Journée AIP / Carrefour Pathologie

Paris, 7 novembre 2019

Microbiopsie ganglionnaire dans les pathologies histiocytaires/myeloïdes

- Panel immunohistochimique
- Place des outils moléculaires

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France

Micro-biopsies ganglionnaires dans les pathologies histiocytaires / myeloïdes

Histiocytoses

- = maladies rares
- Survenant à tout âge (nouveau né à vieillard)
- Atteintes ganglionnaires peu fréquentes dans certaines formes
- Recherche de mutation souvent demandée
  → fixation en formol tamponné pdt 12 à 72h (pas plus)
  → preserver le matériel au maximum

Autres hémopathies

- Infiltration leucémique, sarcome myéloïde,
- mastocytose systemique, sarcome mastocytaire,
- sarcome à cellules folliculaire dendritique

- Les micro-biopsies gangionnaires sont rares dans ces pathologies
- Le diagnostic n'est souvent pas suspecté avant la biopsie

Les histiocytes

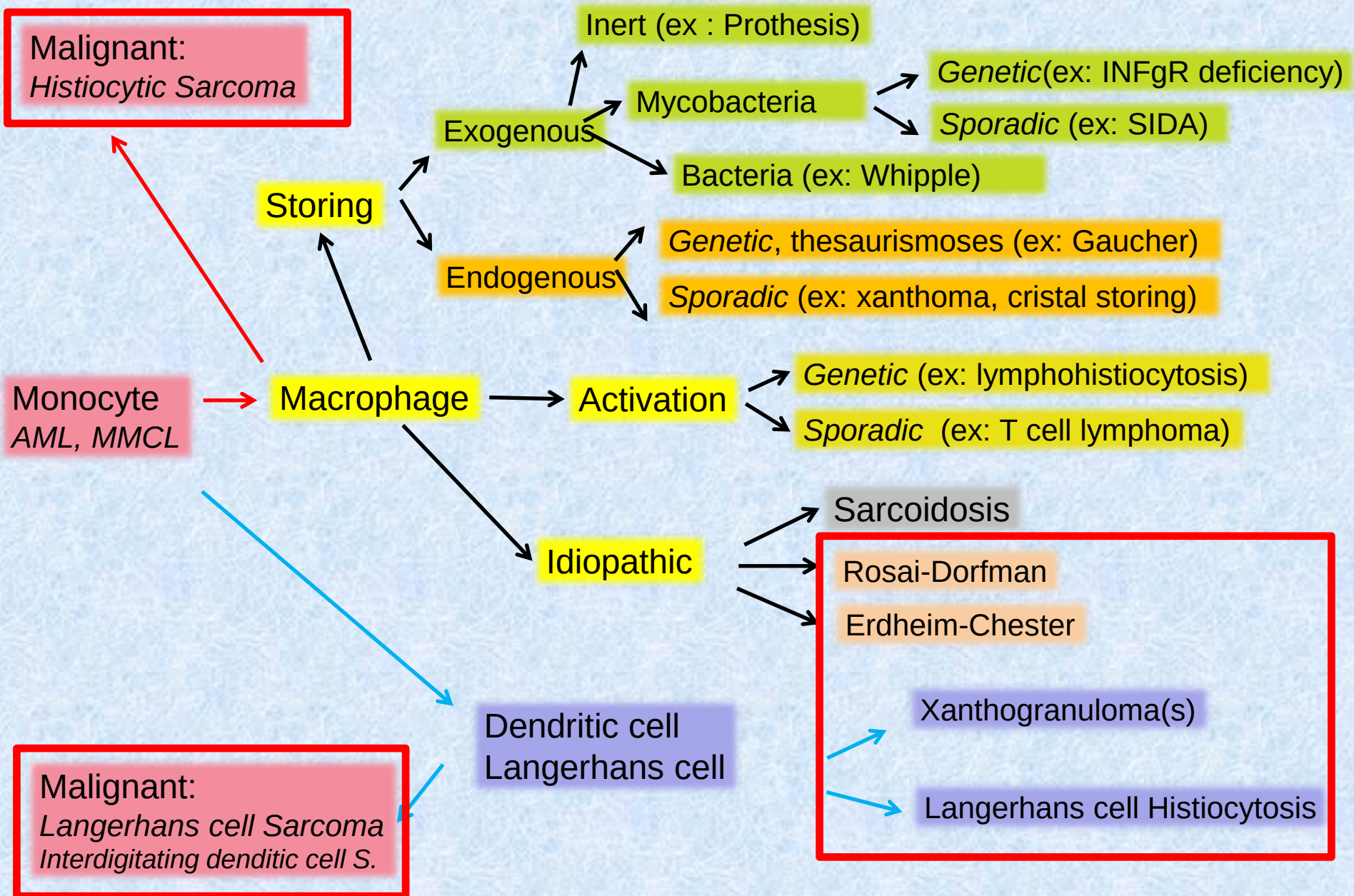
Macrophages

Éboueurs de l'organisme

Cellules dendritiques (DC)

Présentatrices des antigènes

Histiocytoses : de quoi parlons nous ?



Histiocytoses : Rares mais nombreuses !

Table 1. Histiocytoses of the L group

Disease	Subtypes
LCH	LCH SS
	LCH lung$^+$
	LCH MS-RO$^+$
	LCH MS-RO$^-$
	Associated with another myeloproliferative/ myelodysplastic disorder
ICH	
ECD	ECD classical type
	ECD without bone involvement
	Associated with another myeloproliferative/ myelodysplastic disorder
	Extracutaneous or disseminated JXG with MAPK-activating mutation or ALK translocations
Mixed ECD and LCH	

Table 2. Non-LCH of skin and mucosa (C group)

Non-LCH of skin and mucosa	
Cutaneous non-LCH histiocytoses	
XG family	JXG
	AXG
	SRH
	BCH
	GEH
	PNH
Non-XG family	Cutaneous RDD
	NXG
	Cutaneous histiocytoses not otherwise specified
Cutaneous non-LCH histiocytoses with a major systemic component	
XG family	XD
Non-XG family	MRH

Table 3. Malignant histiocytoses (M group)

Localization	Subtype
Primary MH	
Skin	
Lymph node	Histiocytic
Digestive system	or
CNS	IDC
Other or disseminated	or
Secondary MH to	LC
Follicular lymphoma	or
Lymphocytic leukemia/lymphoma	indeterminate cell
Hairy cell leukemia	or
ALL	not specified
Histiocytosis (LCH, RDD, others)	
Another hematologic neoplasia	

Table 4. Histiocytoses of the R group

Histiocytoses of the R group
Familial RDD
Faisalabad (or H) syndrome (OMIM #602782)
FAS deficiency or ALPS-related RDD (OMIM #601859)
Familial RDD not otherwise specified
Classical (nodal) RDD
Without IgG4 syndrome
IgG4 associated
Extranodal RDD
Bone RDD
CNS RDD without IgG4 syndrome
CNS RDD, IgG4 associated
Single-organ RDD other than lymph node, skin, and CNS, without IgG4 syndrome
Single-organ RDD other than lymph node, skin, and CNS, IgG4 associated
Disseminated RDD
Neoplasia-associated RDD
RDD postleukemia
RDD postlymphoma
RDD associated with MH
RDD associated with LCH or ECD
Immune disease-associated RDD
SLE related
IJA related
AIHA associated
HIV associated
Other non-C non-L non-M non-H histiocytoses

Table 5. Histiocytoses of the H group (HLH)

Histiocytoses of the H group
Primary HLH: Mendelian inherited conditions leading to HLH
HLH associated with lymphocyte cytotoxic defects
FHL2 (*PRF1*)
FHL3 (*UNC13D*)
FHL4 (*STX11*)
FHL5 (*STXBP2*)
XLP1 (*SH2D1A*)
Griscelli Syndrome type 2 (*RAB27A*)
Chediak-Higashi Syndrome (*LYST*)
HLH associated with abnormalities of inflammasome activation
XLP2 (*BIRC4*)
NLRC4
HLH associated with defined Mendelian disorders affecting inflammation
Lysinuric protein intolerance (*SLC7A7*)
HMOX1
Other defined Mendelian disorders affecting inflammation
Familial (apparently Mendelian) HLH of unknown origin
Secondary HLH (apparently non-Mendelian HLH)
Infection-associated HLH
Virus-associated HLH
EBV-associated HLH
CMV-associated HLH
HLH associated with other defined herpes virus infections
HIV-associated HLH
Influenza-associated HLH
HLH associated with other defined virus infections
Bacteria-associated HLH*
Parasite-associated HLH*
Fungal-associated HLH*
Malignancy-associated HLH
Malignancy-triggered HLH (HLH at onset of malignancy)
Hematological malignancies
T-cell lymphoblastic lymphoma/leukemia
T-cell non-lymphoblastic lymphomas
B-cell leukemias
B-cell lymphomas (non-Hodgkin)
Hodgkin lymphomas
NK-cell lymphomas/leukemias
Myeloid neoplasia
Other hematological malignancies
Solid tumors
Unclassified malignancies
HLH occurring during chemotherapy (not associated with initial diagnosis of malignancy)*
HLH associated with a malignancy, but not further defined
HLH associated with defined rheumatologic conditions (MAS-HLH, or MAS-HLH)
HLH associated with SoJIA
HLH associated with adult-onset Still disease
HLH associated with SLE
HLH associated with vasculitis
HLH associated with other defined autoimmune conditions
HLH associated with a not defined autoimmune condition
Transplant-related HLH*
HLH associated with iatrogenic immune activation*
HLH associated with iatrogenic immune suppression
HLH associated with other apparently non-Mendelian conditions
HLH of unknown/uncertain origin

Emile et al. Blood 2016

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Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

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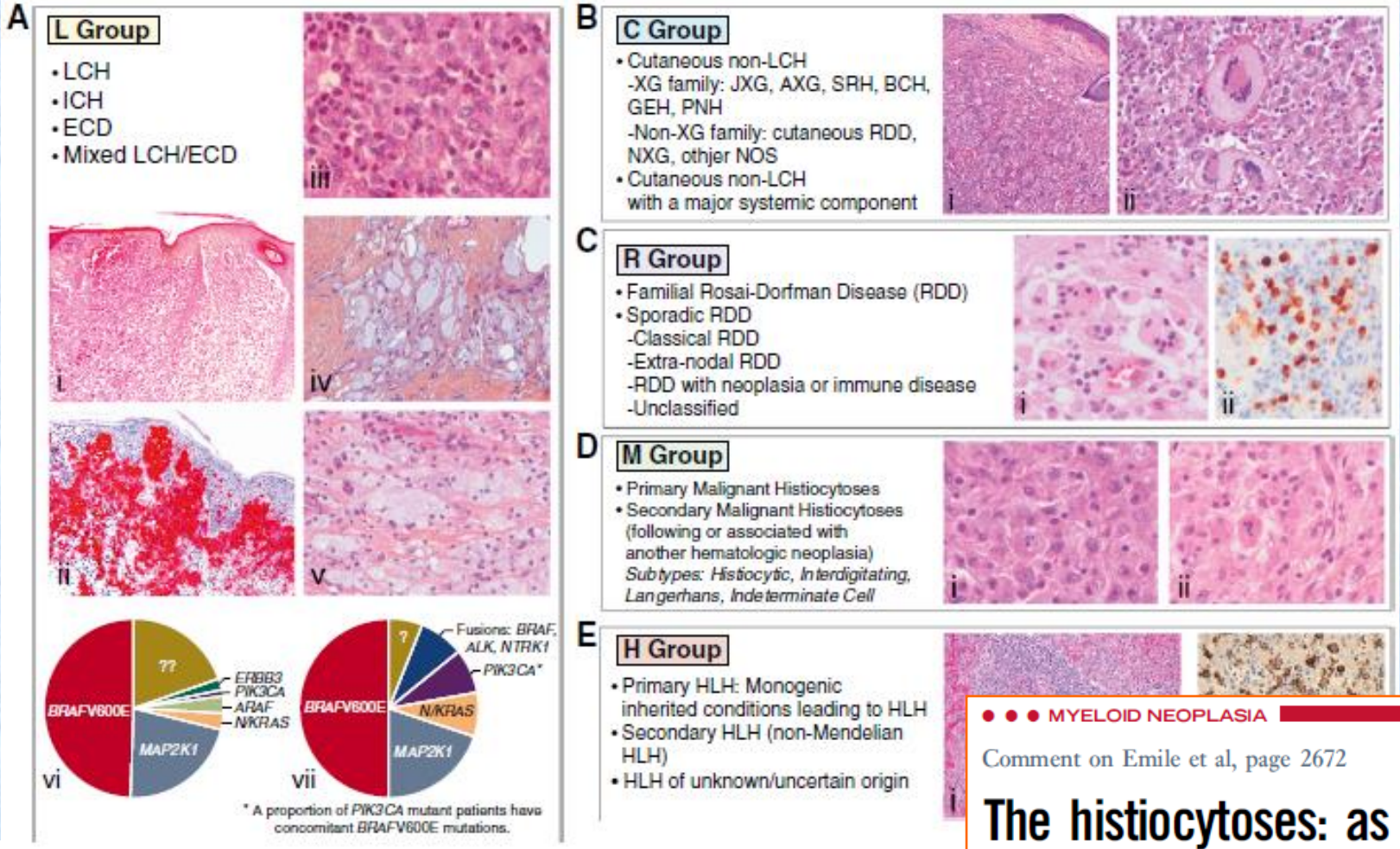


MYELOID NEOPLASIA

Comment on Emile et al, page 2672

The histiocytoses: as easy as ABC (or LCMRH)

Histiocytoses : la démarche diagnostique du pathologiste

- Optimiser l'utilisation du prélèvement
  - Histologie, phénotypage (+/- culture de pathogènes ?)
  - Altérations génétiques
- Eliminer les diagnostics différentiels
  - Accumulation d'histiocytes « normaux »
  - Tumeurs riches en histiocytes
- Typer les histiocytes
- Confronter avec des données cliniques
- Analyses moléculaires

Phénotypage : quels panel minimal ?

- Marqueurs histiocytaires
  - CD163
  - CD68
  - Autres : CD4, CD31,
- Marqueurs dendriques / Langerhans
  - S100
  - CD1a, CD207 (=Langherine)
  - Facteur XIIIa
- Marqueurs d'activation des histiocytes / thérapeutiques
  - phosphoERK (D13.14.4E Mab lapin, cell signaling)
  - ALK (1A4, Mab souris, Diagomics)
  - VE1 (=$BRAF^{V600E}$)
- Marqueurs myéloïdes / lymphoïdes
  - Mastocytes : KIT (=CD117), tryptase
  - Cellules folliculaires dendritiques : CD21, CD23
  - Myéloïdes : CD34, KIT, MPO,
  - Lymphocytes : CD20, CD3, etc…
  - IgG4

Phénotypage en pratique courante

- Histiocytose à cellules de Langerhans (HCL) : CD1a+ CD207+
- Histiocytose à cellules indéterminées : CD1a+ CD207-

- Maladie de Rosai-Dorfman (MRD) : CD68 ou CD163+ S100+ CD1a- et IgG4

- Maladie d'Erdheim-Chester (MEC) : CD163+ CD1a- pERK+ (et clinique ++)

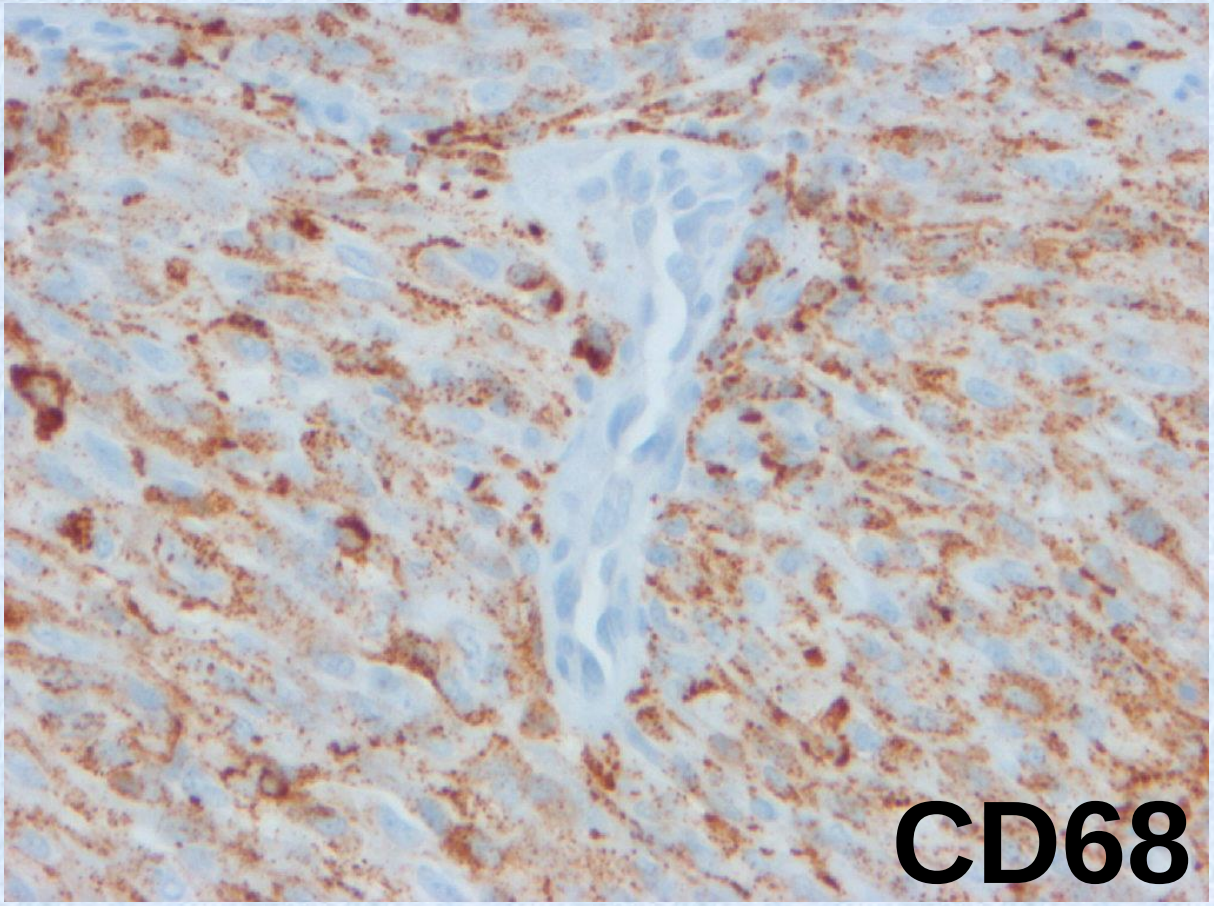
- Xanthogranulome (type juvénile) : CD68 ou CD163+ CD1a- Facteur XIIIa+

- Histiocytose difficile à typer : CD163, CD68, CD1a, S100, pERK, ALK

- Histiocytose maligne : tout le réfrigérateur !

- Mastocytose : KIT+ Tryptase+

Immunohistochimie : Quelques faux amis

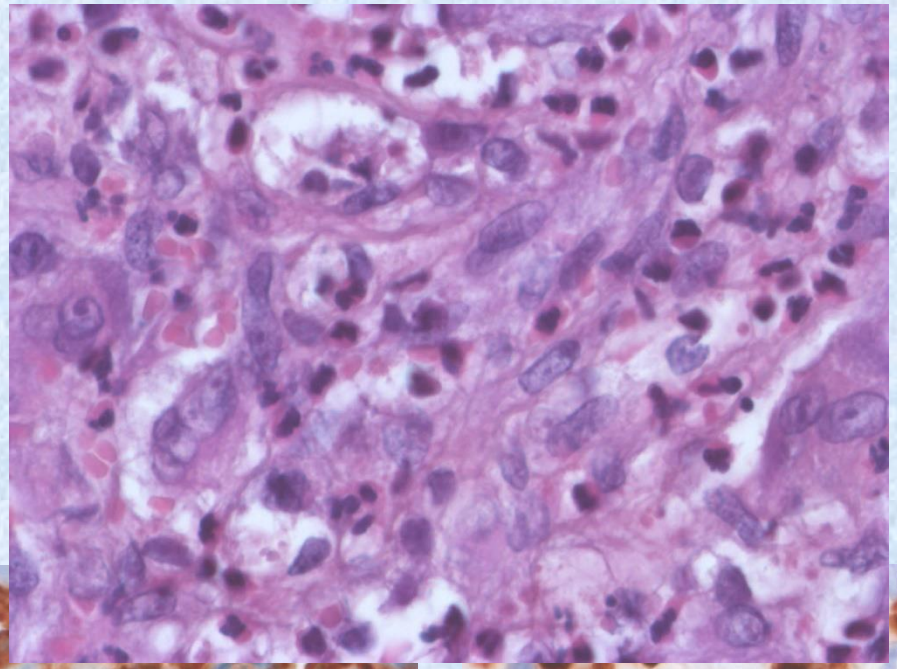


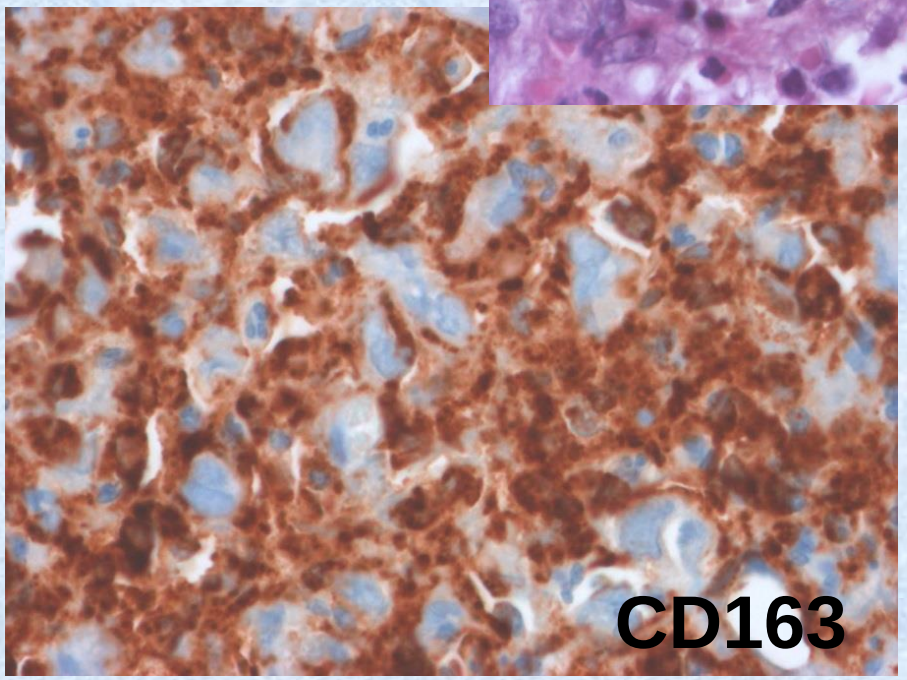
Schwannome

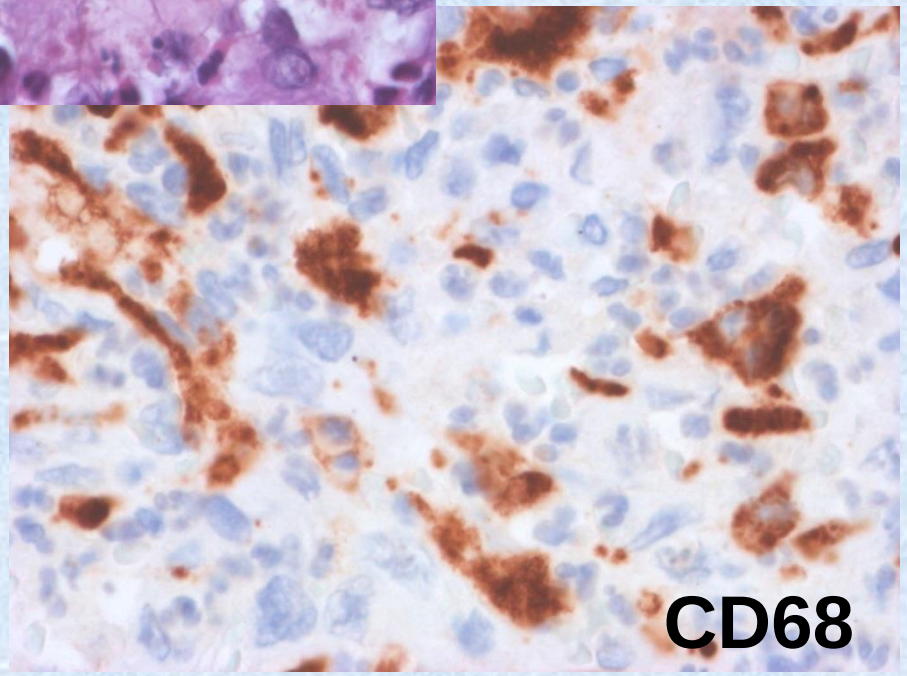
Notamment :

- CD4, CD31 : histiocytoses
- CD2, CD25, CD68 : mastocytoses

Immunohistochimie : expressions aberrantes

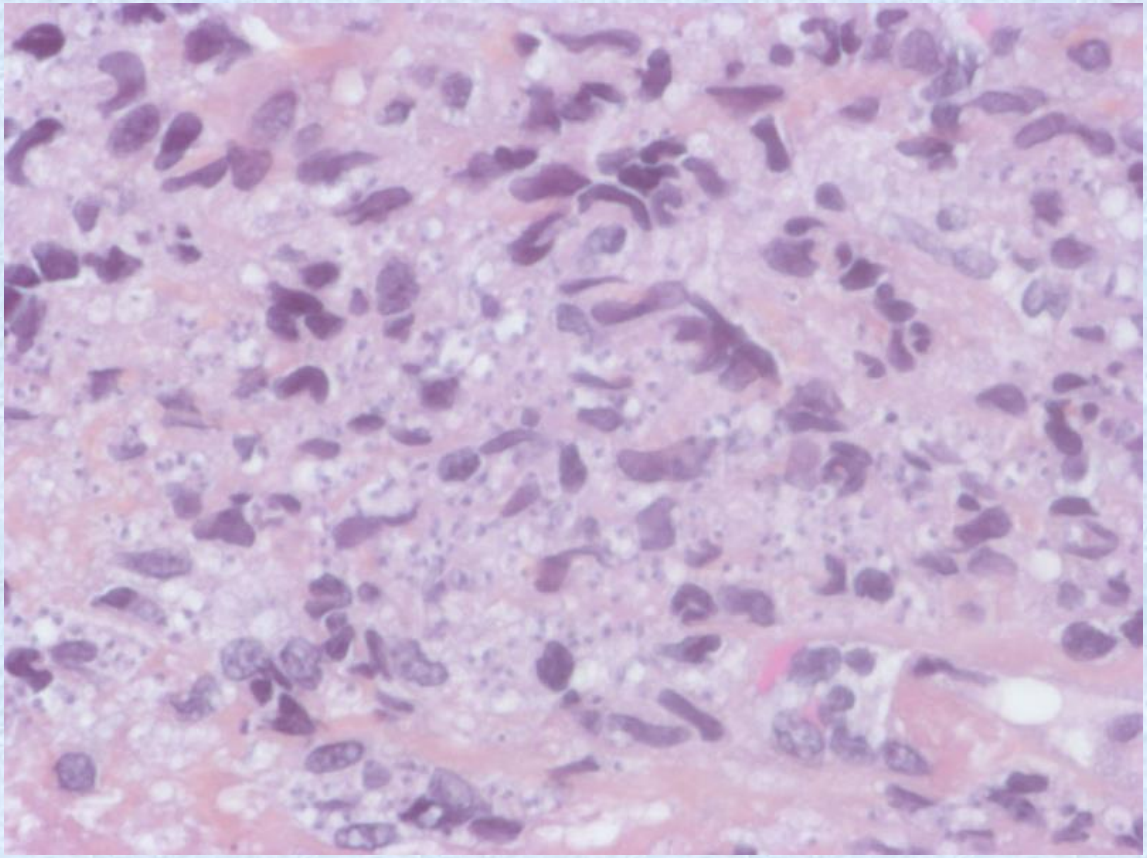


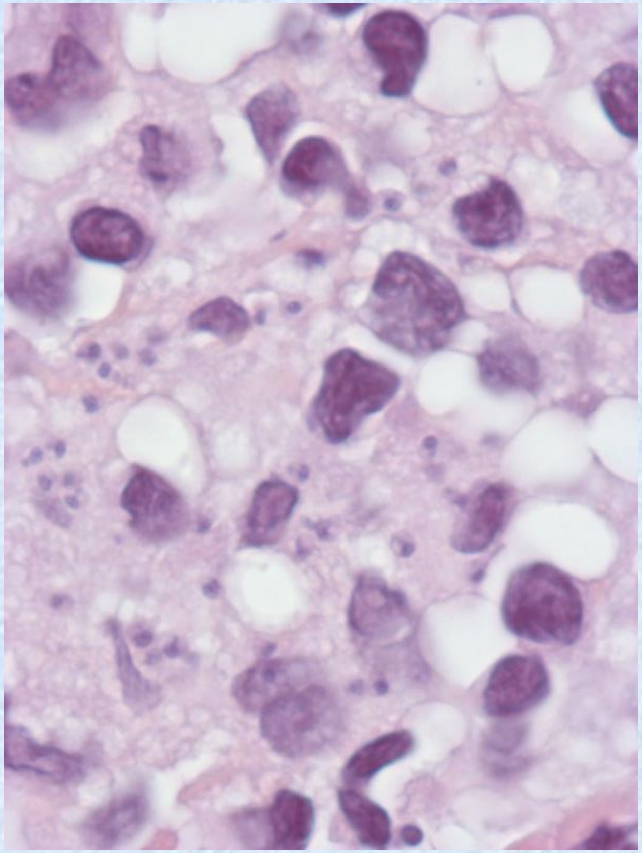




Cas clinique n°1 (19C00212)

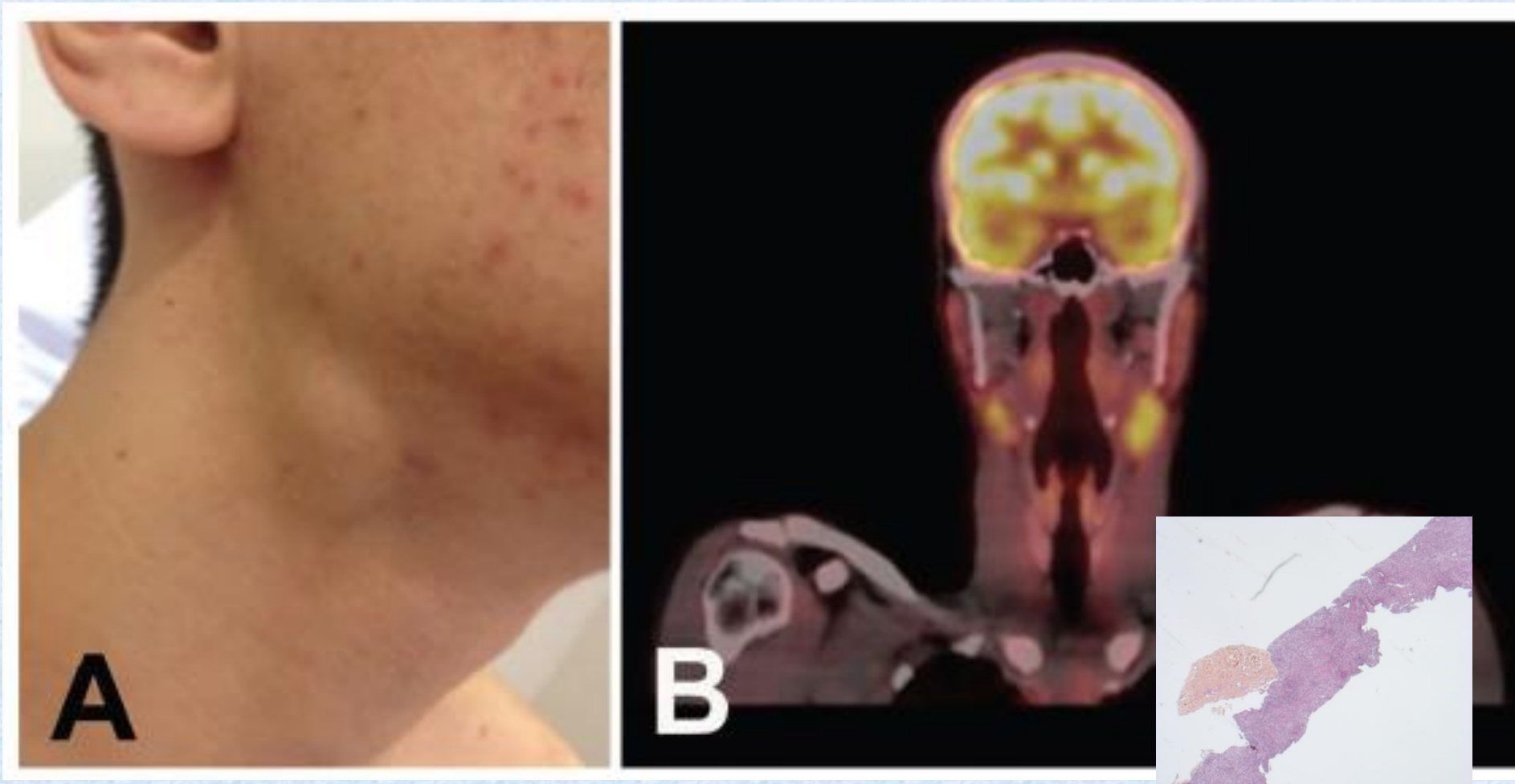
- Homme jeune. Splénomégalie et polyadénopathies





Leishmaniose viscérale

Cas clinique n°2 (19C00236)



Fatobene Haematologica 2018

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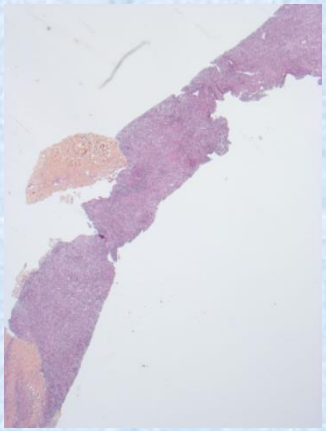
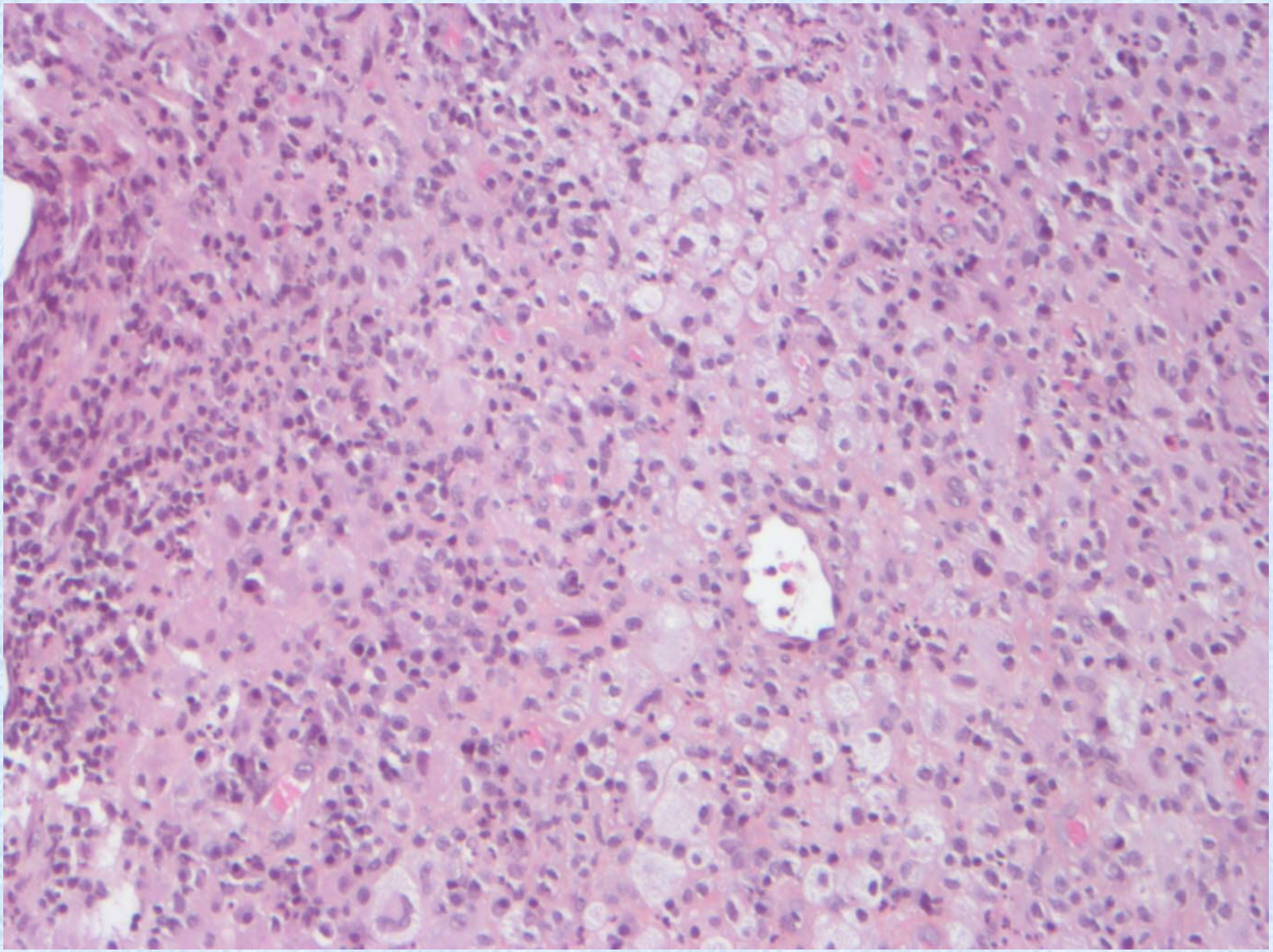
Cas clinique n°2 (19C00236)

- Homme jeune. Volumineuses adénopathies cervicales bilatérales





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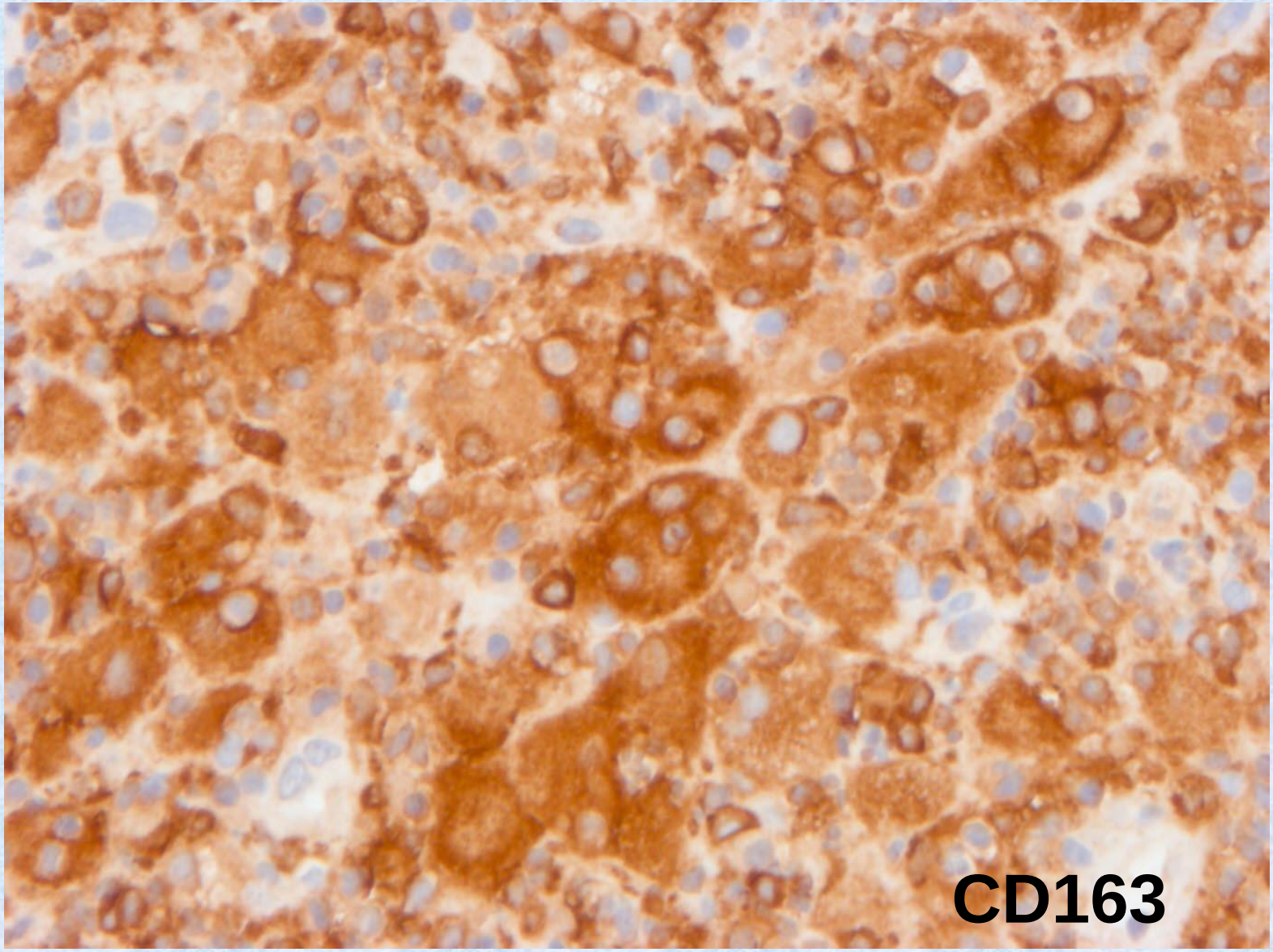

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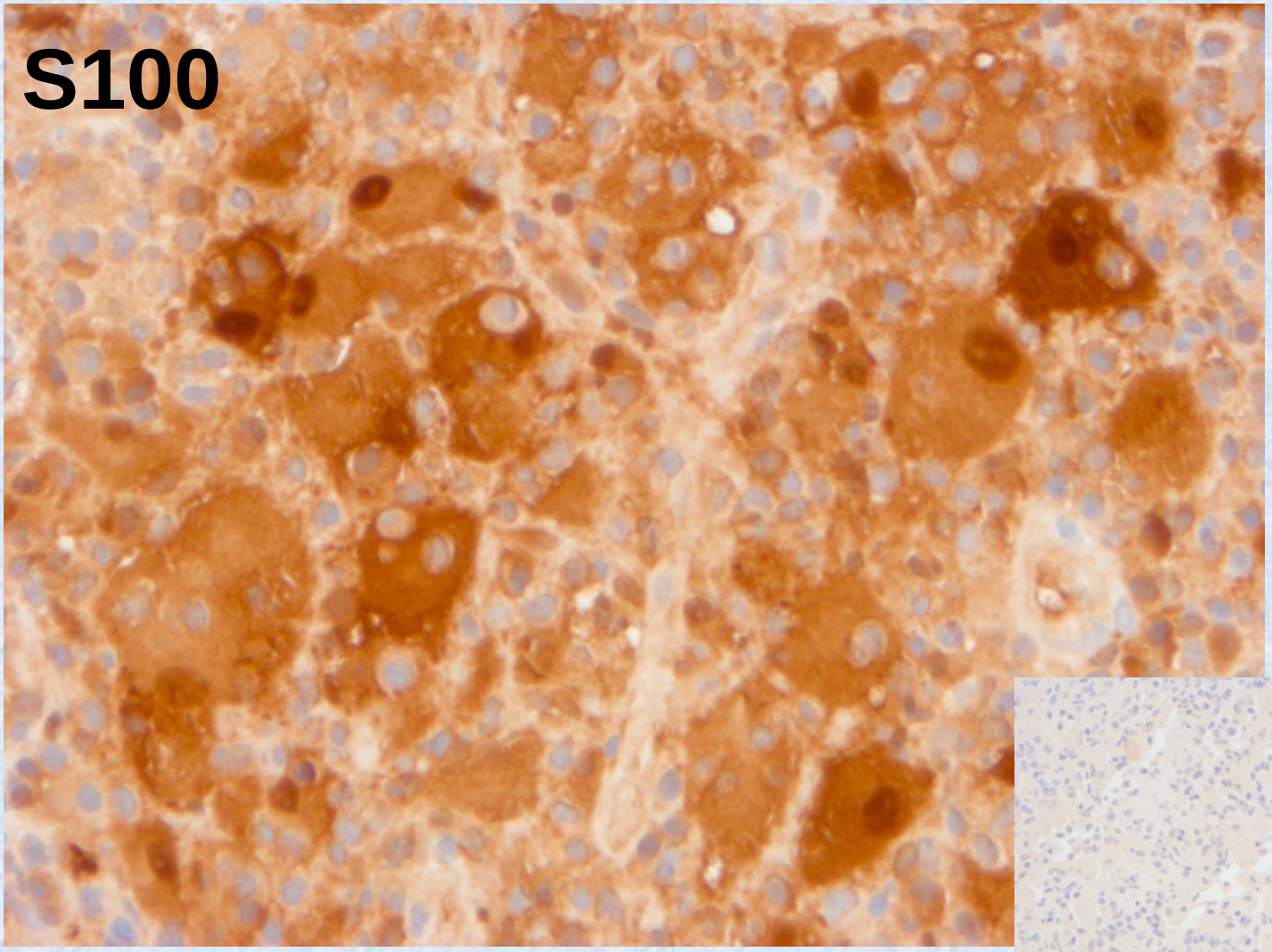
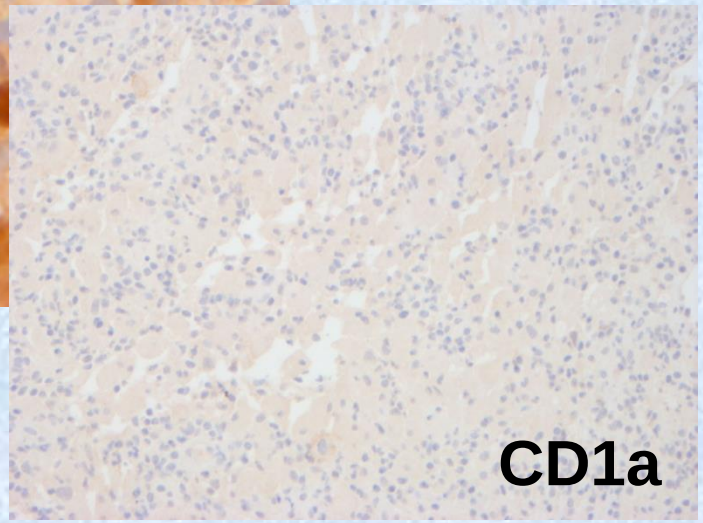
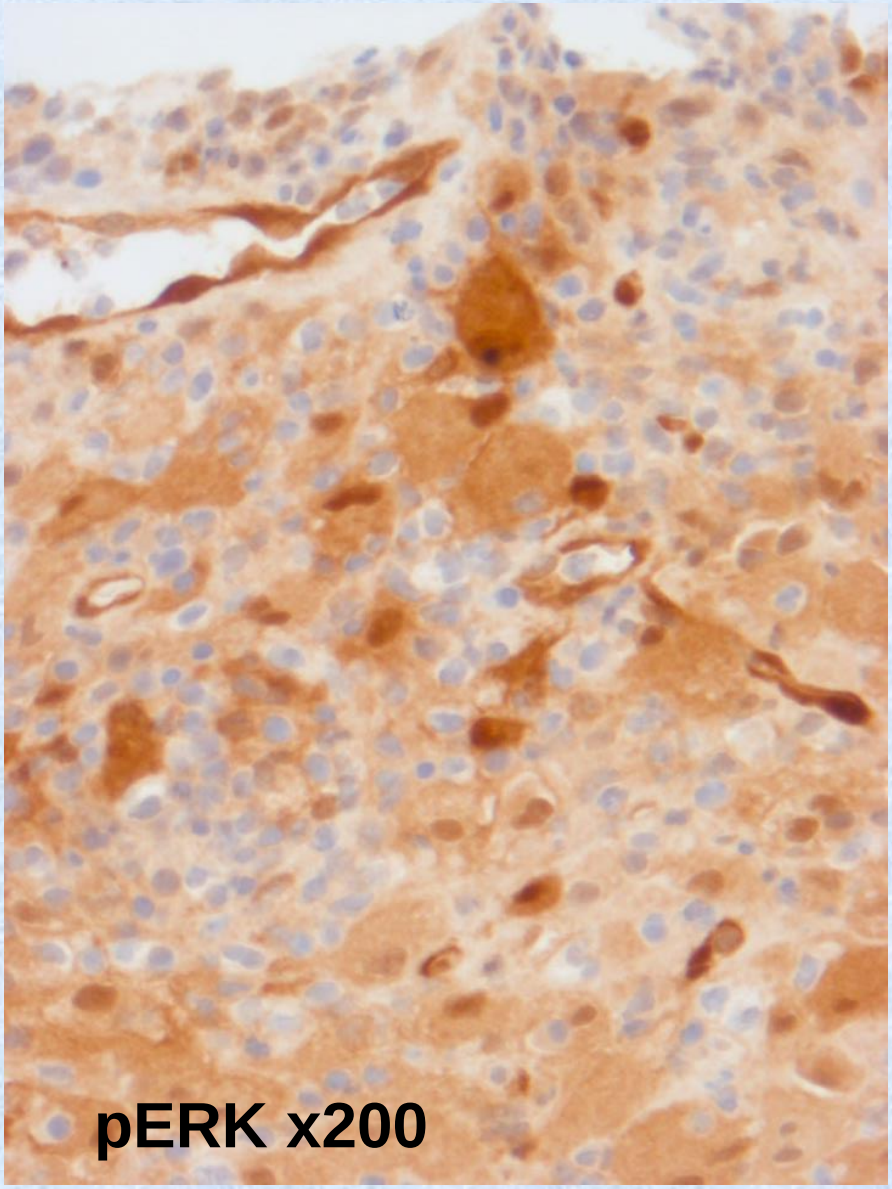
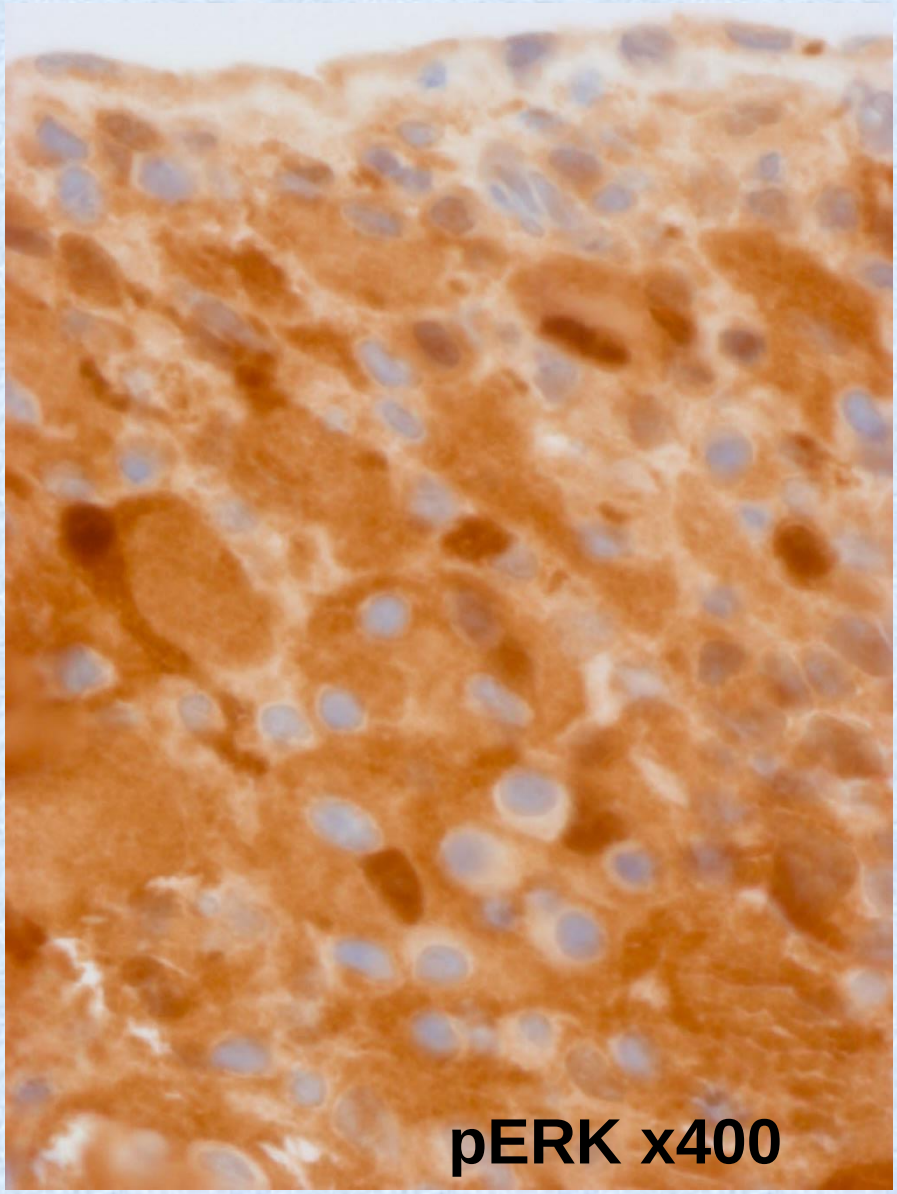




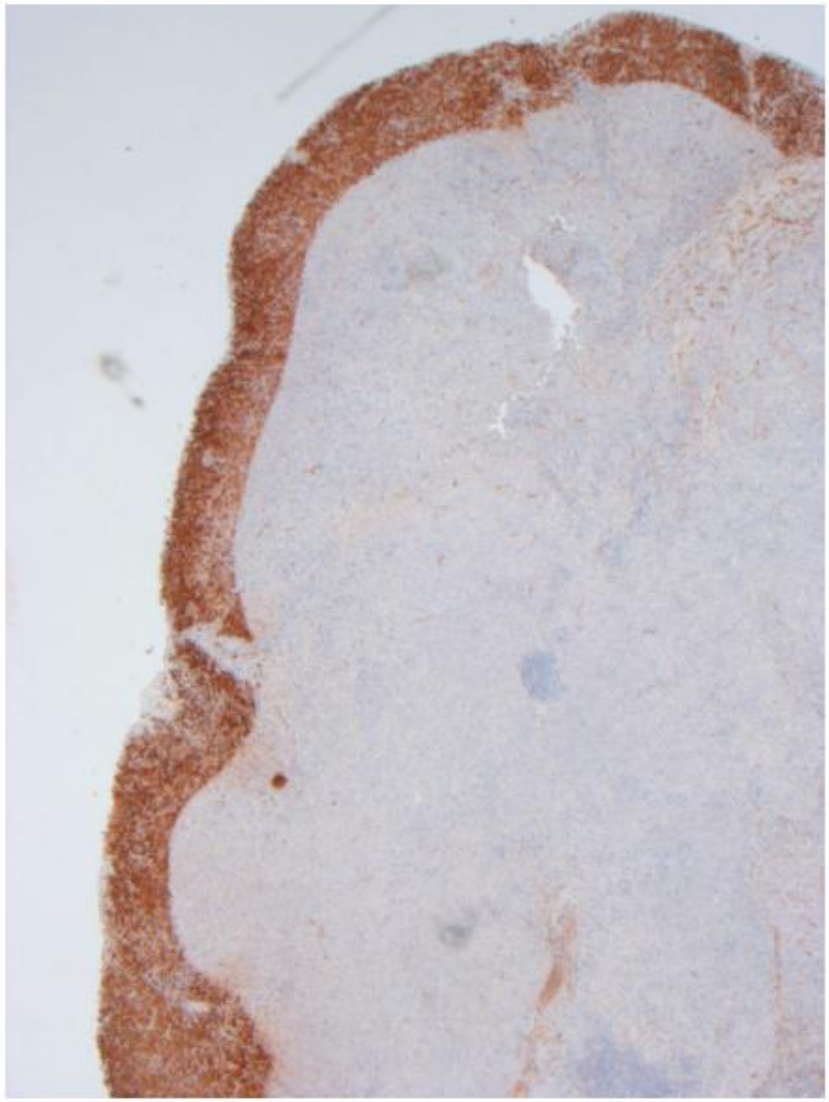
Maladie de Rosai-Dorfman

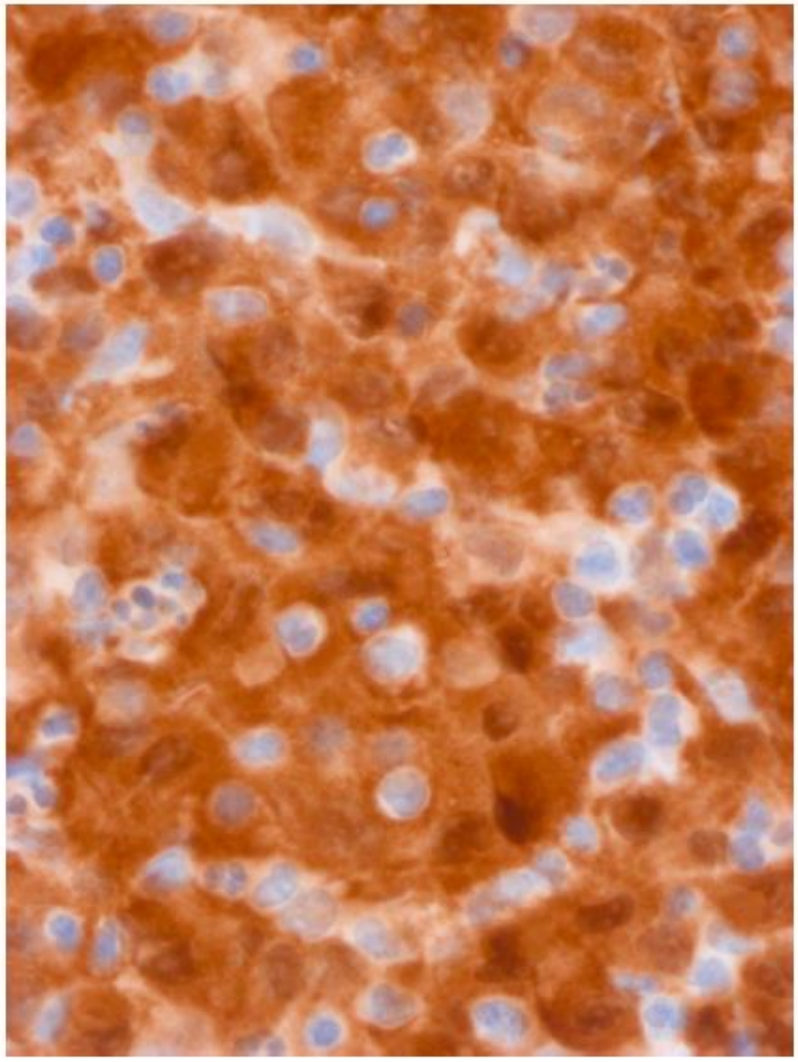
Cas clinique n°2 (19C00236)





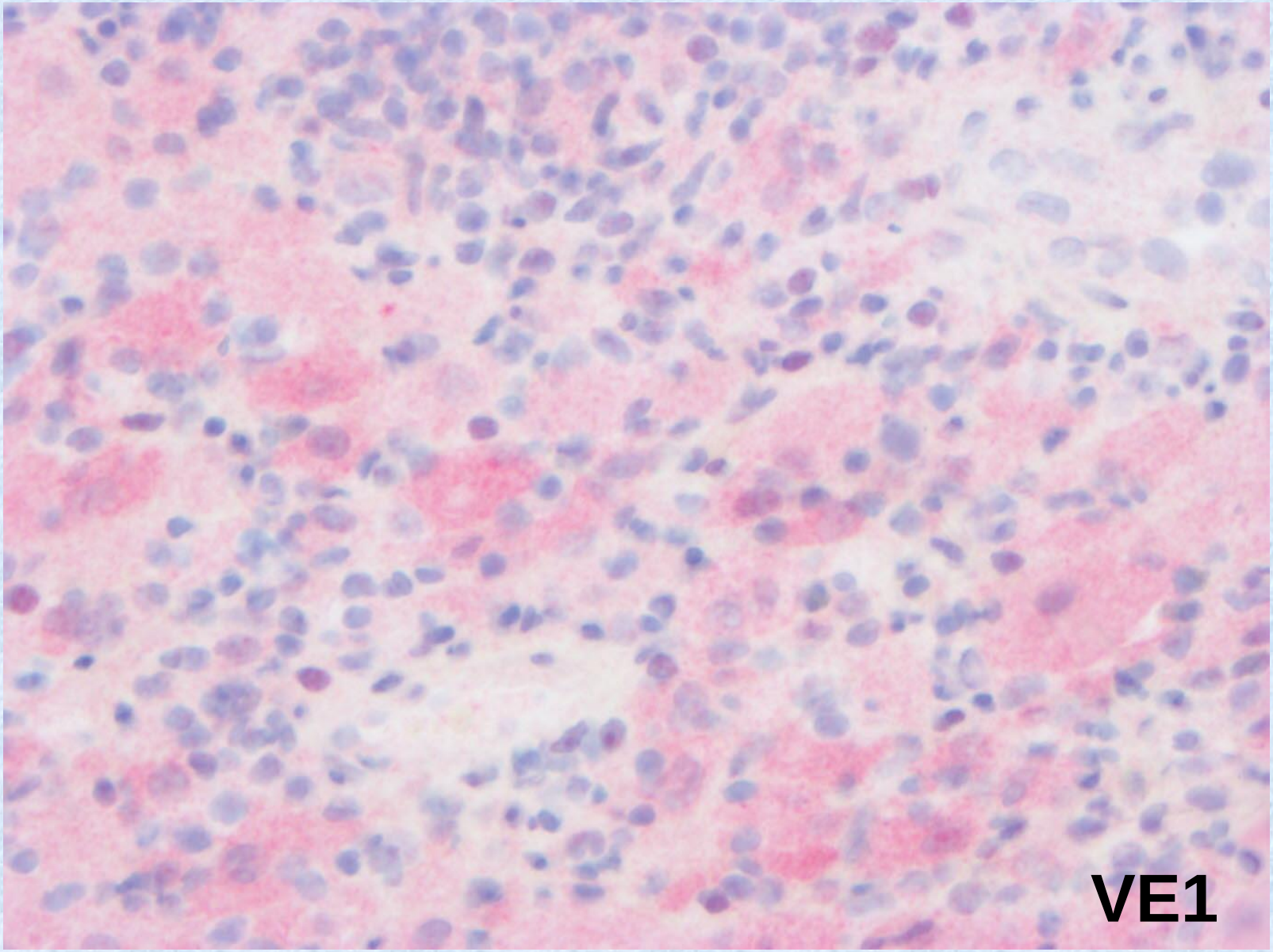
Marquage phosphoERK





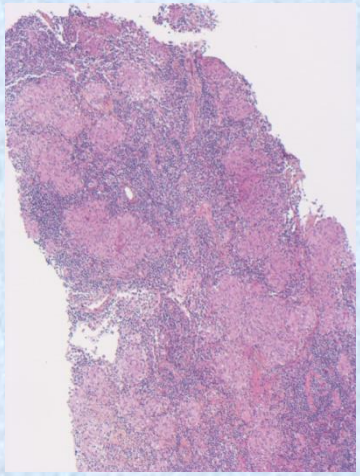
Très sensible à la fixation

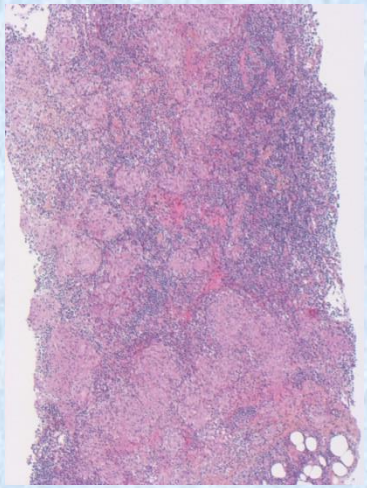
Cas clinique n°2 (19C00236)

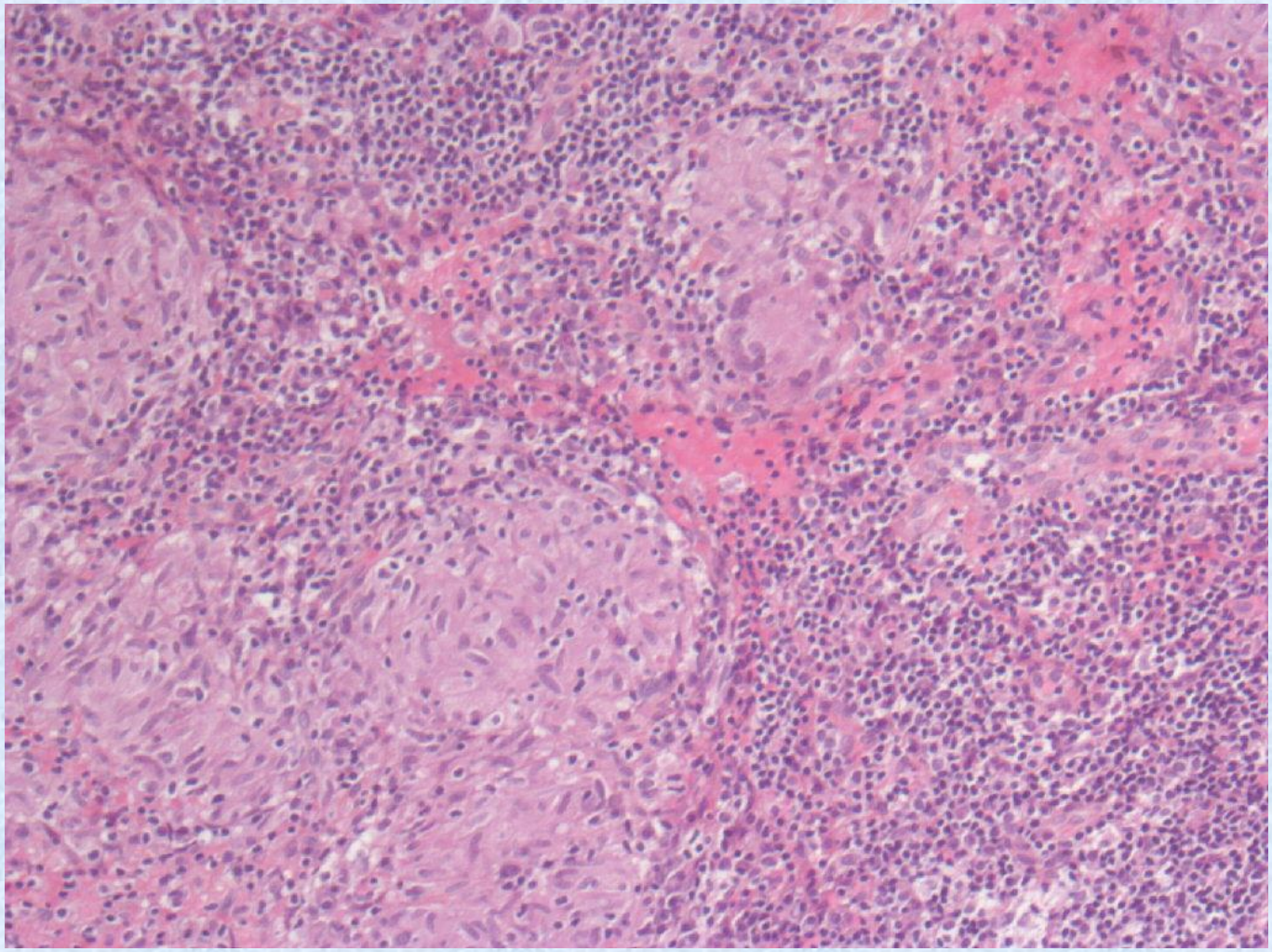


Cas clinique n°3 (C160016778)

• Homme 57 ans. Maladie d'Erdheim-Chester avec mutation de *BRAF*, traité par vemurafenib. Excellente réponse.
→ Apparition d'adénopathies : Rechute ?



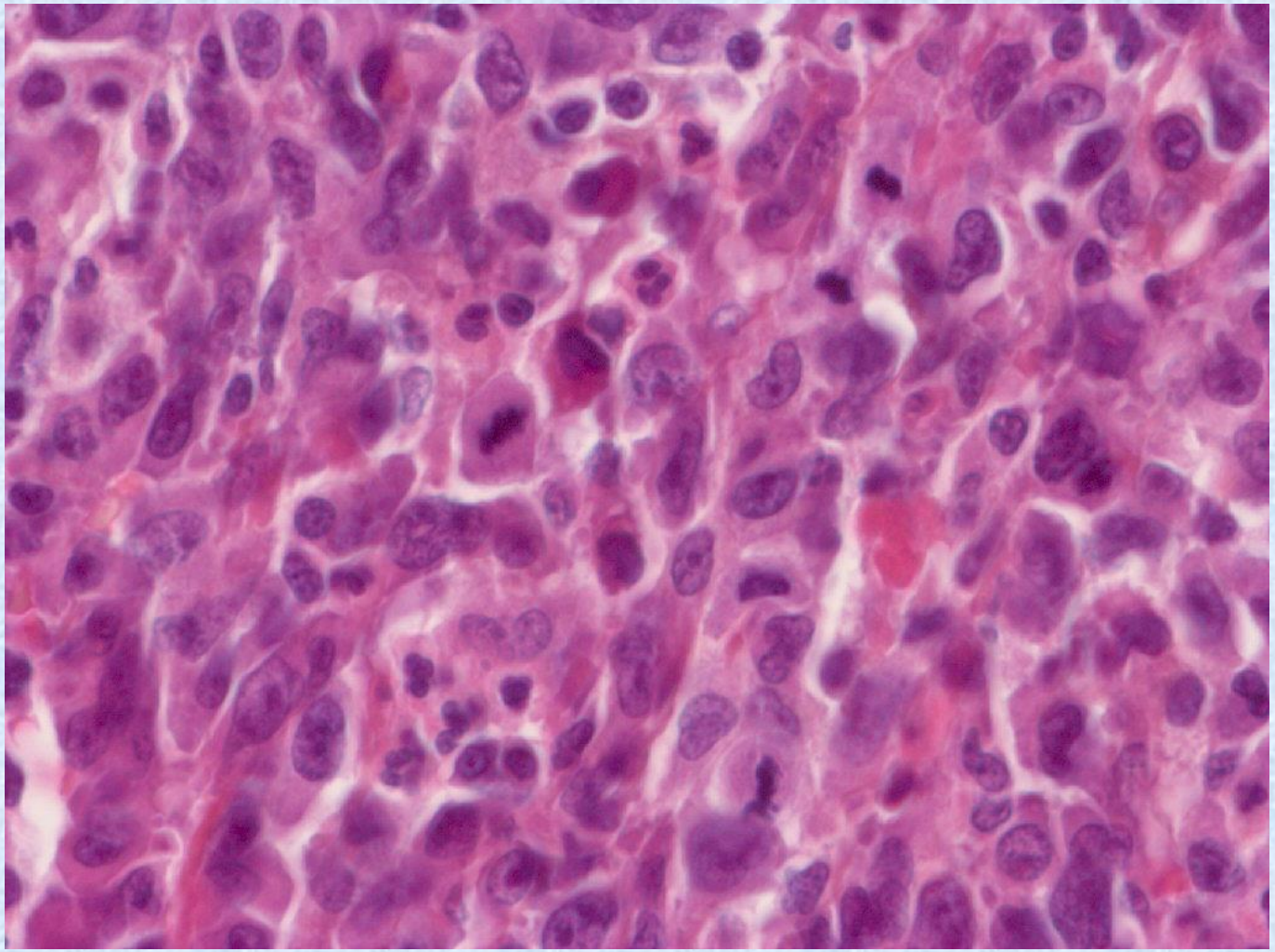




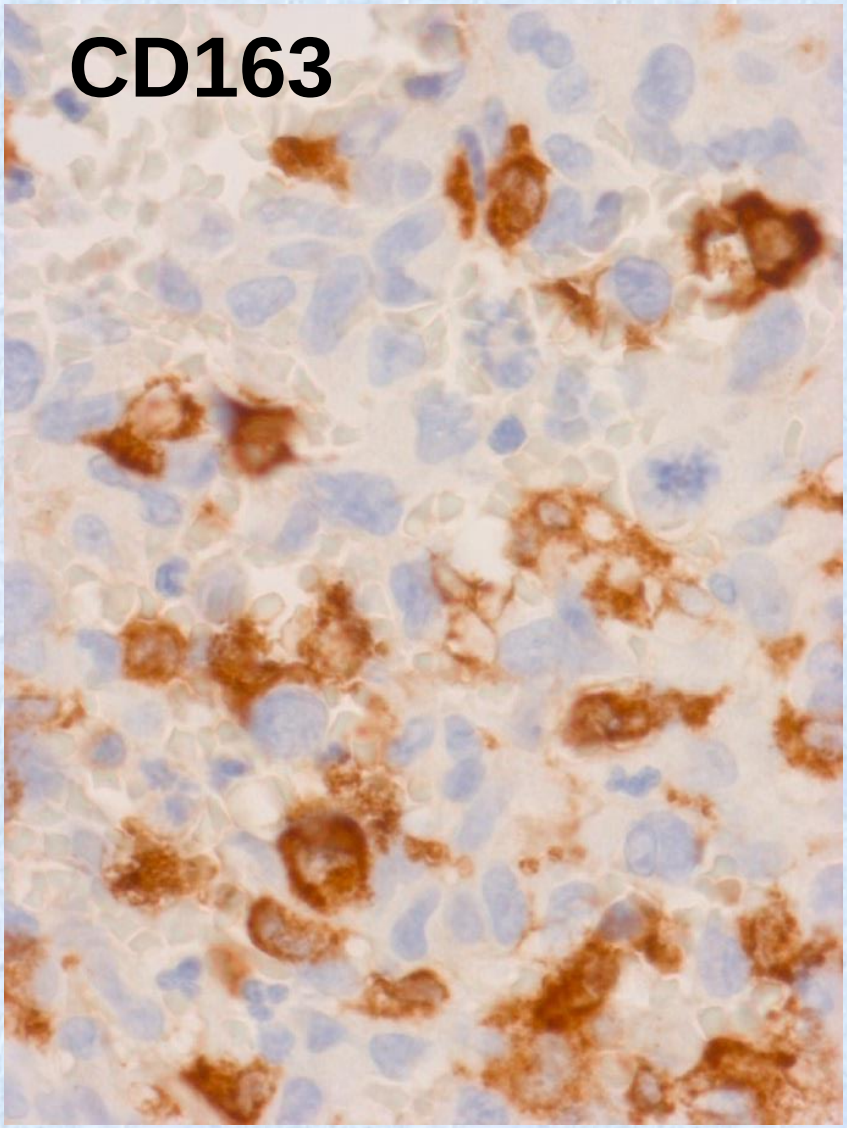
Amoura JEADV 2019

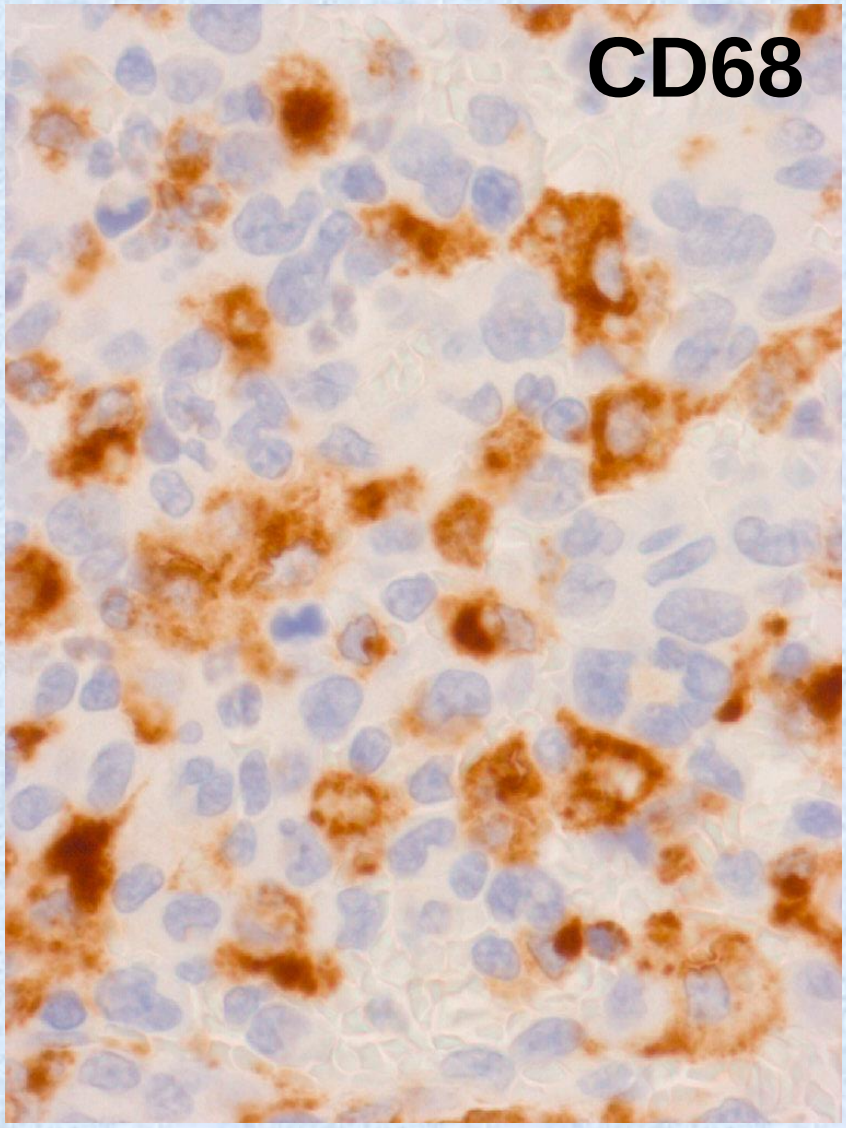
Cas clinique n°4 (C16000351))

- Histiocytose maligne ?



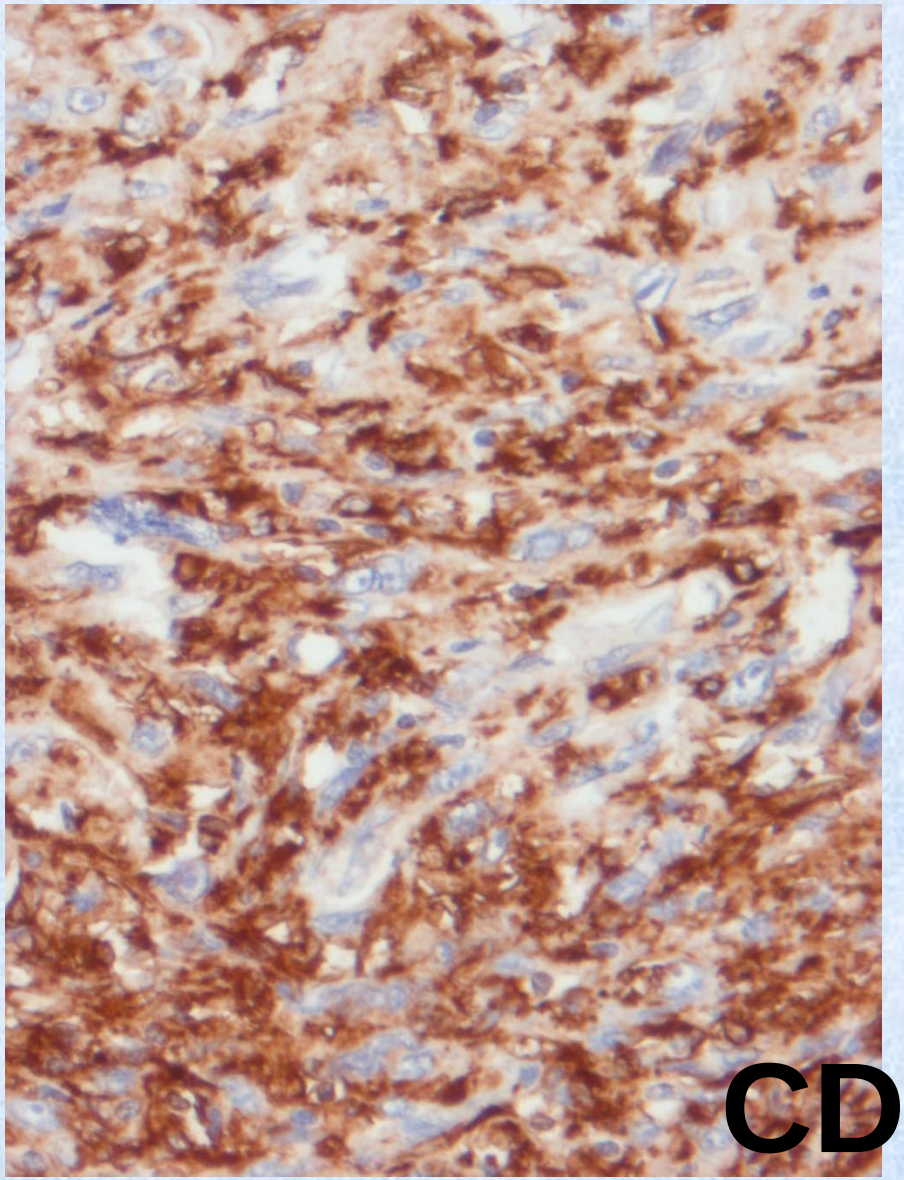
Cas clinique n°4 (C16000351)

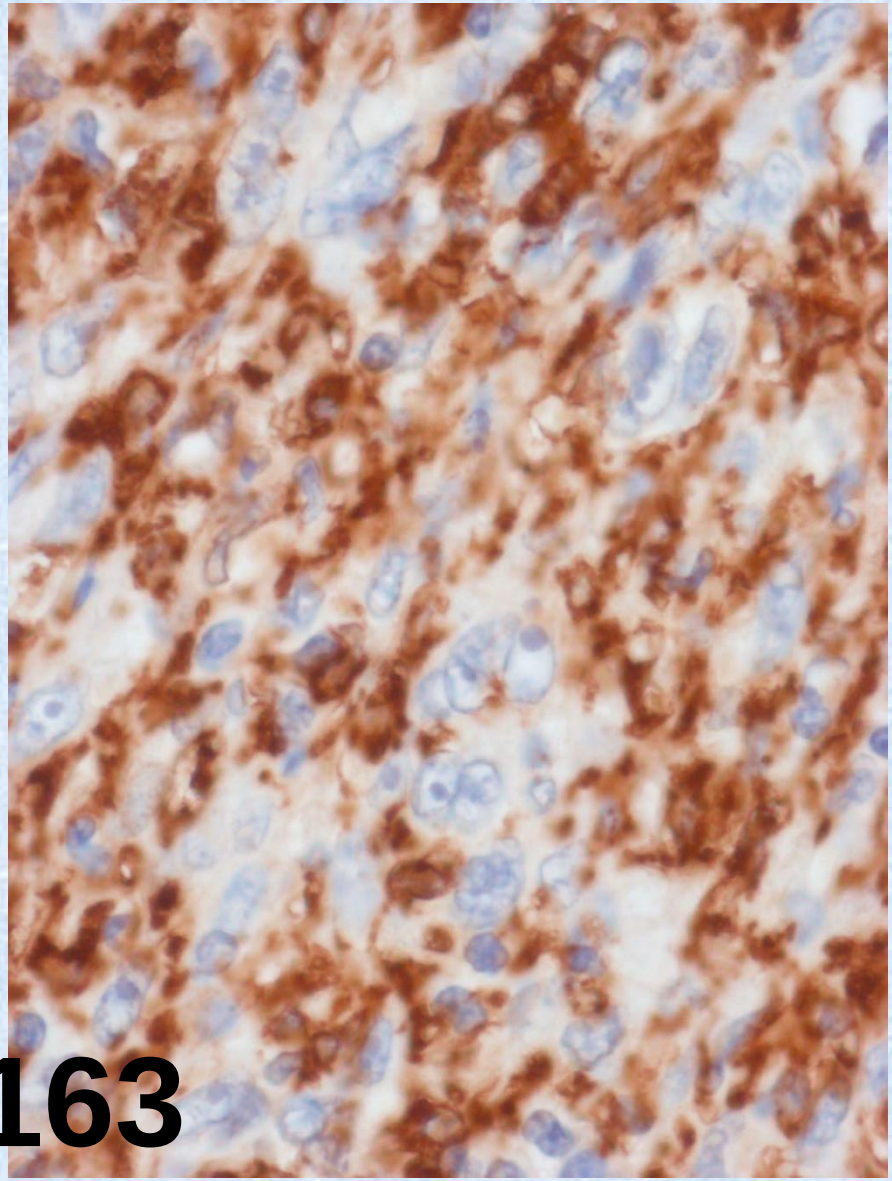




Tumeurs « muettes » riches en histiocytes

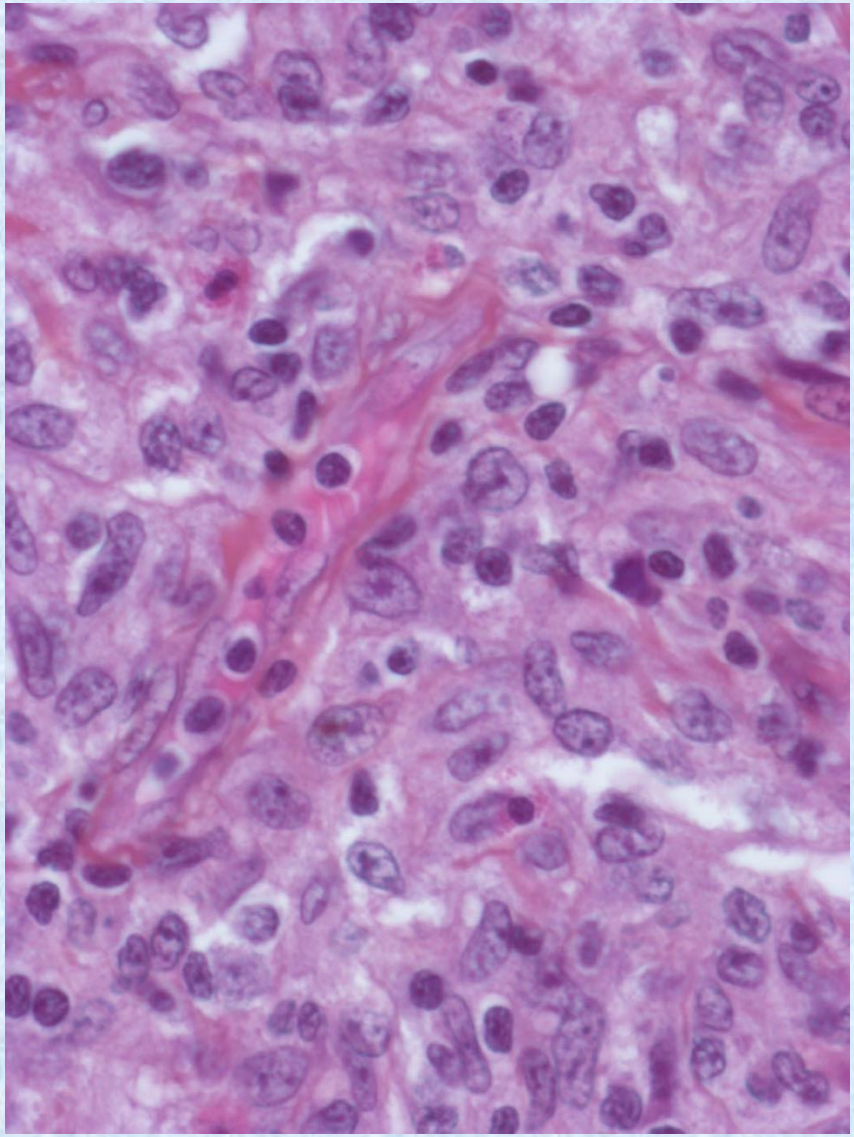
Stroma riche en histiocytes (19C00397)

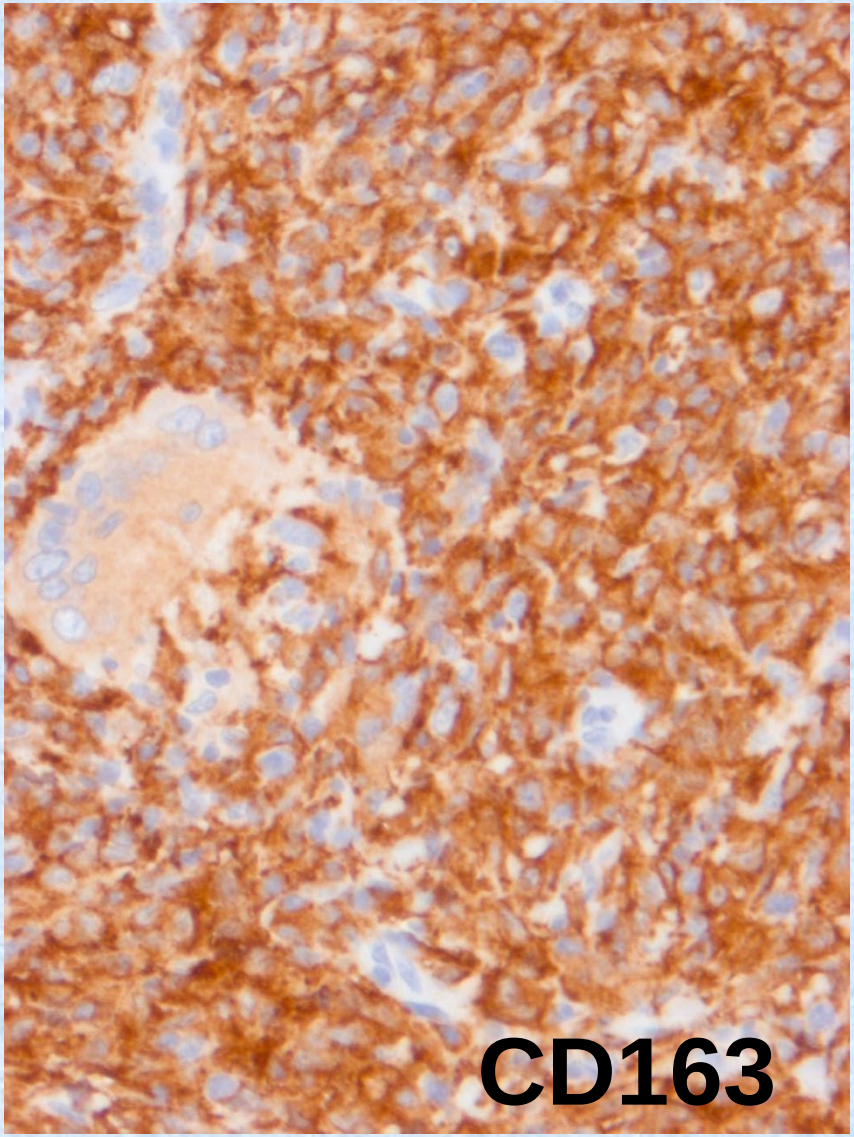




CD163

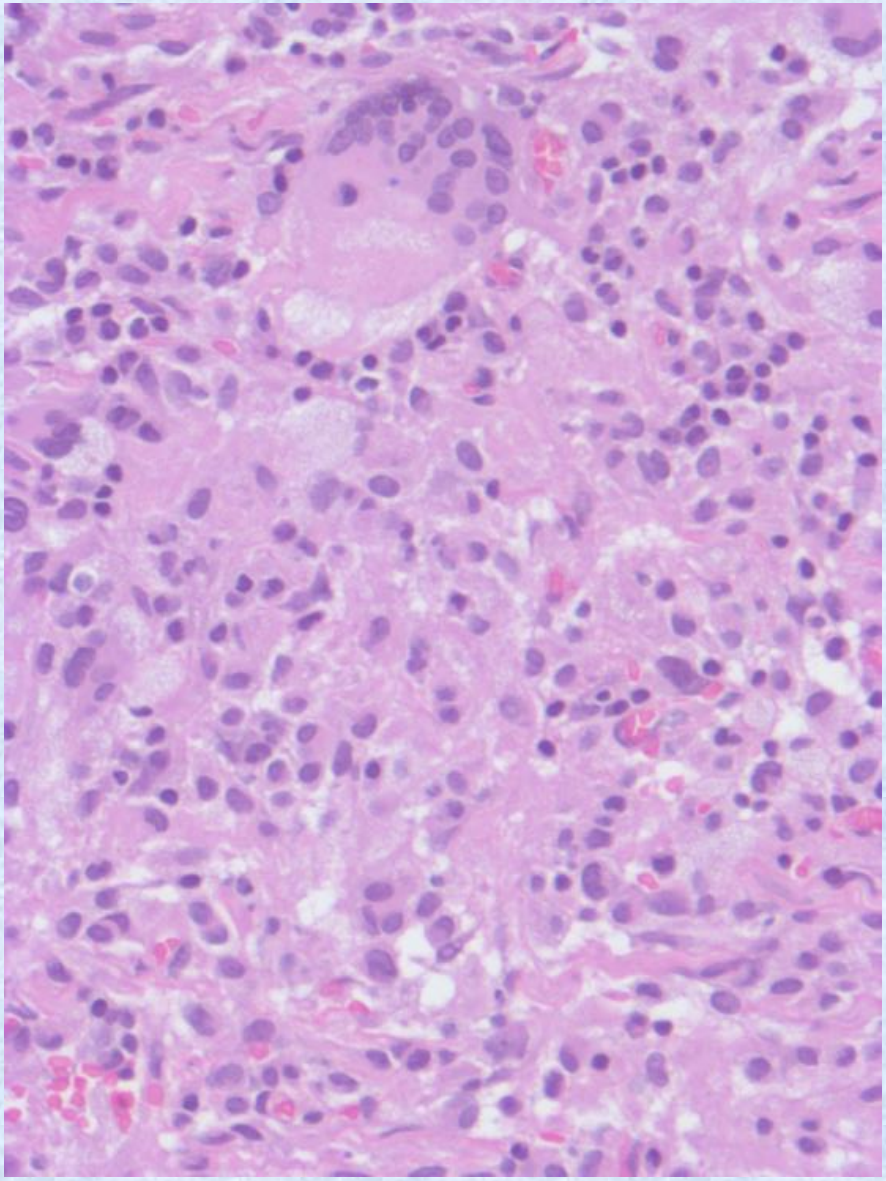
Stroma riche en histiocytes (19C00554)

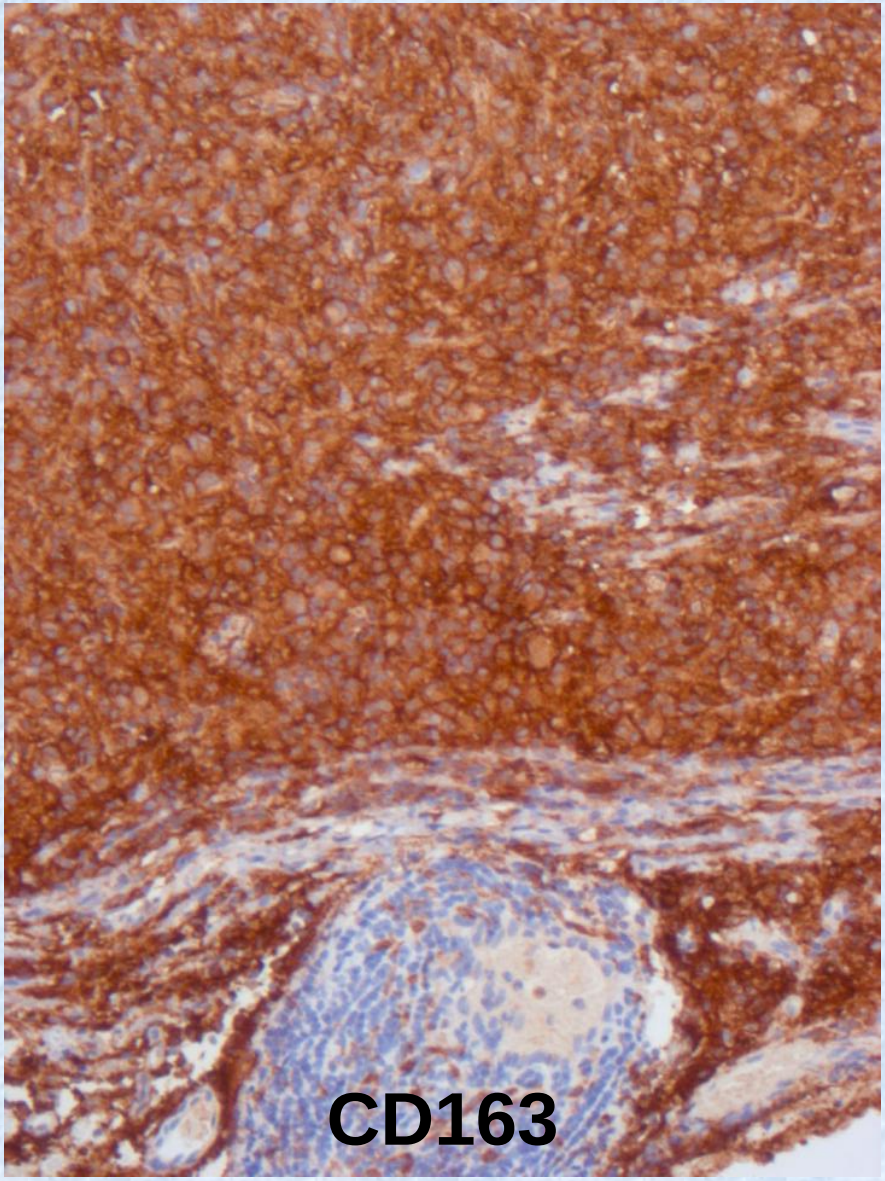




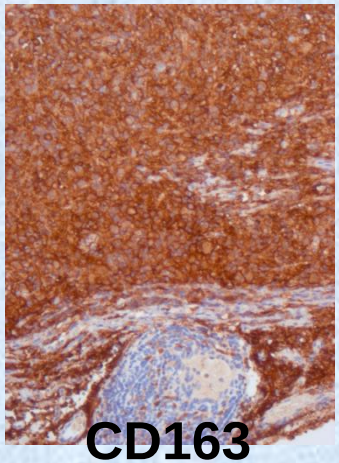
Lymphome T !

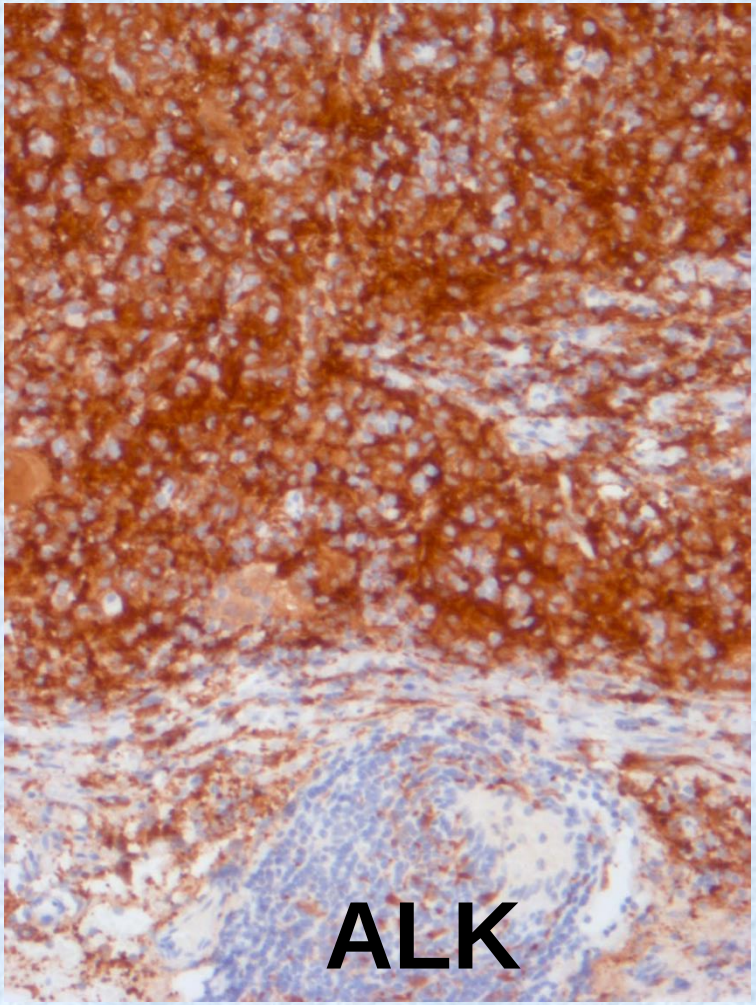
Cas clinique n°5 (19C00458)

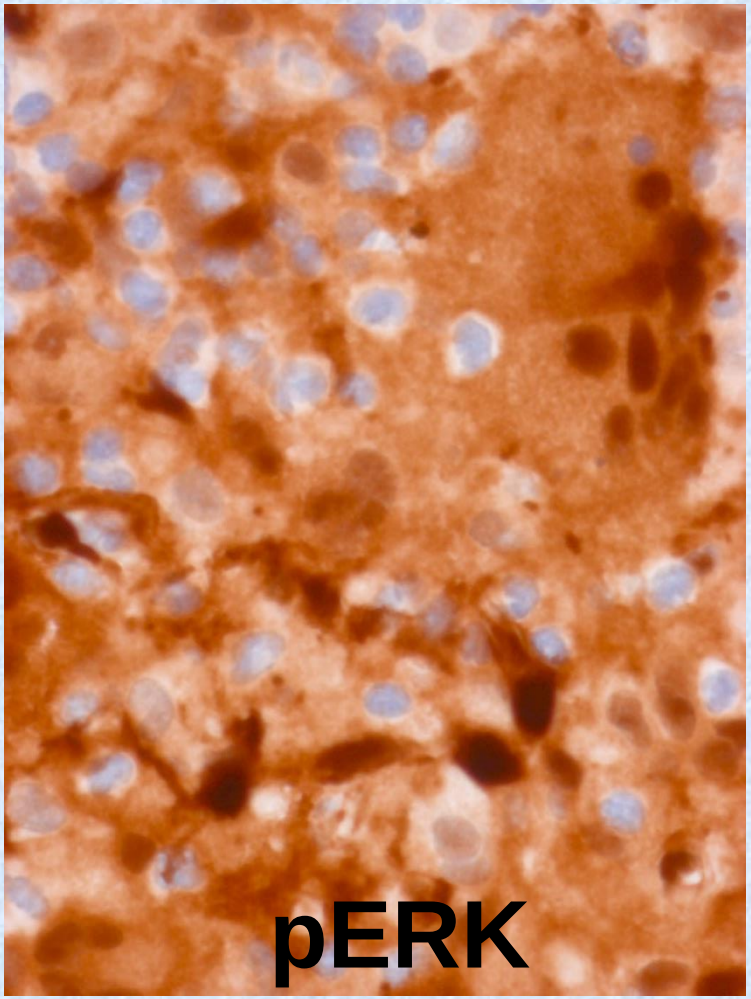




Cas clinique n°5 (19C00458)



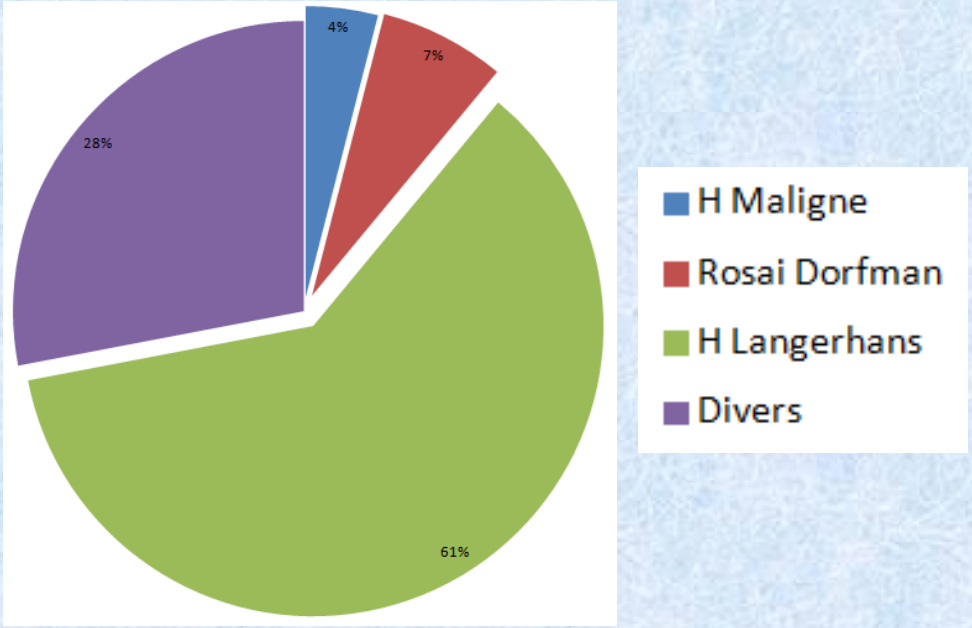




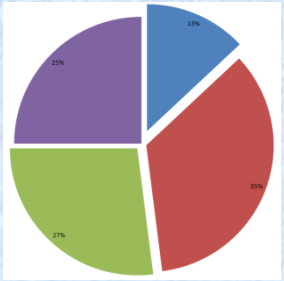
marqueurs d’intérêt thérapeutiques

Histiocytoses en seconde lecture

Proportions sur 1514 cas



Biopsies ganglionnaires : 7,5%



Histiocytoses : Intérêt de l'analyse moléculaire

Physiopathogénie / Classification

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages

Jean-François Emile,[1,2] Oussama Abla,[3] Sylvie Fraitag,[4] Annacarin Horne,[5] Julien Haroche,[6,7] Jean Donadieu,[1,8] Luis Requena-Caballero,[9] Michael B. Jordan,[10] Omar Abdel-Wahab,[11] Carl E. Allen,[12] Frédéric Charlotte,[7,13] Eli L. Diamond,[14] R. Maarten Egeler,[3] Alain Fischer,[15,16] Juana Gil Herrera,[17] Jan-Inge Henter,[18] Filip Janku,[19] Miriam Merad,[20] Jennifer Picarsic,[21] Carlos Rodriguez-Galindo,[22] Barret J. Rollins,[23,24] Abdellatif Tazi,[25] Robert Vassallo,[26] and Lawrence M. Weiss,[27] for the Histiocyte Society

BLOOD, 2 JUNE 2016

Diagnostic

. Microbiopsies,

. Diagnostics difficiles

Recurrent *BRAF* mutations in Langerhans cell histiocytosis

Gayane Badalian-Very,[1-3] Jo-Anne Vergilio,[4,5] Barbara A. Degar,[6-8] Laura E. MacConaill,[9] Barbara Brandner,[1-3] Monica L. Calicchio,[4] Frank C. Kuo,[5,10] Azra H. Ligon,[5,10,11] Kristen E. Stevenson,[12] Sarah M. Kehoe,[9] Levi A. Garraway,[1-3,9,13] William C. Hahn,[1-3,9,13] Matthew Meyerson,[1,2,9,13] Mark D. Fleming,[4,5] and Barrett J. Rollins[1-3]

BLOOD, 16 SEPTEMBER 2010

Pronostic

BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy

Sébastien Héritier, Jean-François Emile, Mohamed-Aziz Barkaoui, Caroline Thomas, Sylvie Fraitag, Sabah Boudjemaa, Florence Renaud, Anne Moreau, Michel Peuchmaur, Catherine Chassagne-Clément, Frédérique Dijoud, Valérie Rigau, Despina Moshous, Anne Lambilliotte, Françoise Mazingue, Kamila Kebaili, Jean Miron, Eric Jeziorski, Geneviève Plat, Nathalie Aladjidi, Alina Ferster, Hélène Pacquement, Claire Galambrun, Laurence Brugières, Guy Leverger, Ludovic Mansuy, Catherine Paillard, Anne Deville, Corinne Armari-Alla, Anne Lutun, Marion Gillibert-Yvert, Jean-Louis Stephan, Fleur Cohen-Aubart, Julien Haroche, Isabelle Pellier, Frédéric Millot, Brigitte Lescoeur, Virginie Gandemer, Christine Bodemer, Roger Lacave, Zofia Hélias-Rodzewicz, Valérie Taly, Frédéric Geissmann, and Jean Donadieu

J Clin Oncol 34. © 2016

Suivi sous traitement

Thérapies ciblées

Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the *BRAF* V600E mutation

*Julien Haroche,[1,2] *Fleur Cohen-Aubart,[1,2] *Jean-François Emile,[3] *Laurent Arnaud,[1,2] Philippe Maksud,[4] Frédéric Charlotte,[5] Philippe Cluzel,[6] Aurélie Drier,[7] Baptiste Hervier,[1,2] Neïla Benameur,[8] Sophie Besnard,[9] Jean Donadieu,[10] and Zahir Amoura[1,2]

(*Blood*. 2013;121(9):1495-1500)

Histiocytoses : Thérapie ciblée par vemurafenib

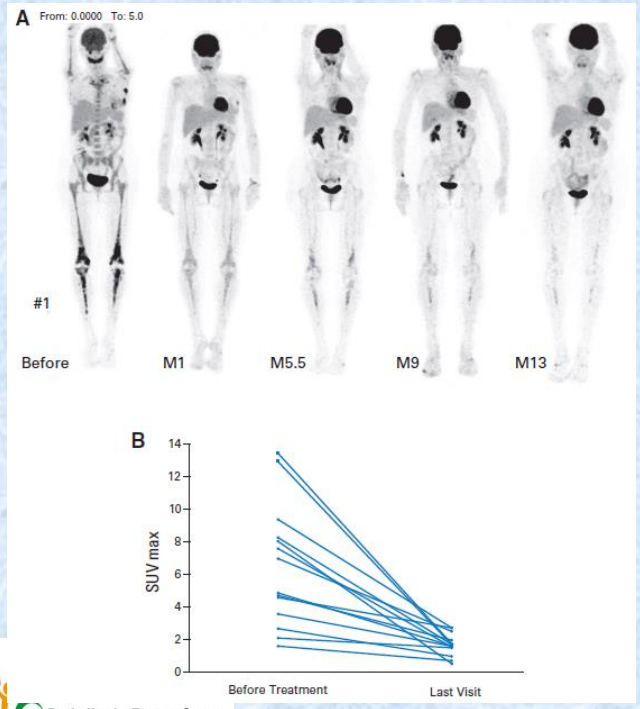
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

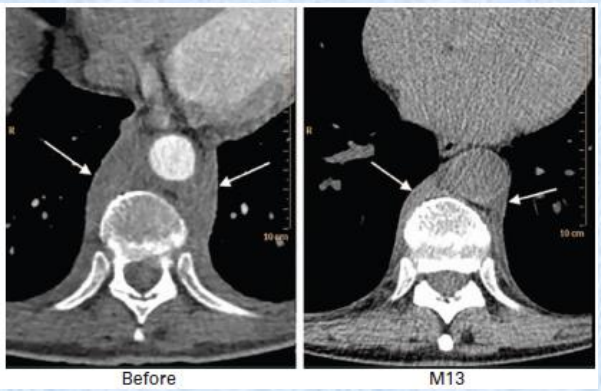
Reproducible and Sustained Efficacy of Targeted Therapy With Vemurafenib in Patients With *BRAF*^{V600E}-Mutated Erdheim-Chester Disease

Julien Haroche, Fleur Cohen-Aubart, Jean-François Emile, Philippe Maksud, Aurélie Drier, Dan Tolédano, Stéphane Barete, Frédéric Charlotte, Philippe Cluzel, Jean Donadieu, Neïla Benameur, Philippe A. Grenier, Sophie Besnard, Jean-Paul Ory, François Lifermann, Ahmed Idbaih, Brigitte Granel, Bruno Graffin, Baptiste Hervier, Laurent Arnaud, and Zahir Amoura

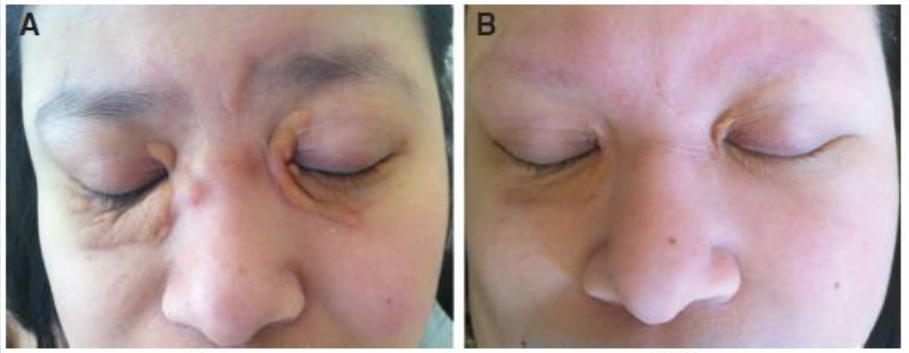
J.H., F. C.-A., and J.-F.E. contributed equally to this work.

J Clin Oncol 32. © 2014





8 patients with ECD or ECD/LCH



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RIS-SACLAY

Histiocytoses : Thérapie ciblée par vemurafenib

Vemurafenib for Refractory Multisystem Langerhans Cell Histiocytosis in Children: An International Observational Study

Jean Donadieu, MD, PhD[1]; Islam Amine Larabi, MD[2]; Mathilde Tardieu, MD[3]; Johannes Visser, MD[4]; Caroline Hutter, MD[5]; Elena Sieni, MD[6]; Nabil Kabbara, MD[7,8]; Mohamed Barkaoui, MSc[1]; Jean Miron, MSc[1]; François Chalard, MD[1]; Paul Milne, MD, PhD[9]; Julien Haroche, MD, PhD[10]; Fleur Cohen, MD[10]; Zofia Hélias-Rodzewicz, MD[11]; Nicolas Simon, MD[12]; Mathilde Jehanne, MD[13]; Alexandra Kolenova, MD[14]; Anne Pagnier, MD[3]; Nathalie Aladjidi, MD[15]; Pascale Schneider, MD[16]; Geneviève Plat, MD[17]; Anne Lutun, MD[18]; Anne Sonntagbauer, MD[19]; Thomas Lehrnbecher, MD[19]; Alina Ferster, MD[20]; Viktoria Efremova, MD[21]; Martina Ahlmann, MD[22]; Laurence Blanc, MD[23]; James Nicholson, MD[4]; Anne Lambilliote, MD[24]; Houda Boudiaf, MD[25]; Andrej Lissat, MD[26]; Karel Svojgr, MD[27]; Fanette Bernard, MD[28]; Sarah Elitzur, MD[29]; Michal Golan, MD[30]; Dmitriy Evseev, MD[31]; Michael Maschan, MD[31]; Ahmed Idbaih, MD, PhD[32]; Olga Slater, MD[33]; Milen Minkov, MD[5]; Valerie Taly, MD, PhD[34]; Matthew Collin, MD, PhD[9]; Jean-Claude Alvarez, MD, PhD[2]; Jean-François Emile, MD, PhD[11]; and Sébastien Héritier, MD, PhD[1,11]

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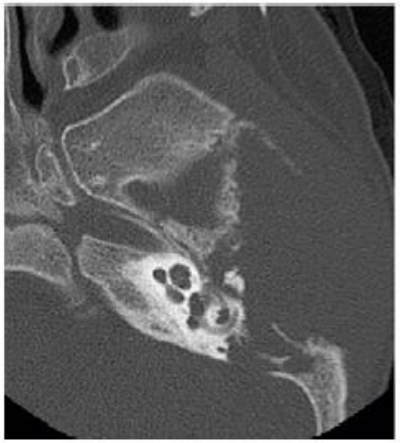
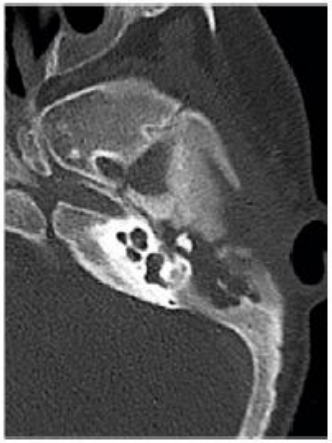
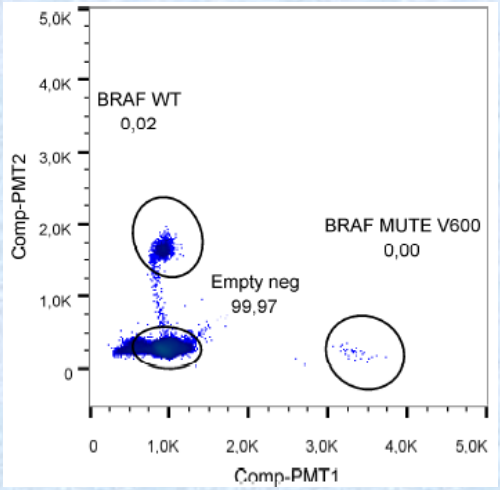
44 pts → At 8 weeks 36 CR and 16 PR





Détection des mutations : comment ?

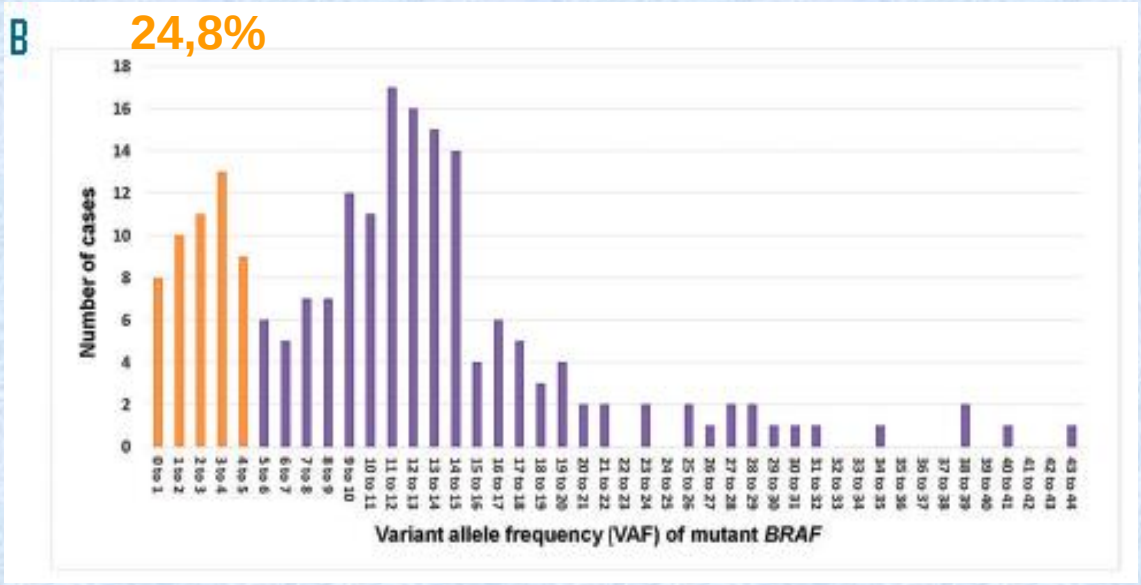


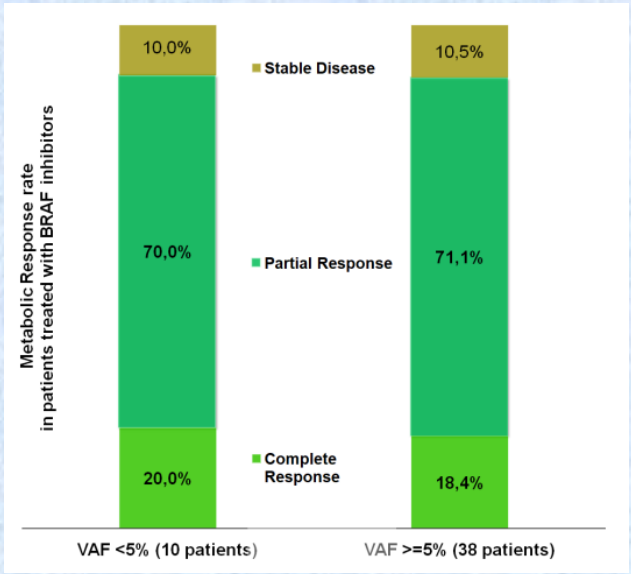
Digital dropplet PCR

Highly sensitive methods are required to detect mutations in histiocytoses

haematologica 2019; 104:e98

Sarah Melloul,[1] Zofia Hélias-Rodzewicz,[1,2]* Fleur Cohen-Aubart,[3,4]* Frédéric Charlotte,[3,5] Sylvie Fraitag,[6] Nathalie Terrones,[1,2] Quentin Riller,[4] Thibaud Chazal,[4] Sébastien Héritier,[1,7] Anne Moreau,[8] Marianne Kambouchner,[9] Marie Christine Copin,[10] Jean Donadieu,[1,7] Valérie Taly,[11] Zahir Amoura,[3,4] Julien Haroche[3,4] and Jean François Emile[1,2]*





→ **To be perfomed in plateforms experienced in analysing histiocytosis samples**

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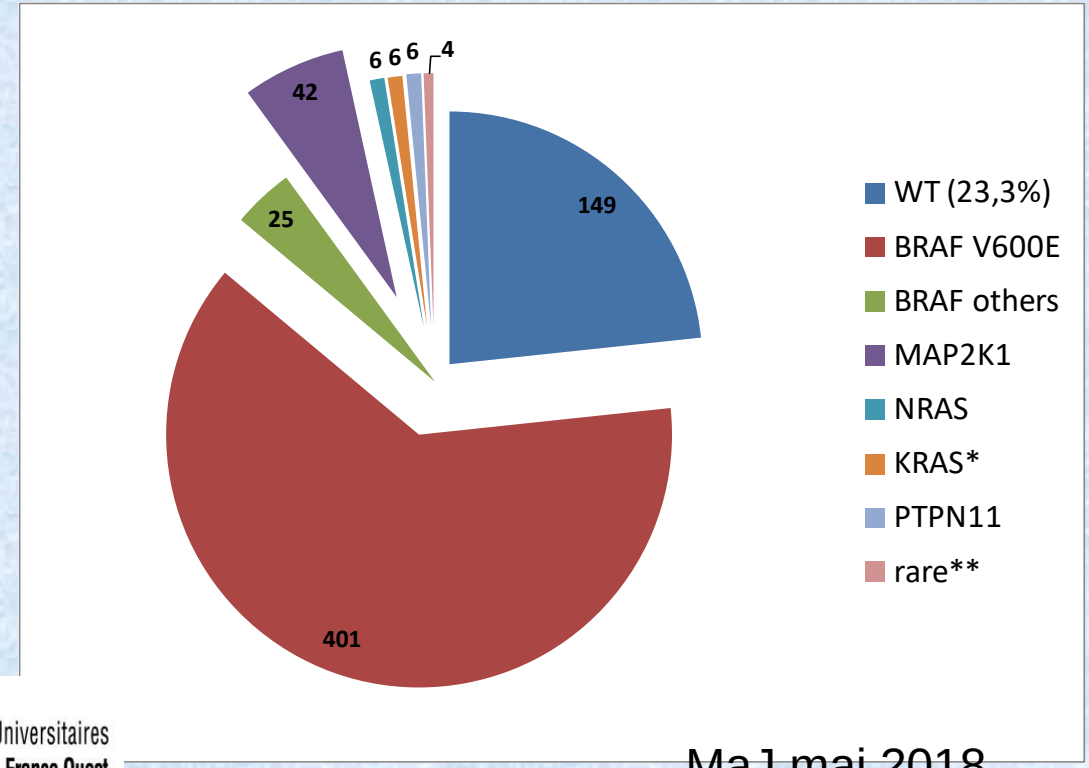
université PARIS-SACLAY

Mutations sur la voie des MAP kinases: Data of French network

639 échantillons de tout type d'histiocytoses (adultes)

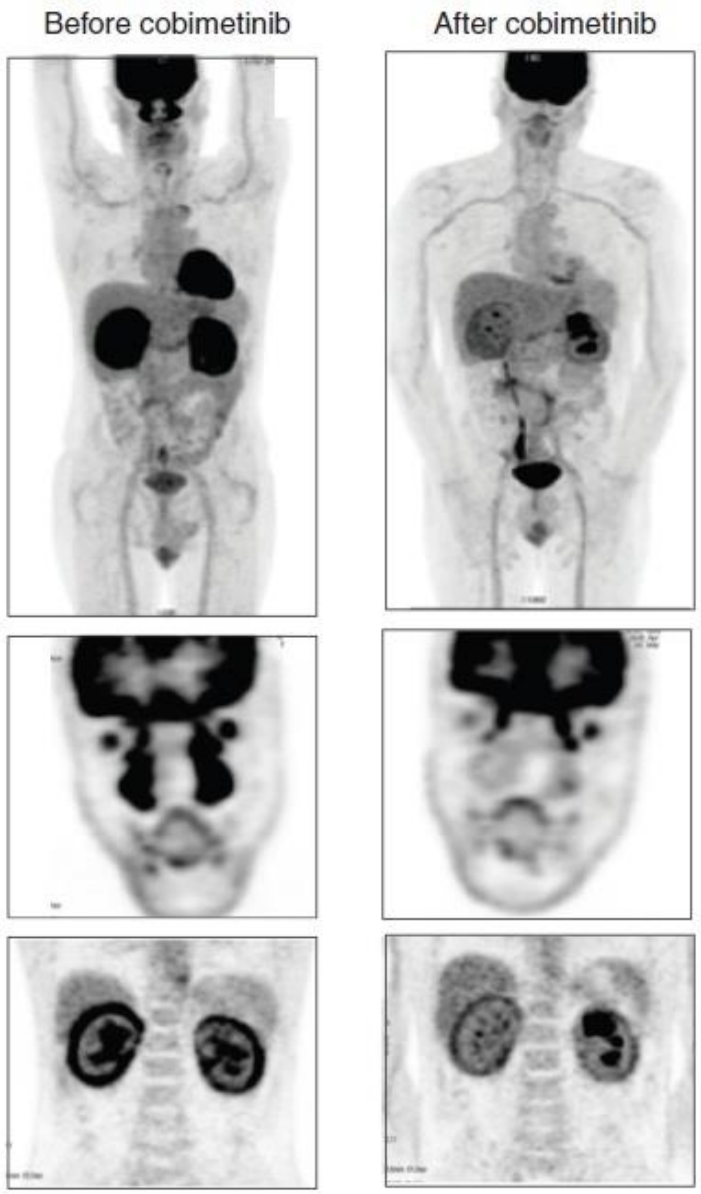
Analysés pour

- *BRAF*^{V600E} avec un haute sensibilité (au minimum 1000 goutellettes amplifiées)
- Et/ou NGS ciblé sur des gènes de la voie de signalisation des MAP kinase



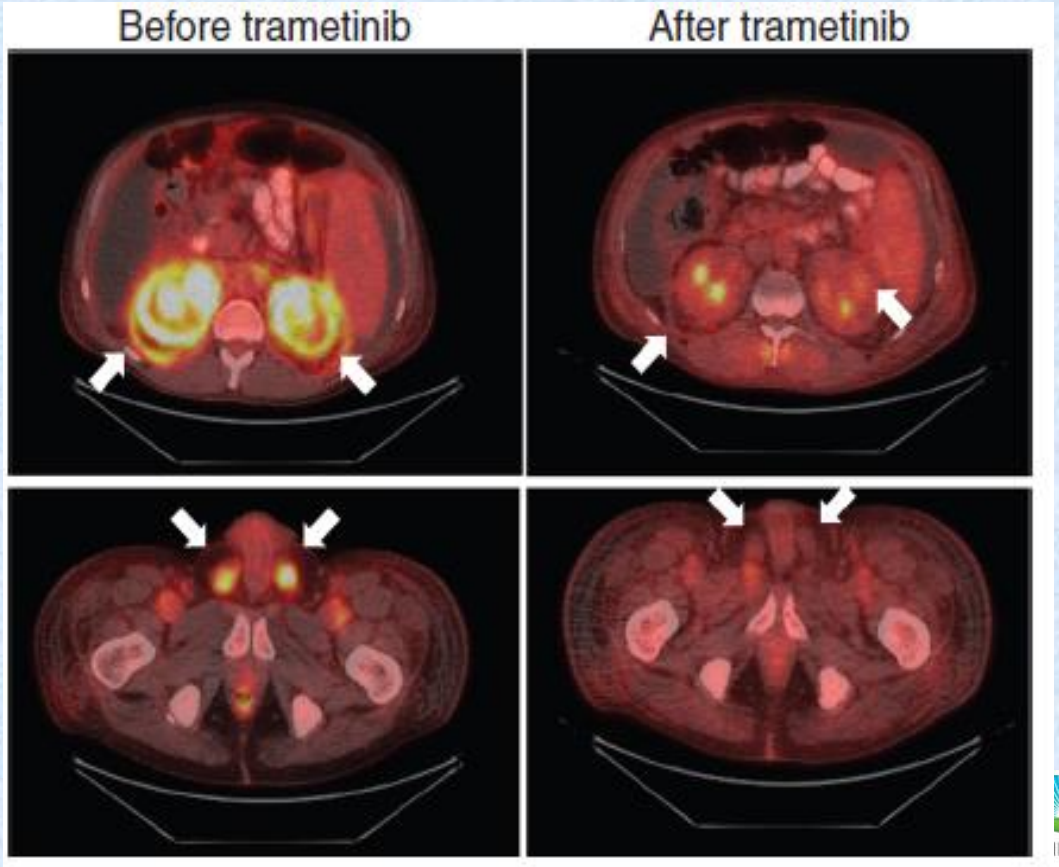
MaJ mai 2018

Thérapies ciblées pour les autres mutations



Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms

Eli L. Diamond[1], Benjamin H. Durham[2], Julien Haroche[3], Zhan Yao[4], Jing Ma[5], Sameer A. Parikh[6], Zhaoming Wang [7], John Choi[5], Eunhee Kim[8], Fleur Cohen-Aubart[3], Stanley Chun-Wei Lee[8], Yijun Gao[4], Jean-Baptiste Micol[8], Patrick Campbell[9], Michael P. Walsh[5], Brooke Sylvester[8], Igor Dolgalev[10], Olga Aminova[10], Adriana Heguy[10], Paul Zappile[10], Joy Nakitandwe[5], Chezi Ganzel[11], James D. Dalton[5], David W. Ellison[5], Juvianee Estrada-Veras[12], Mario Lacouture[13], William A. Gahl[12], Philip J. Stephens[14], Vincent A. Miller[14], Jeffrey S. Ross[14], Siraj M. Ali[14], Samuel R. Briggs[1], Omotayo Fasan[15], Jared Block[16], Sebastien Héritier[17,18], Jean Donadieu[17,18], David B. Solit[8], David M. Hyman[19], José Baselga[19], Filip Janku[20], Barry S. Taylor[8], Christopher Y. Park[2,8], Zahir Amoura[3], Ahmet Dogan[2], Jean-Francois Emile[16,21], Neal Rosen[4], Tanja A. Gruber[5,9], and Omar Abdel-Wahab[8,22]

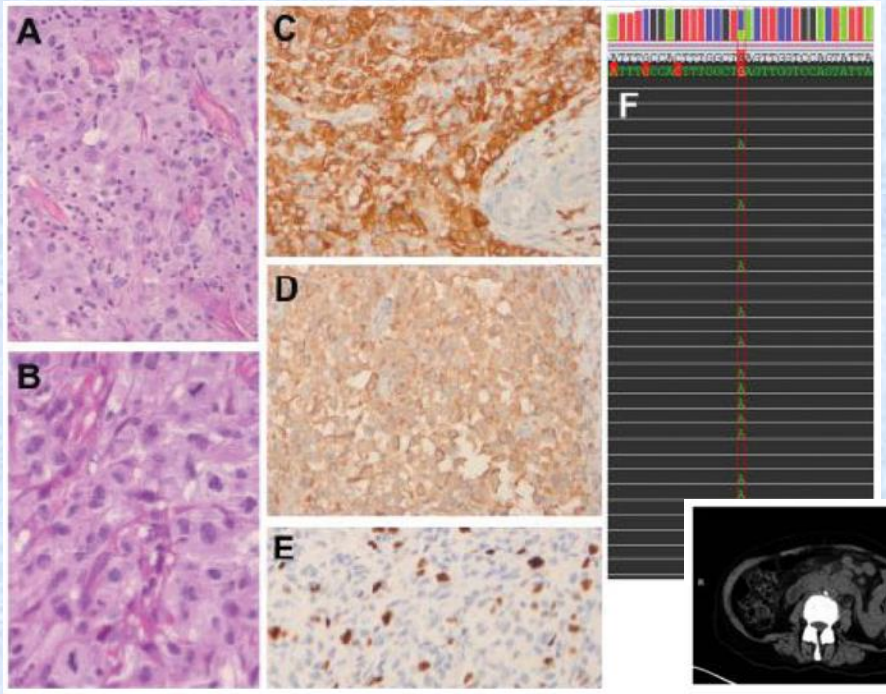


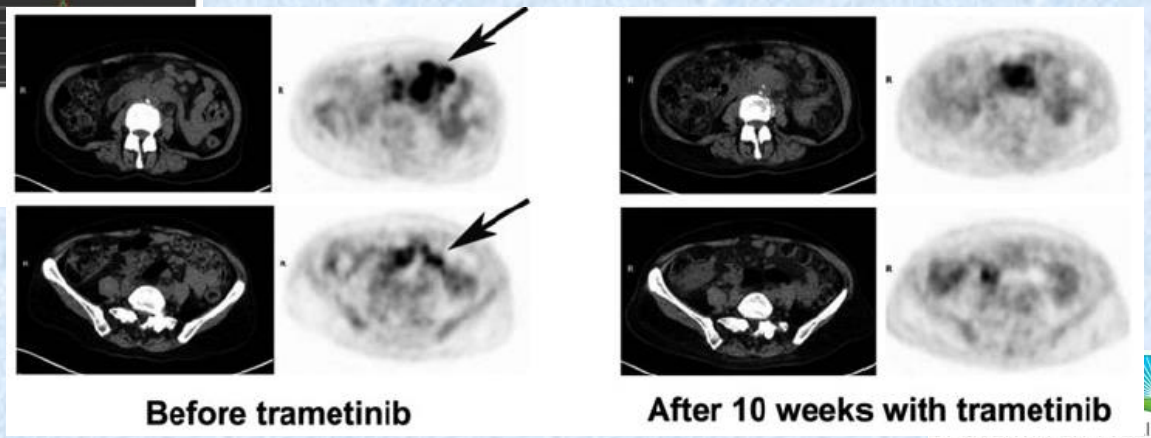
Thérapies ciblées pour les autres mutations

Response to trametinib of histiocytosis with an activating *PTPN11* mutation

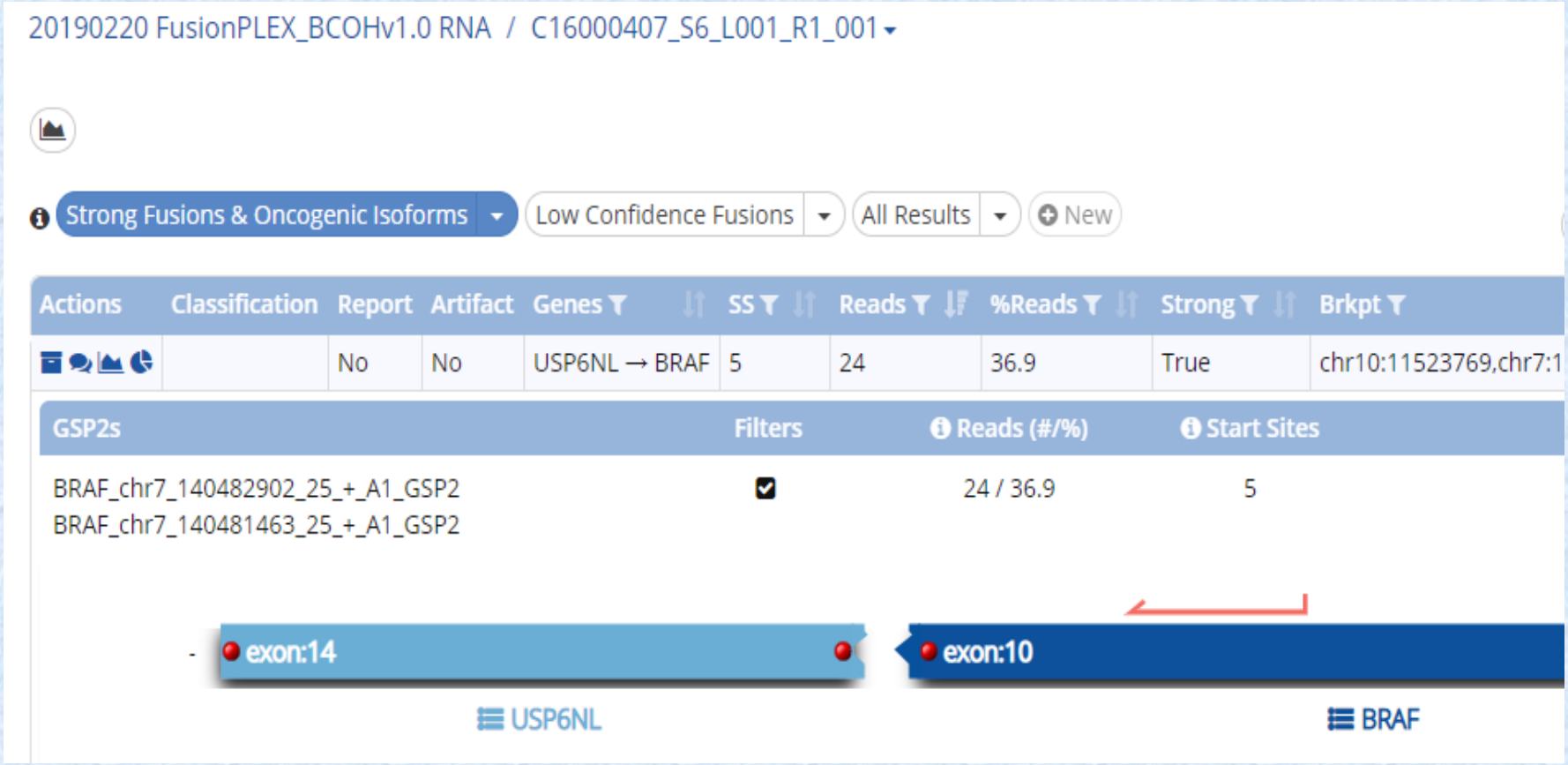
Laure Farnault, Zofia Hélias-Rodzewicz, Geoffroy Venton, Raphaelle Fanciullino, Sophie Gabriel, Lénaïg Mescam, Julien Haroche, Jean Donadieu & Jean-François Emile

Leukemia & Lymphoma





Altérations somatiques histiocytoses : Intérêt du RNA seq



Détection of gene fusion sur ARN extraits de tissus fixés et inclus en paraffine

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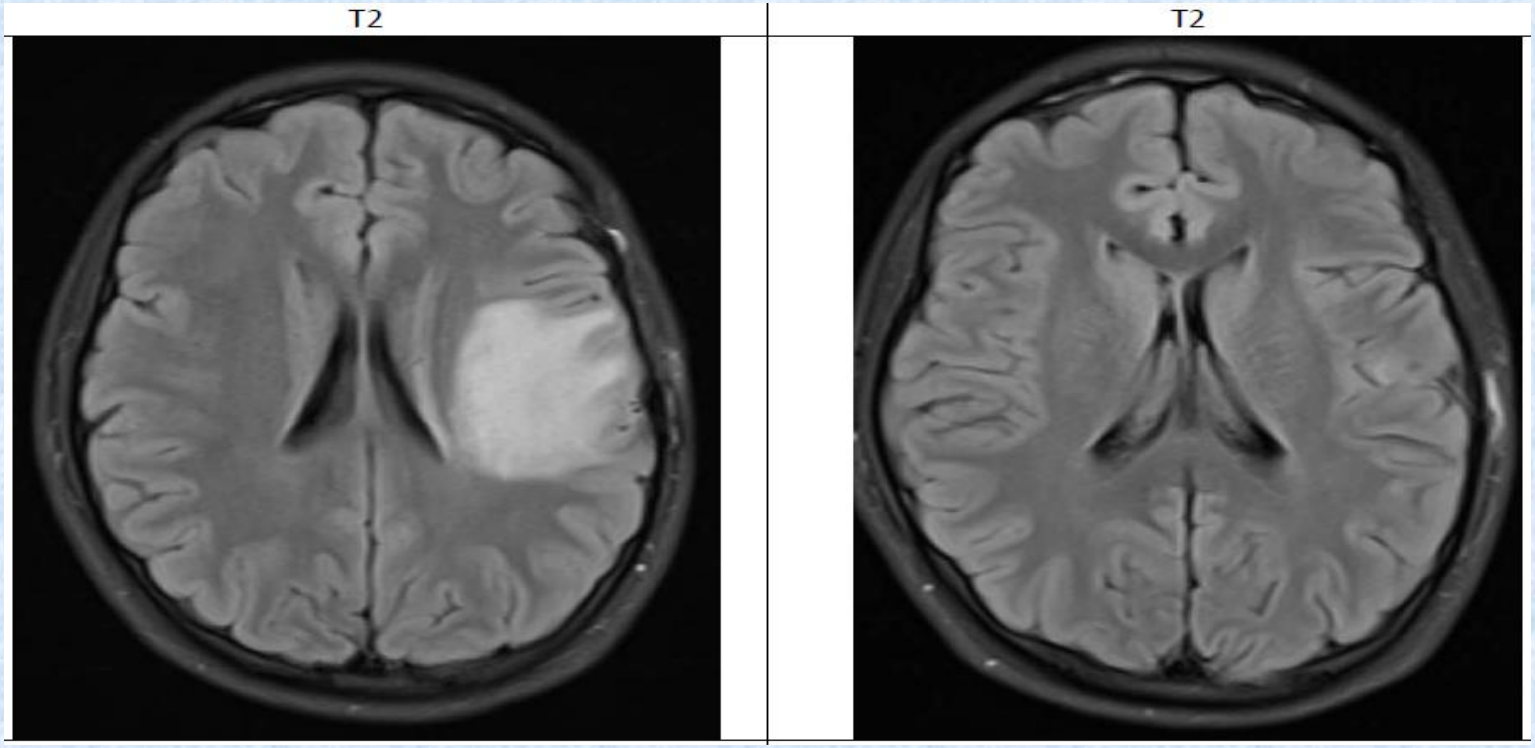
Histiocytose ALK+



Alectinib (2 mois)

Courtoisie de A Beilken

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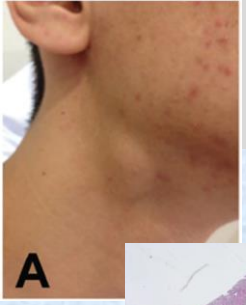
Les pièges

- Accumulation d'histiocytes (prothèse, mycobactéries, Gaucher, etc...)
- Empéripolèse (pas spécifique de MRD)
- Hyper-éosinophilie (pas dans HLC)

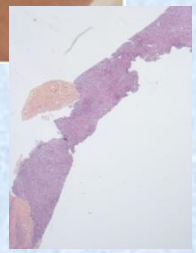
- Lymphadénite dermatopathique (et autres infiltrats CD1a+)
- Immunohistochimie trompeuse
    - Tumeur indifférenciée riches en histiocytes « histiocytoses malignes »
    - Marqueurs « histiocytaires » CD68, marqueurs « d'autres types cellulaires » CD4, CD31

- Analyses moléculaires
    - Echec / matériel fixé trop longtemps ou épuisé
    - Faux négatifs (manque de sensibilité ou panel inadapté)
    - D'autres tumeurs peuvent être mutés pour *BRAF*

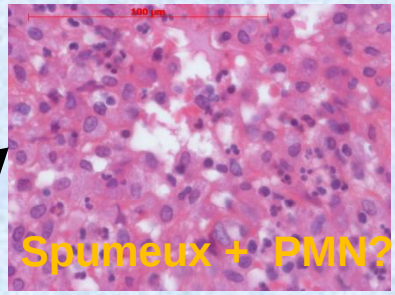
Conclusions - Take home message



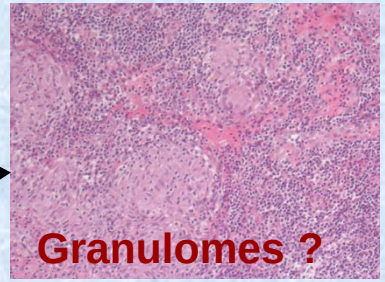
Clinique
Imagerie



HES + 5 LB



Ziehl, Mycobactérie ?
Autre pathogène ?



Sarcoidose ?
Mycobactérie ?
Autre pathogène ?
DICV ?

Rosai-Dorman ?
CD163, S100, CD1a,
pERK, IgG4
Pathol Mol*

CD1a, CD207, CD163
Pathol Mol*

Autre

Tumeur maligne ?
CD163, CD68, S100,
PAX5, CD3, etc…
+/- Pathol Mol*

* Plateforme traitant au minimum 30 histiocytoses par an

Remerciements

- **Pathologistes**,

  . Membres des groupes de relecture : S Boudjema, F Charlotte, C Chassagne, C Copie-Bergman, F Dijoud, S Fraitag, V Meignin, K Mokhtari, A Moreau
  . et tous les pathologistes qui nous transmettent les blocs/lames, dans le cadre des réseaux Français ou Européen

- Z Hélias-Rodzewicz, S Melloul, et techniciens du Laboratoire d'Ambroise Paré

- Scientifiques : R Chakraborty (Houston), V Taly (Paris)
- Collègues du MSKCC: O Abdel-Wahab, EL Diamond

- **Réseau français des histiocytoses, et notamment**
  J Donadieu, J Haroche, F Cohen-Aubart, S Héritier, A Idbaih, A Tazi, MA Barkaoui

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