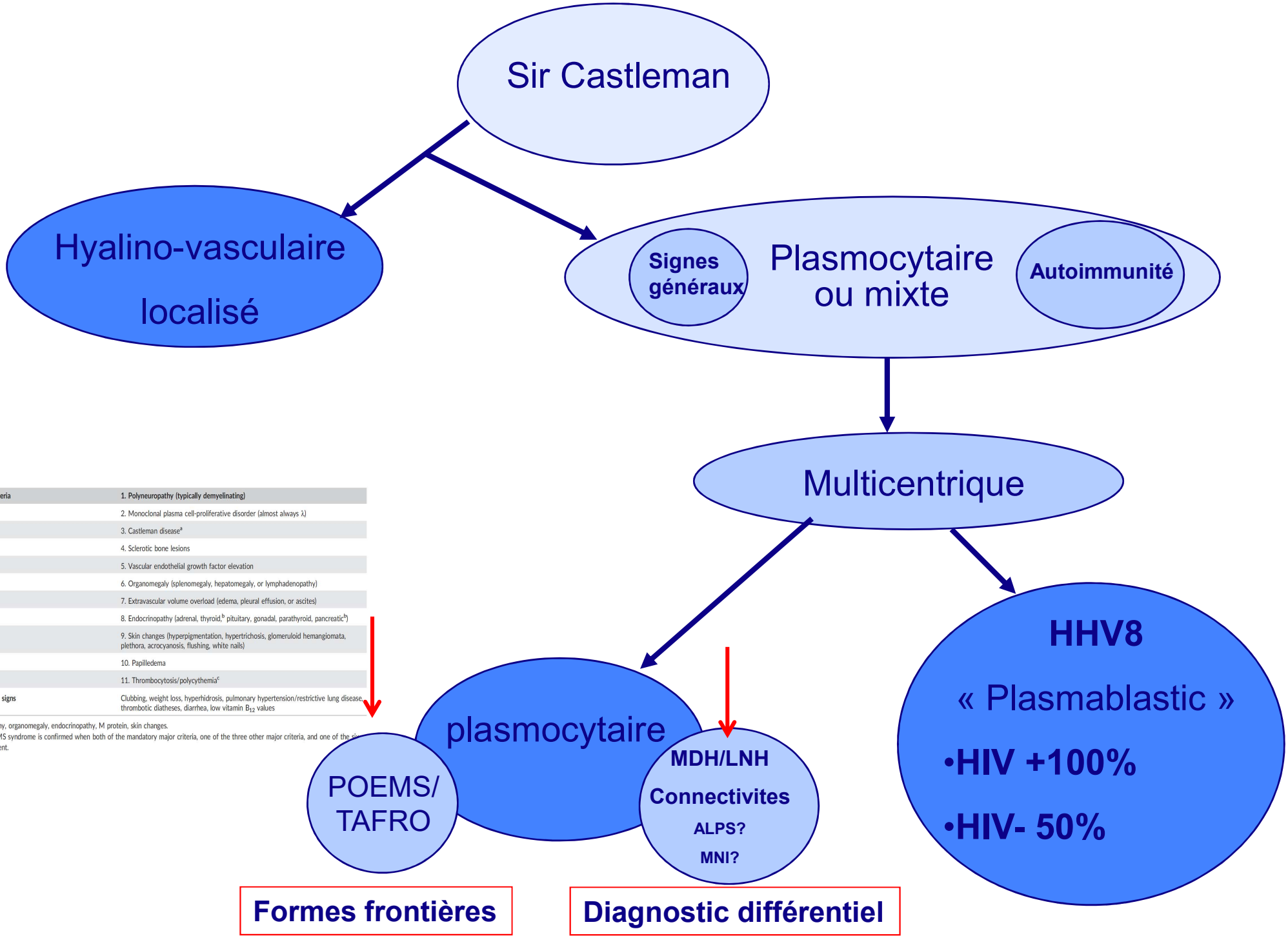
- ✓ Ganciclovir, cidofovir: résultats décevants

Splénectomie

- ✓ Cytopénies sévère, splénomegalie persistente ou réponse partielle

Immunothérapie

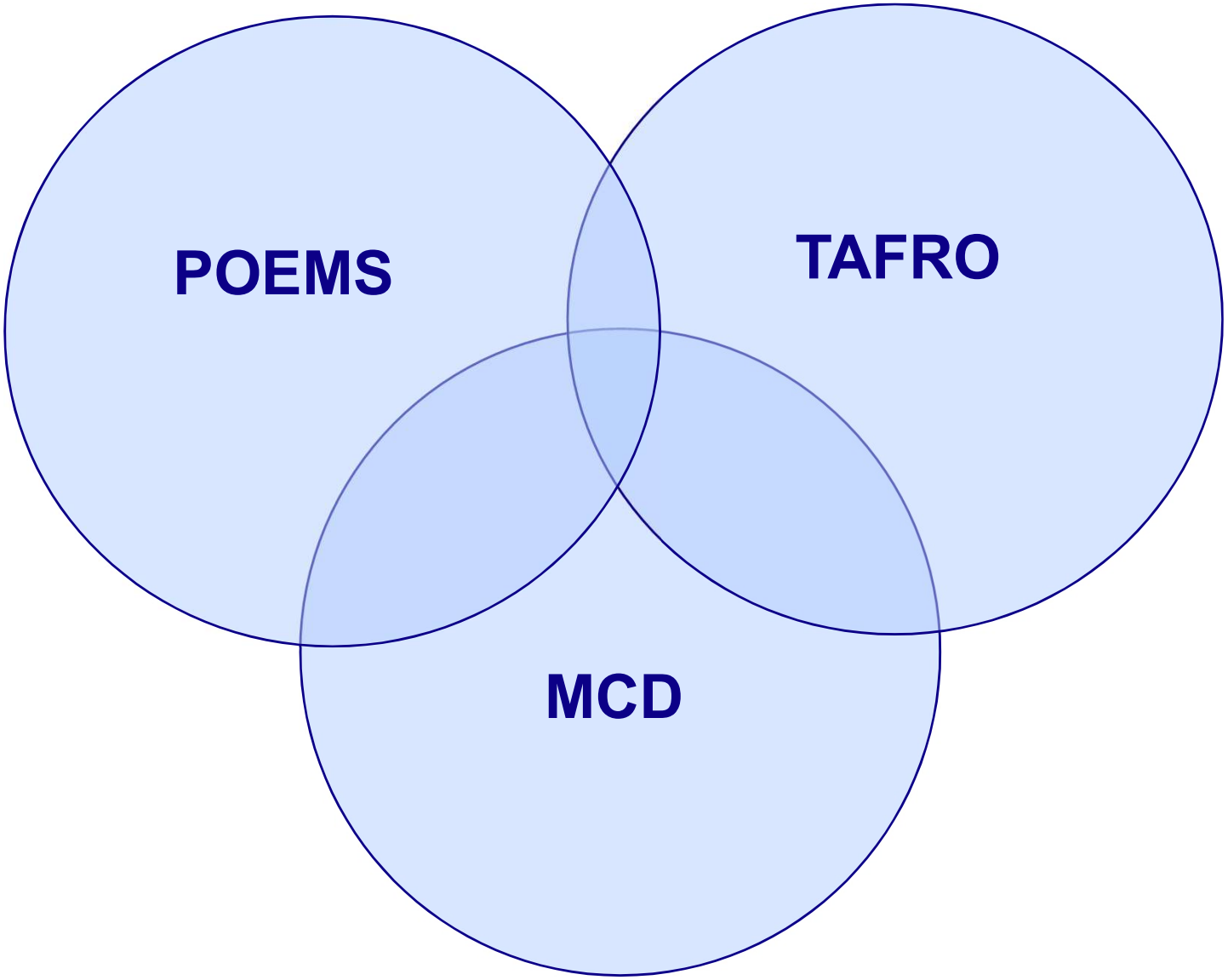
- ✓ Rituximab (!Kaposi!)
- ✓ Anti IL6 R : données sporadiques



Mandatory major criteria	**1. Polyneuropathy (typically demyelinating)**
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria	3. Castleman disease[a]
(one required)	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,[b] pituitary, gonadal, parathyroid, pancreatic[b])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[c]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

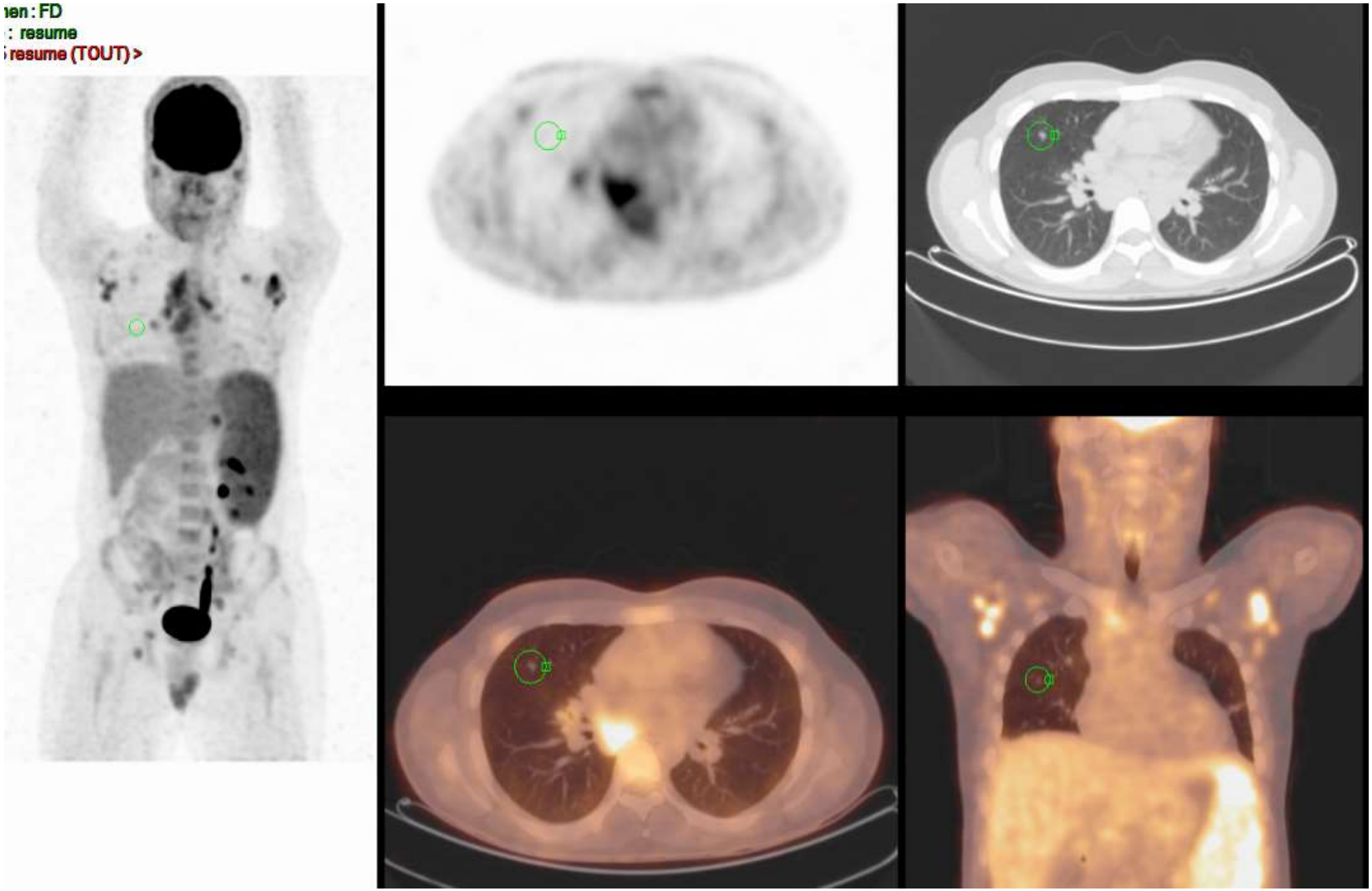
POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.
The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present.

Formes frontières
Castleman / POEMS / TAFRO



Castleman – Le piège

Homme 30 ans, AEG fébrile, polyadénopathie



Castleman – lymphome (50 cas)

- Castleman « régional » MdH 27/50
- Castleman multicentrique LNH 23/50
  - 40% LNH du manteau

Larroche, *Am J Hematol* 2002

Castleman – Lymphome

….Le piège….

Compléments histologiques (CD30,…)

Ne pas hésiter à rebiopsier

Intérêt du TEP

Intensification thérapeutique

Castleman plasmocytaire : que faire ?

- **Localisé (PET ?) → chirurgie + / - radiothérapie**

Multicentrique

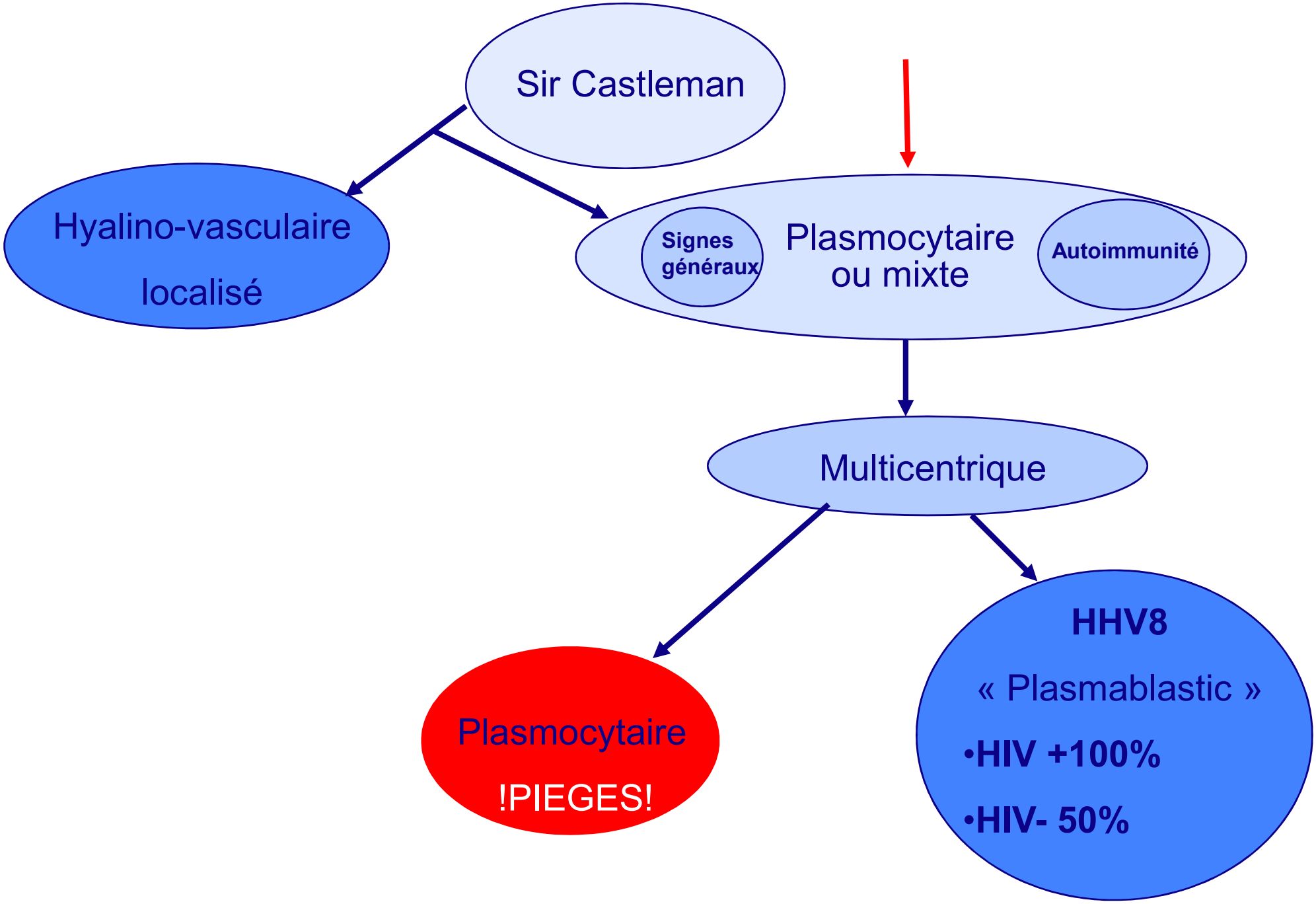
Ecarter un diagnostic différentiel avec histologie de Castleman

POEMS

HHV8
« plasmablastique »

- **Anti IL6R**
- **Rituximab**
- **Sirolimus**
- **VLB, VP16, EDX, Bortezomib**
- **Immunosuppresseur (EDX +cs)**
- **Inhibiteurs de JAK**
- **Polychimiothérapie**

Conclusion : 1 histologie, plusieurs maladies



Thank you!

Patients

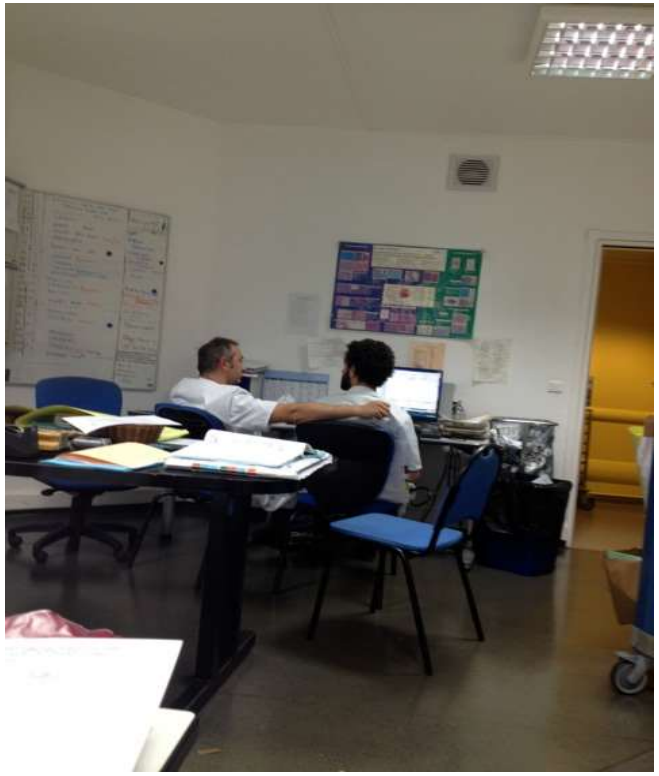
Clinicians
E. Oksenhendler, L. Galicier, C. Fieschi, L. Gérard, M. Malphettes , A. Dossier, R. Bertinchamp, J. Fadlallah, M.Garzaro, C. Lebbé, X. Lescure

Pathology Department
V. Meignin, J. Calvani

U976 Castleman team
Hôpital Saint Louis
A. Vanjak, J. Poirot, M. Garzaro, Z. Sbihi, M. Chbihi, M. Chevalier, E. Oksenhendler, G. Carcelain, V. Soumelis

UMR1163, Institut Imagine
S. Latour, A. Fischer, JP. de Villartay
E. Martin, S. Winter, B. Fournier

Castleman Disease Collaborative Network



www.castleman.fr