Maladie d'Erdheim-Chester

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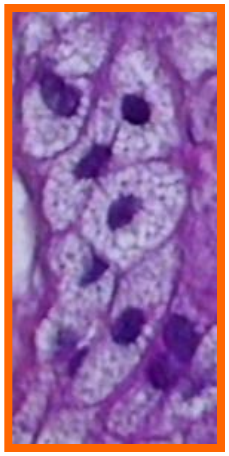
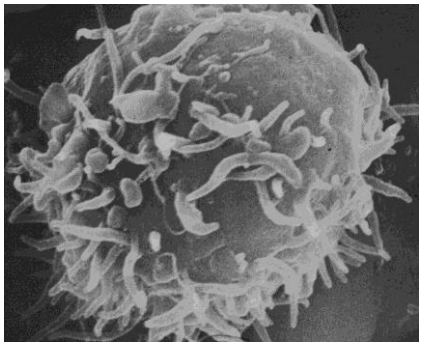
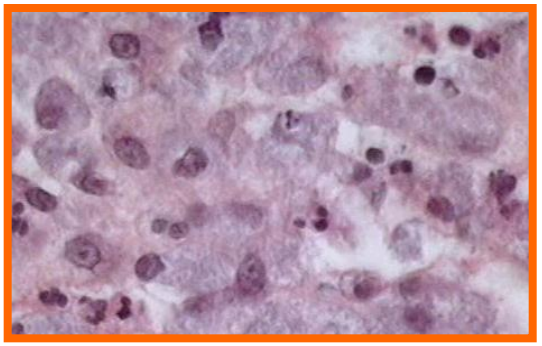
DIU
22 Juin 2018

Le macrophage : une cellule caméléon

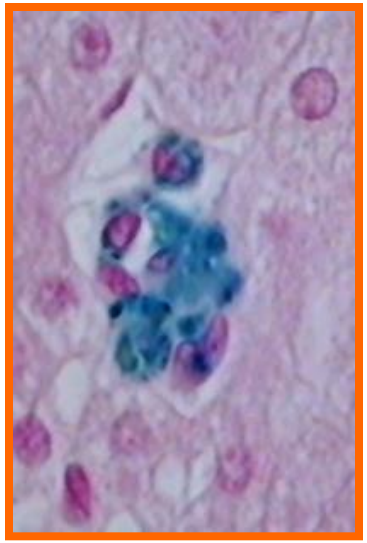


Lipophage

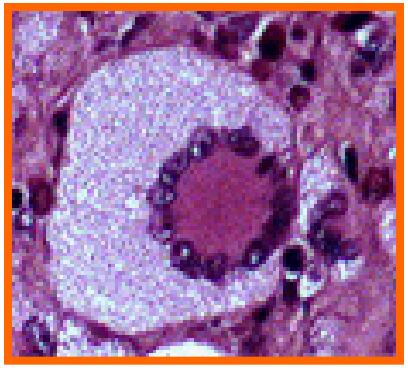




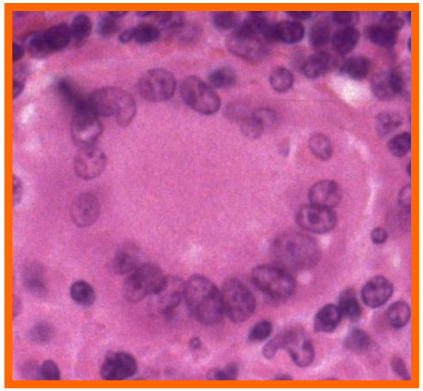
Cellule de Virchows (lèpre)



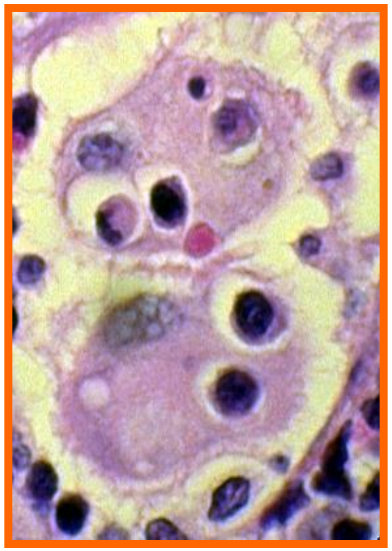
Sidérophage



Cellule de Touton (xanthogranulome)



Ç de Langhans (tuberculose)



Hémophagocytose

D'une cellule CD34^{+} à l'histiocyte

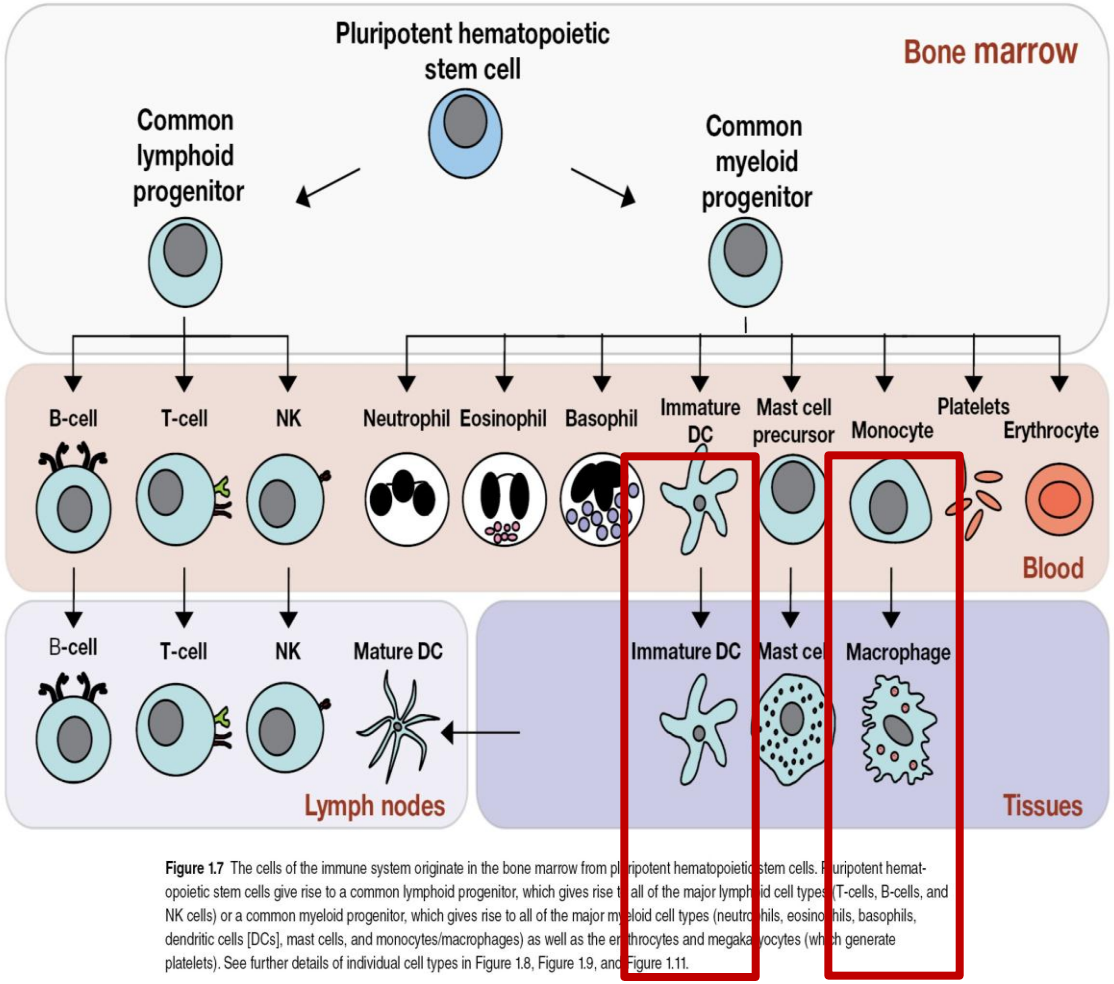


Figure 1.7 The cells of the immune system originate in the bone marrow from pluripotent hematopoietic stem cells. Pluripotent hematopoietic stem cells give rise to a common lymphoid progenitor, which gives rise to all of the major lymphoid cell types (T-cells, B-cells, and NK cells) or a common myeloid progenitor, which gives rise to all of the major myeloid cell types (neutrophils, eosinophils, basophils, dendritic cells [DCs], mast cells, and monocytes/macrophages) as well as the erythrocytes and megakaryocytes (which generate platelets). See further details of individual cell types in Figure 1.8, Figure 1.9, and Figure 1.11.

Histiocyte = aspect morphologique d'un macrophage résident

Les histiocytoses

Histiocytoses non Langerhansiennes (CD68+, CD1a-)

- Histiocytoses d'origine exogène
- Histiocytoses infectieuses: Whipple, mycobactéries atypiques, granulomatose septique
- Histiocytoses hémophagocytaires: SAM secondaires (DI primitifs ou acquis, EBV, lymphomes…), SAM primitifs (Chediak-Higashi, Griscelli), Rosai-Dorfman
- Histiocytoses héréditaires: Gaucher, Farber, Niemann-Pick, Hermansky-Pudlak, Tangier…
- Histiocytoses sporadiques: Xanthogranulomes, Xanthoma disseminatum, Histiocytose éruptive généralisée, Maladie d'Erdheim-Chester

Cas clinique

Monsieur D. né en 1954

1989: Dyslipidémie

1997: Lombalgies inflammatoires
(HLA B27+, SPA ?)
1997: HTA (aggravation récente: 220/120)

2-2000 : Découverte d'une insuffisance rénale

créatinine 182 micromoles/l

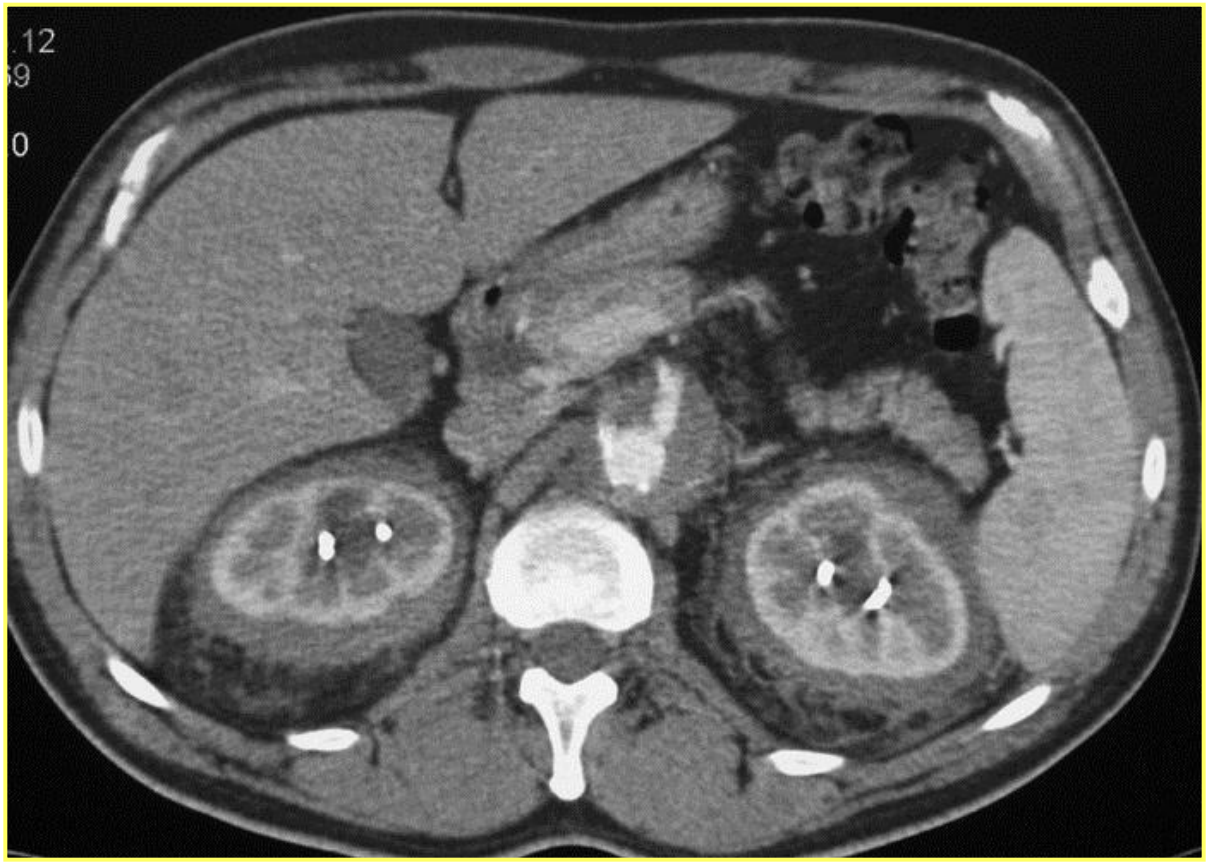
3-2000 : syndrome inflammatoire

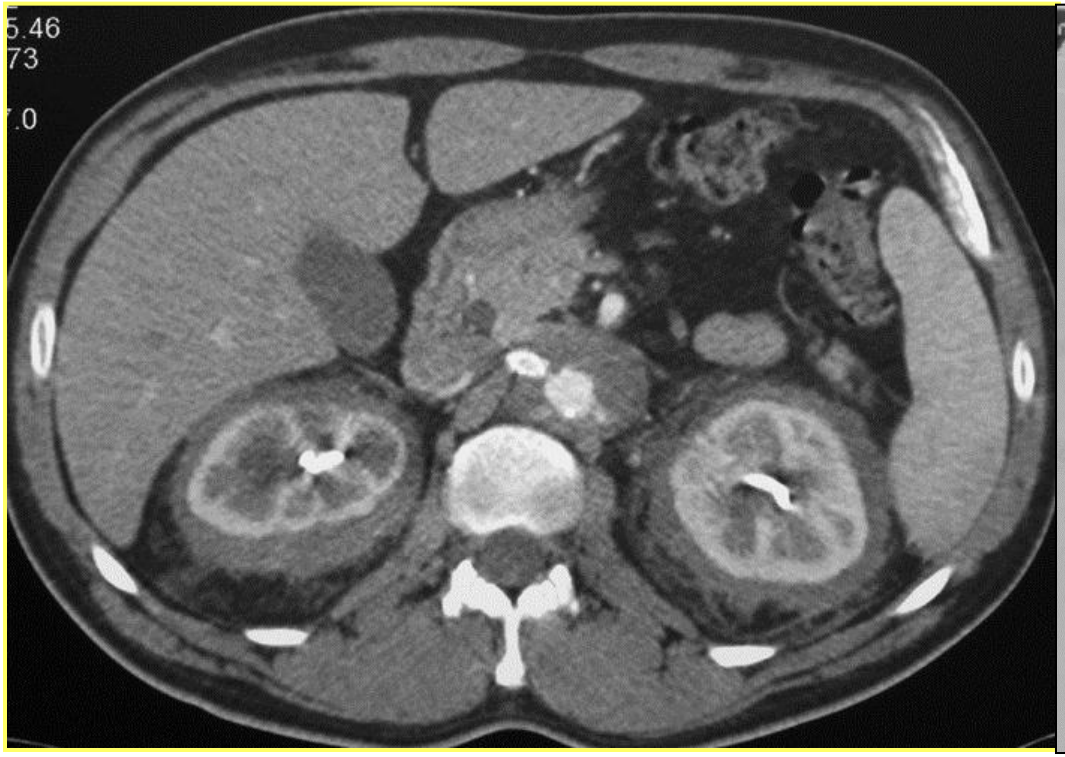
CRP 71 mg/l, VS 121 mm

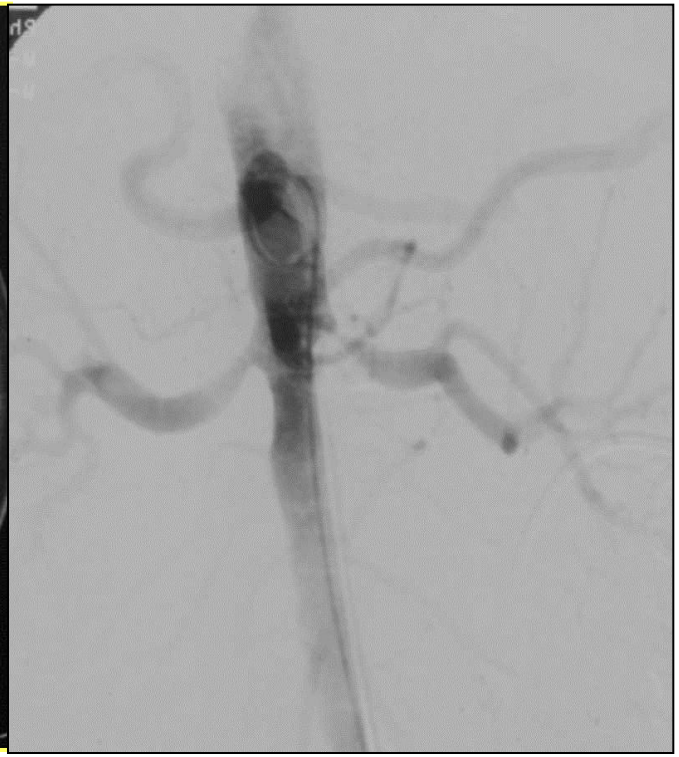
Fibrose Rétropéritonéale

Hydronéphrose bilatérale

=> Sondes JJ

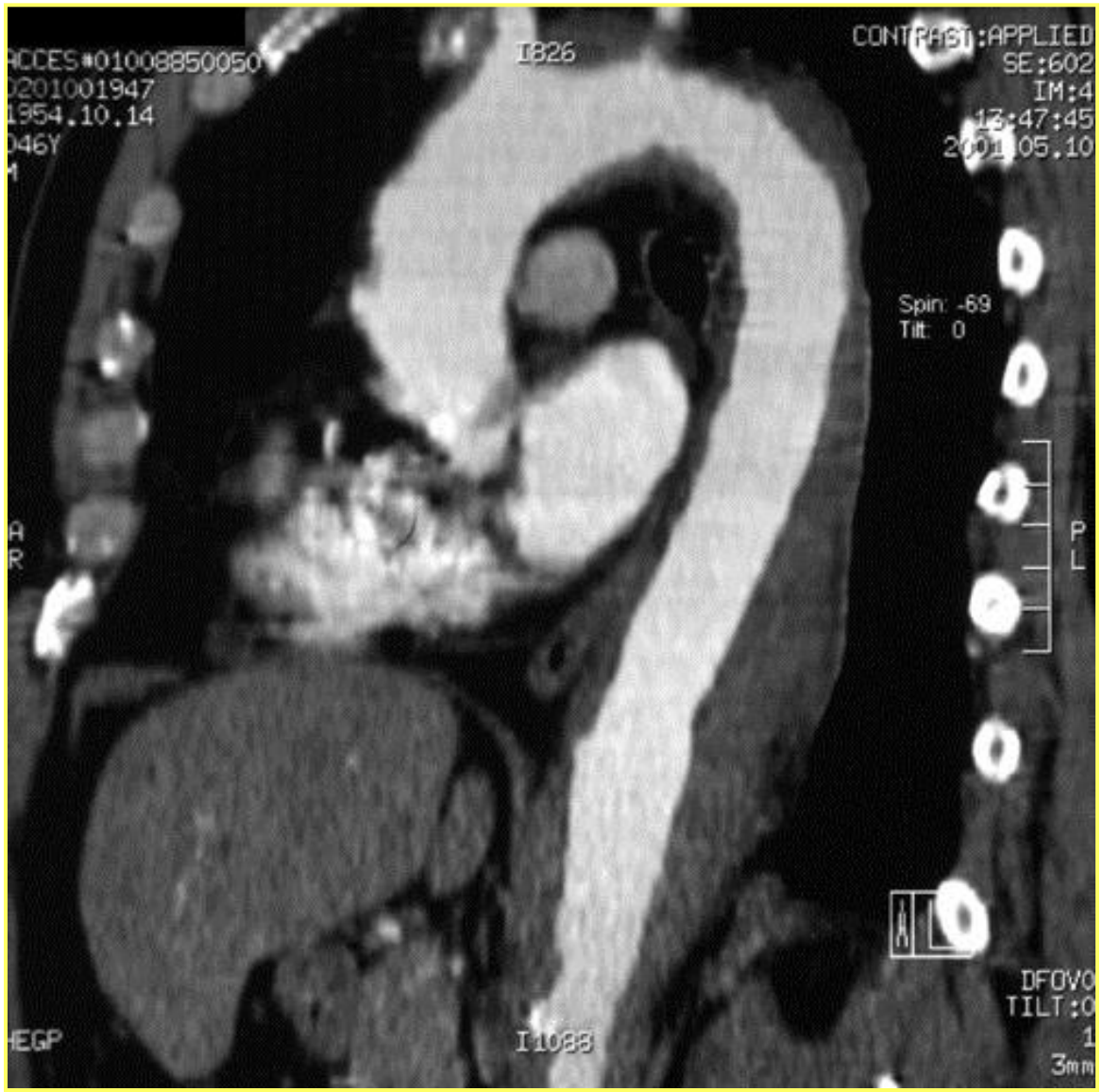




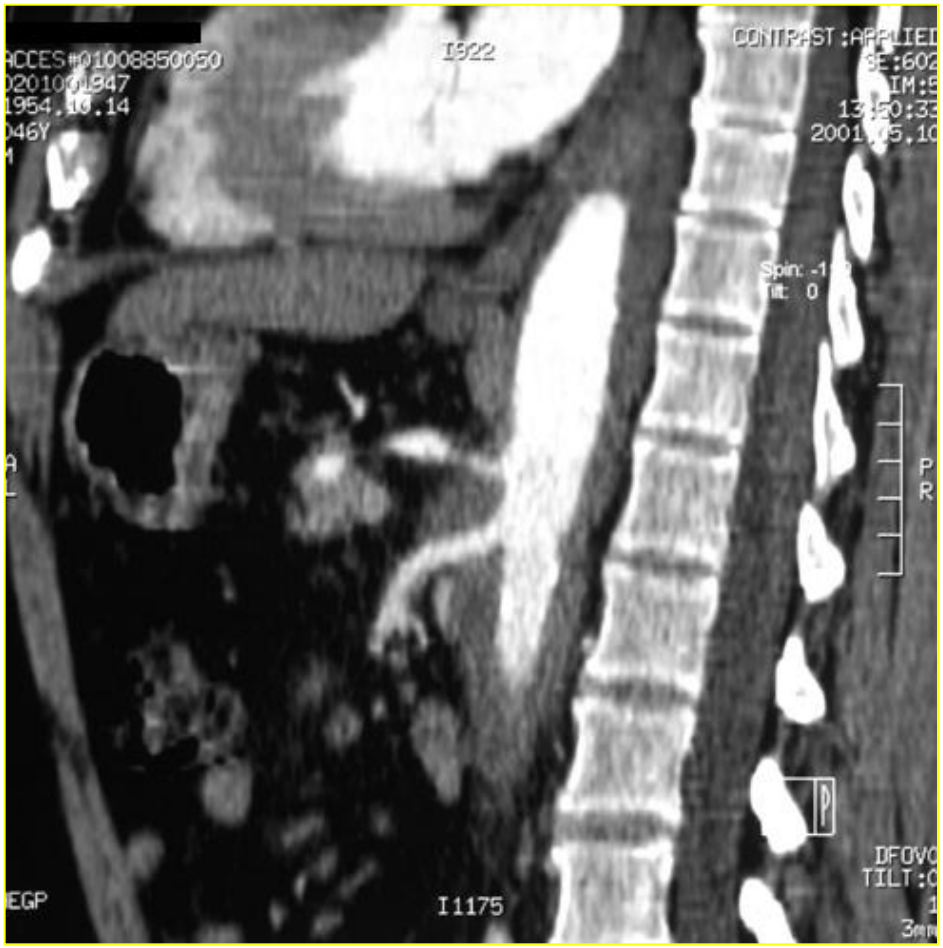


Sténose artérielle rénale => stent

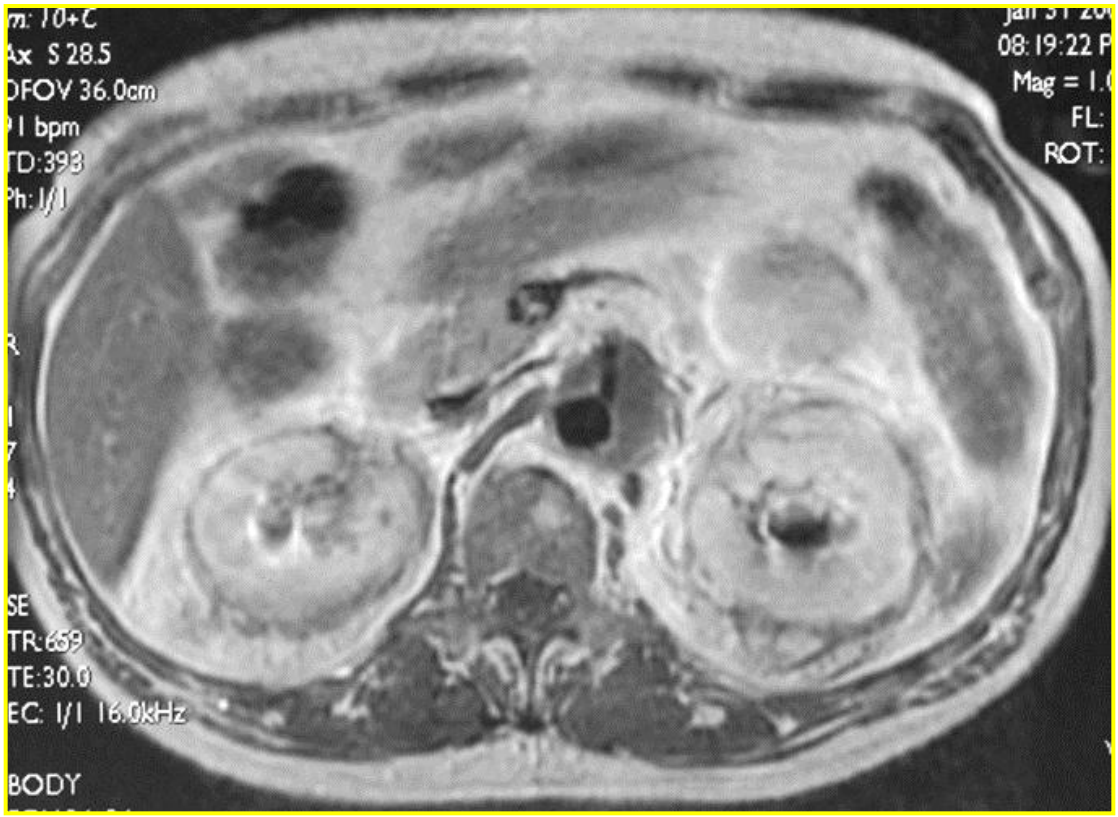
L'aorte thoracique est aussi touchée…
reconstruction sagittale



Le tronc cœliaque et
l'artère mésentérique supérieure
sont également engainés
dans cette « fibrose »…



… visible à l'IRM :
Hyper-signal en T1
de la partie interne
du mur aortique



4-2000: CT générale (1mg/kg/j)

9-2000: ↓ progressive à 20 mg/j

Inefficacité…

11-2000: Xanthélasma paupière G

Inflammation persistante

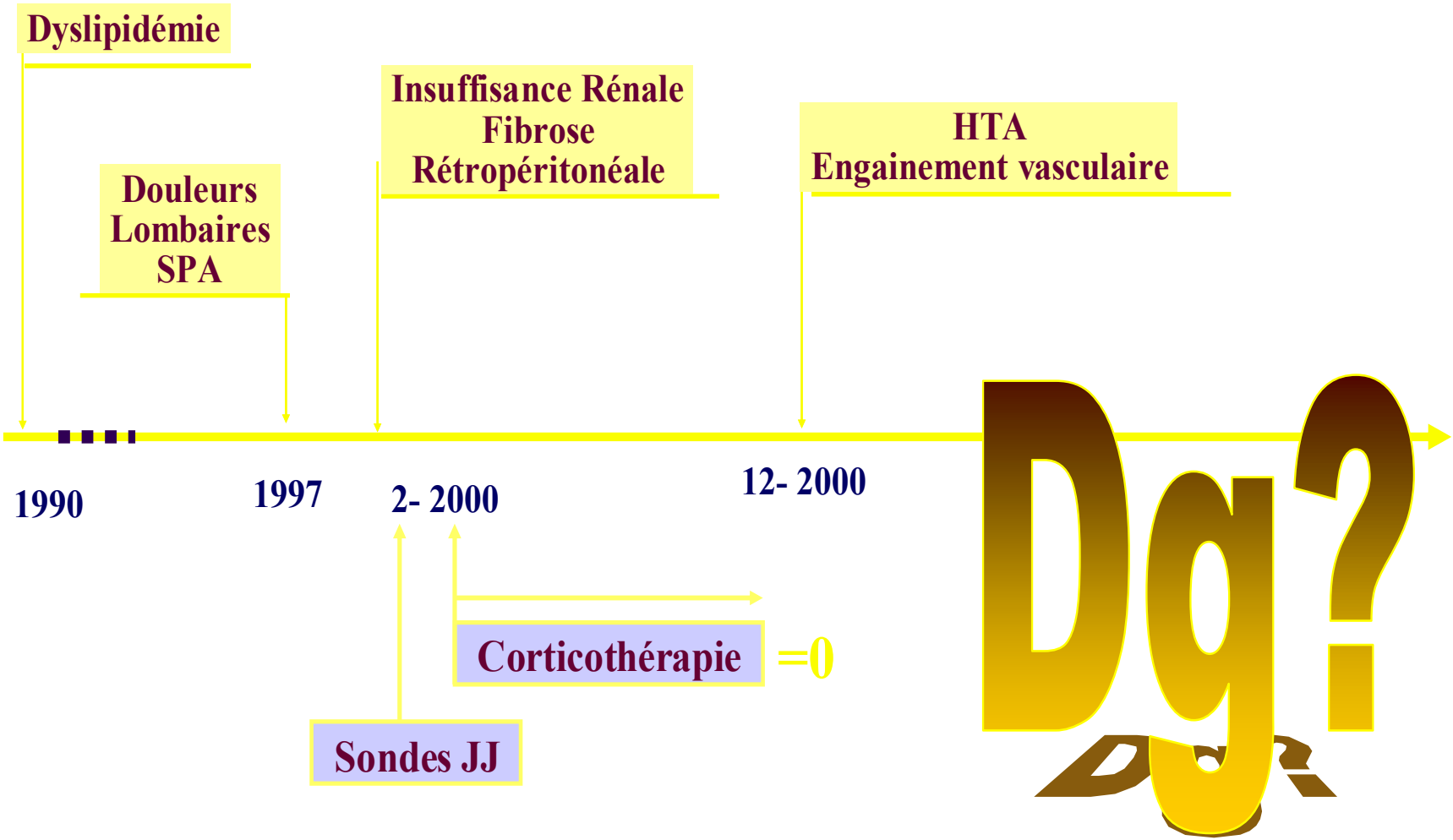
TDM inchangé

Janvier 2001
Adressé pour échec thérapeutique

. Raideur rachidienne : indice de Schober à 2 cm

. HTA : 180/110 mmHg sous traitement par
Nicardipine
Avlocardyl

Mr D... Gérard Né en 1954



Mr D... Gérard Né en 1954

Dyslipidémie

Douleurs Lombaires SPA

Insuffisance Rénale Fibrose Rétropéritonéale

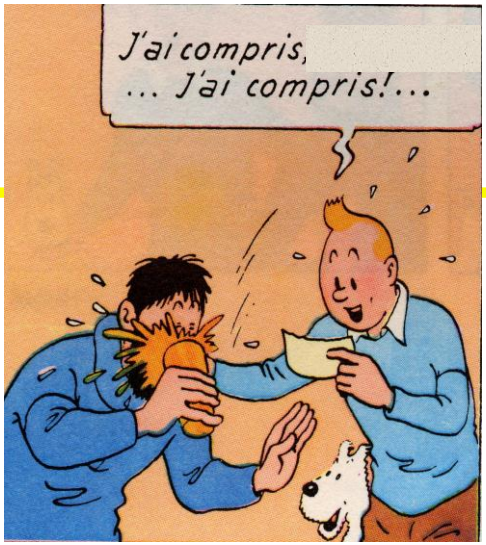
HTA Engainement vasculaire

1990 — 1997 — 2- 2000 — 12- 2000

Corticothérapie =0

Sondes JJ

… et hyperfixation à la **scintigraphie osseuse**



Erdheim-Chester

Virchows Arch Pathol Anat
1930; 279: 561-602

(Aus dem pathologisch-anatomischen Institut des Krankenhauses der Stadt Wien
[Vorstand: Prof. Dr. *J. Erdheim*].)

Über Lipoidgranulomatose[1].

Von

Dr. **William Chester**, New-York.

Mit 9 Abbildungen im Text.

(Eingegangen am 29. Mai 1930.)

Inhaltsübersicht.

Einleitung.

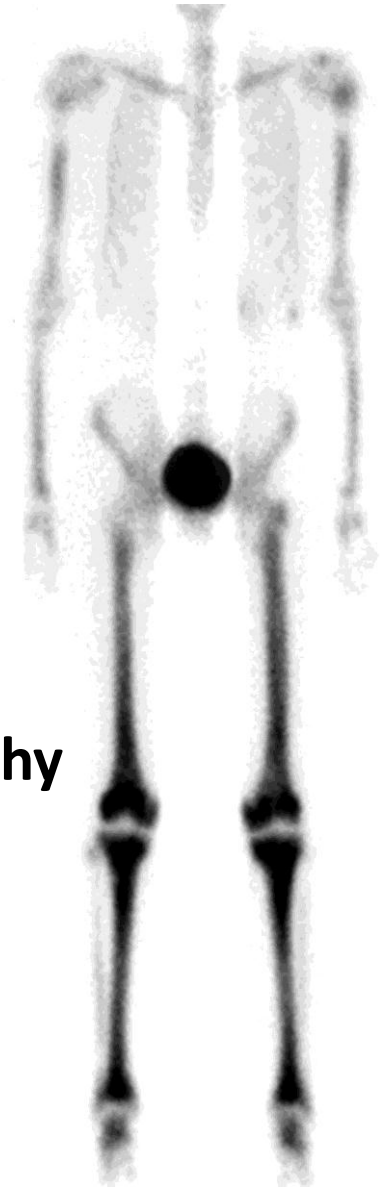
In der vorliegenden Arbeit wird von Lipoidgranulom und Lipoidgranulomatose die Rede sein. Zur vorläufigen Orientierung des Lesers sei hier gleich gesagt, daß darunter das zu verstehen ist, was im Schrifttum mit Xanthom und Xanthomatose bezeichnet wird. Die Begründung, weshalb dieser frühere Namen verworfen und ein neuer vorgeschlagen wird, folgt dann später an passender Stelle.

Die Frage der Lipoidgranulomatose sowie die der Ablagerung auch anderer pathologischer Substanzen in den verschiedensten Geweben ist derzeit in ein Stadium sehr reger Forschung eingetreten. Im Beginn galt das Lipoidgranulom als eine ausschließlich den Dermatologen angehende Erkrankung und auch heute noch müssen wir zugeben, daß die Haut, wenn auch nicht die ausschließliche, so doch bei weitem die häufigste Fundstätte des Lipoidgranuloms darstellt. Allerdings bietet auch die Lokalisation in der Haut schon eine große Mannigfaltigkeit dar, denn bald sitzt das Lipoidgranulom ausschließlich an den Augenlidern — und dies ist die weitaus häufigste Lokalisation überhaupt — bald aber findet es sich, wenn auch sehr viel seltener an vielen Stellen über die Haut verstreut. Bald ist es eine Begleiterscheinung

[1] Mit Unterstützung der *Emanuel Libman-* und *Herbert L. Celler Fellowship-*Funds.

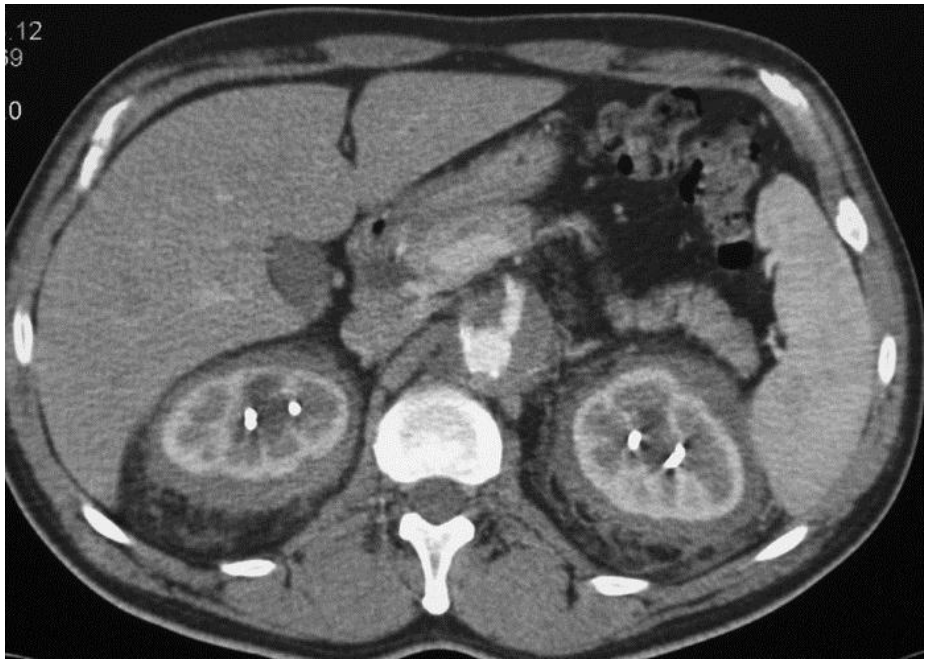
Maladie d’Erdheim-Chester (MEC)

- Histiocytose non Langerhansienne de l’adulte d’age mûr
- 1930 "lipoid granulomatose"
- Rare…
- …mais > 1100 cas publiés (Juine 2018)
- Infiltration tissulaire d’histiocytes spumeux CD68+, CD1a- , PS100- (80% des cas)
- Atteinte osseuse bilatérale et symétrique des os longs



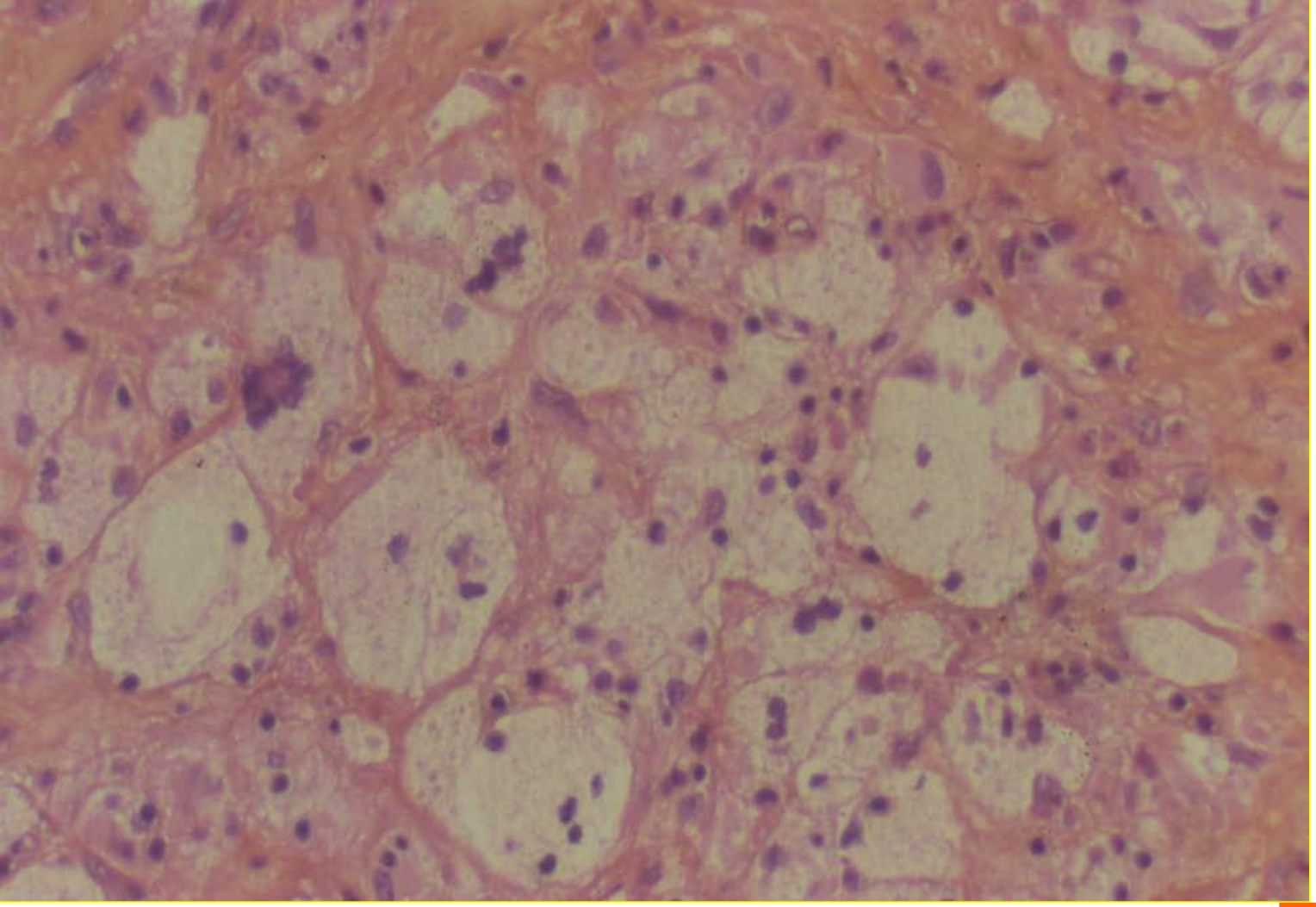
Bone scintigraphy
(^{99} Tc)

(96%)

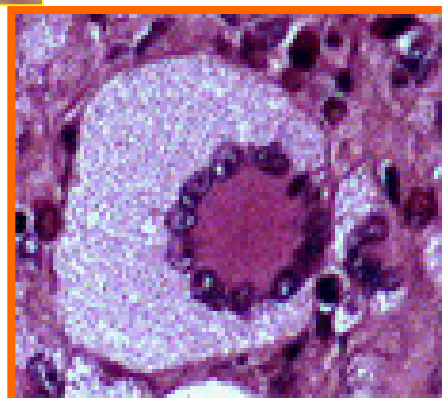


"Hairy kidney aspect"
and peri-renal infiltration

(≈ 50%)



Touton Cell
(xanthogranuloma)



Diagnostic criteria for ECD

a)Typical histologic findings: infiltration with foamy histiocytes nested among polymorphic granuloma and fibrosis or xanthogranulomatosis with $CD68^{+}$ and $CD1a^{-}$ immunohistochemical staining;

b)Typical skeletal findings:

1)X-rays showing bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in the long bones

and/or

2)Symmetric and abnormally increased labeling of the distal ends of the long bones of the lower limbs, and sometimes the upper limbs, on 99Tc bone scintigraphy.

Veyssier-Belot et al, *Medicine* 1996 Haroche et al, *Medicine* 2004

Natural history unknown

- Asymtomatic forms of the disease

- Multisystemic & life-threatening forms of the disease

Experience of Pitié-Salpêtrière (April 2016)

165 patients (119 M, 44 F)

(40 abroad mainly EU)

14%

21 patients with LCH + ECD

1 patient with LCH + ECD + Rosai-Dorfman

1 patient with ECD + Rosai-Dorfman

38 deaths (23%)

Cohen-Aubart, Am J Hematol 2018

Extra-osseous involvement
≈ 98% of patients

• Xanthelasma	43 pts (26%)
• Exophthalmos	36 pts (22%)
• Diabetes insipidus	46 pts (28%)
• Central nervous system (CNS)	60 pts (37%)
Cerebellar	28 pts (17%)
• Pulmonary involvement	58 pts (36%)
• Peri-renal (“hairy kidney”)	95 pts (58%)
• “Retro-peritoneal fibrosis” / HN	40 pts (25%)
	75 pts (46%)
• Coated aorta	29 pts (18%)
• Reno-vascular hypertension	51 pts (31%)
• Pericardial	61 pts (37%)
• Pseudo-atrial tumor	

165 patients ECD (1992 - 2016)

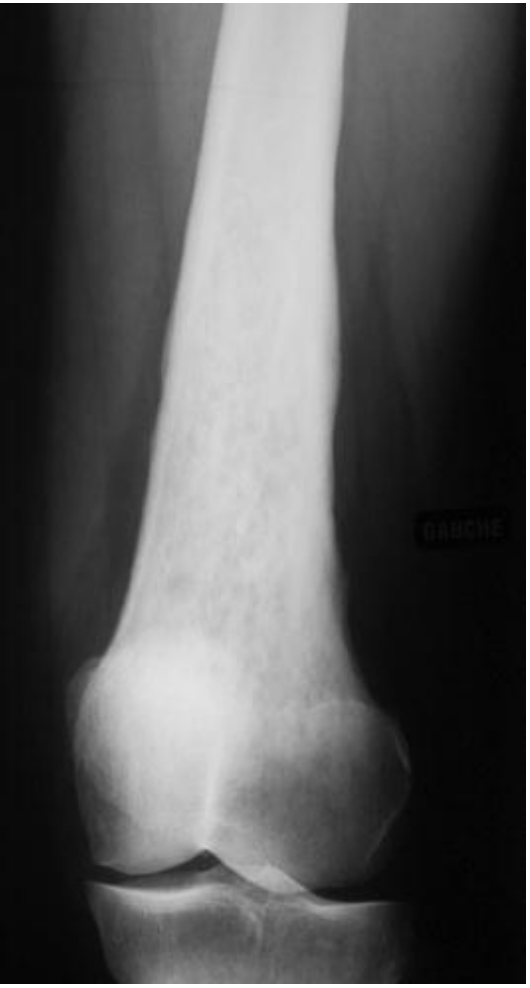
- Mean age at diagnosis: 56.1 yr (14.4), range: 5-80
- Mean age at first sign: 51.9 yr (15.8)
- Mean diagnostic delay : 48 mo (up to 372 mo)

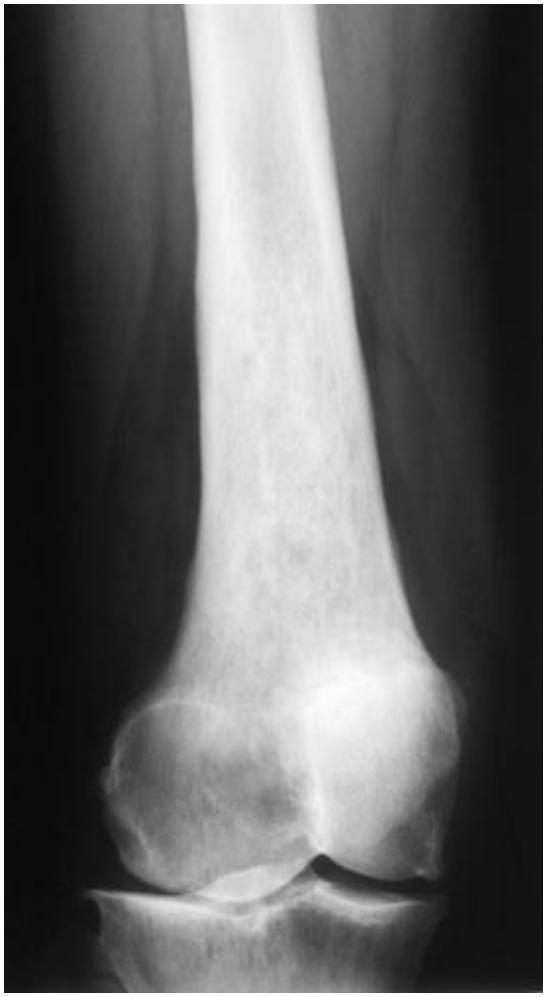
- Increased levels of acute inflammatory protein (CRP) : 87 pts (71%)

- 1st symptom extremely variable (bone pain 10%, diabetes insipidus 16%) but also exophthalmos, seizures, sinusitis…

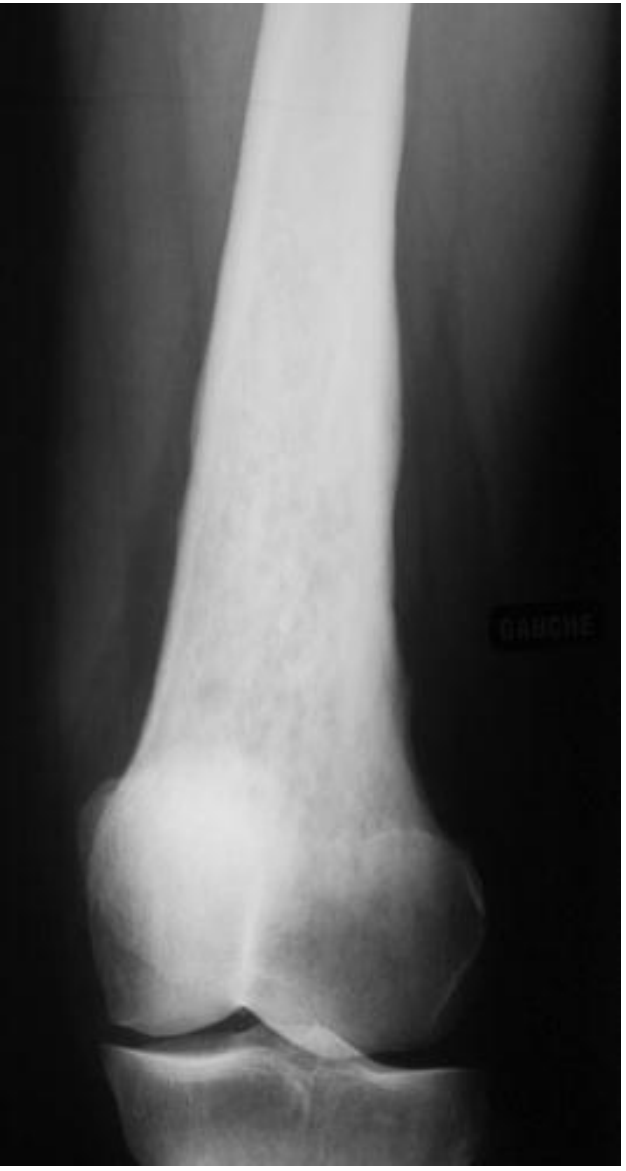
Manifestations rhumatologiques

Douleurs osseuses : 56 pts (38%)
Atteinte osseuse souvent asymptomatique

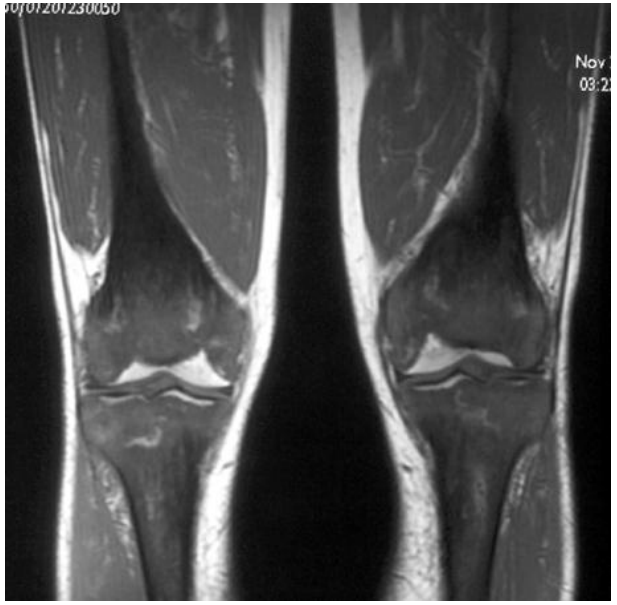


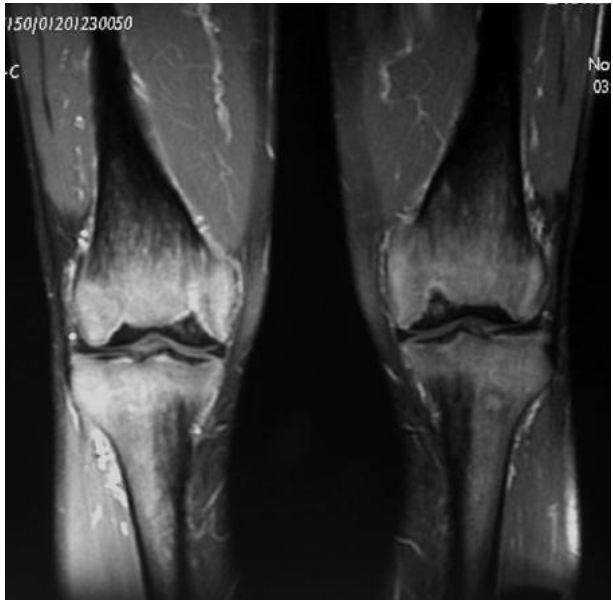


Manifestations rhumatologiques



Atteinte osseuse souvent latente





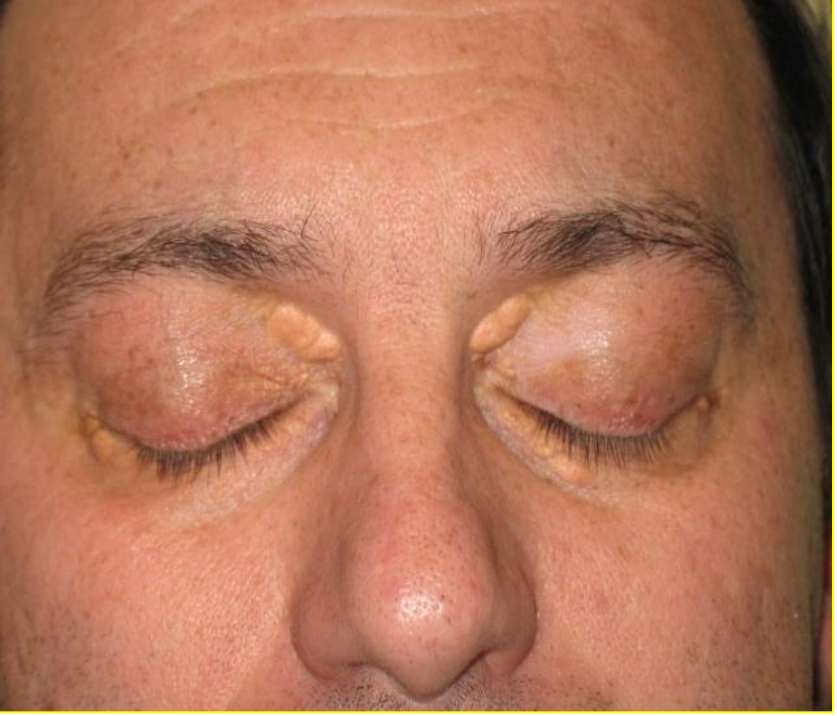
Bone Involvement in Erdheim-Chester Disease: Imaging Findings including Periostitis and Partial Epiphyseal Involvement[1]

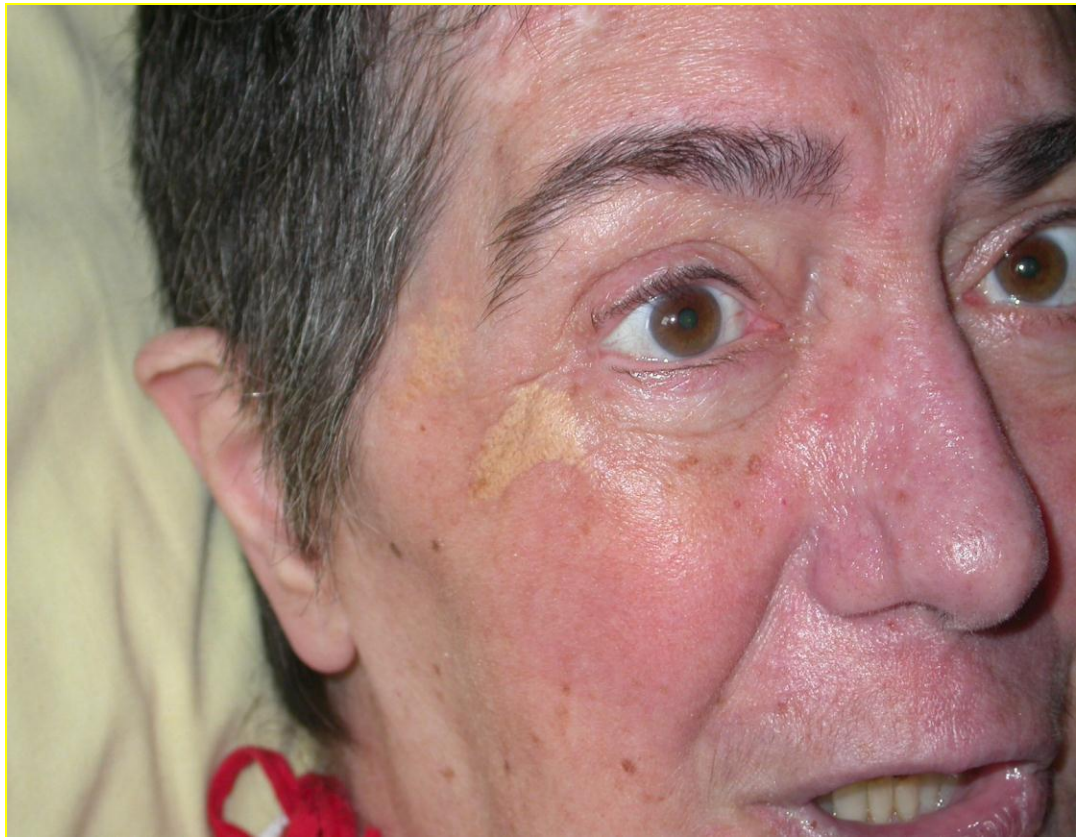
Radiology: Volume 238: Number 2—February 2006

Sémiologie Radiographique

- Ostéocondensation bilatérale et symétrique
- Diaphyse et métaphyse…
- …mais aussi épiphyse (45% des cas)
- Périostose
- Endostéose
- Pas d'ostéolyse (≠ HL)
- Respect du squelette axial

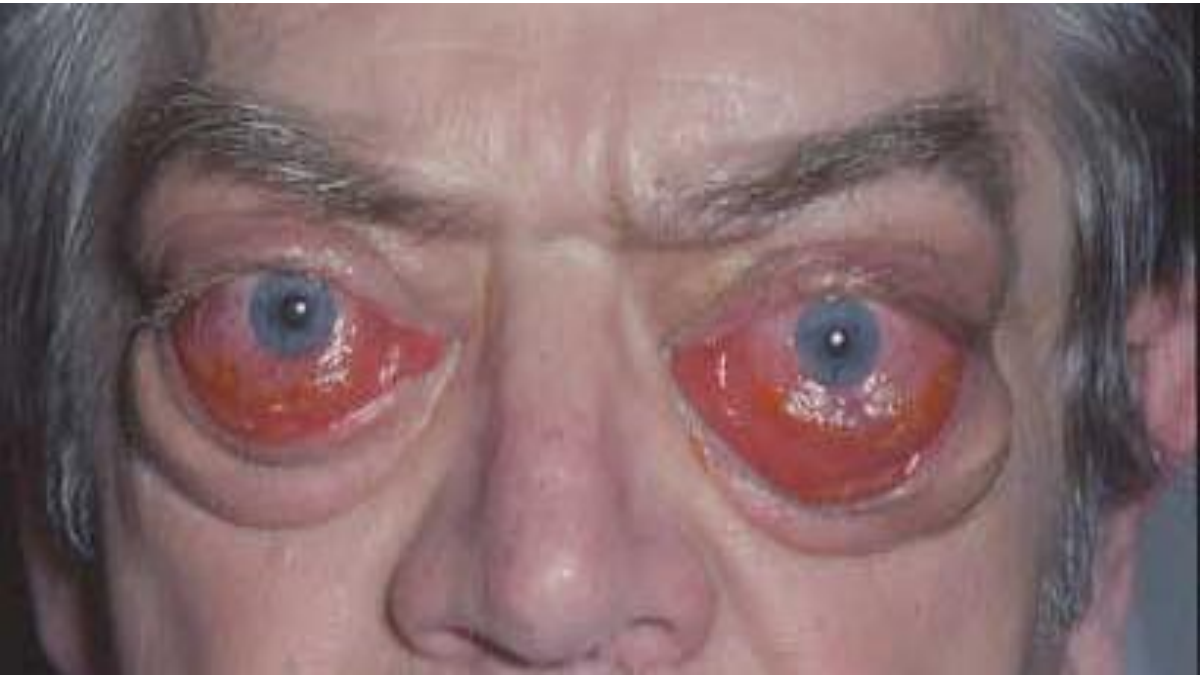
Xanthelasmas

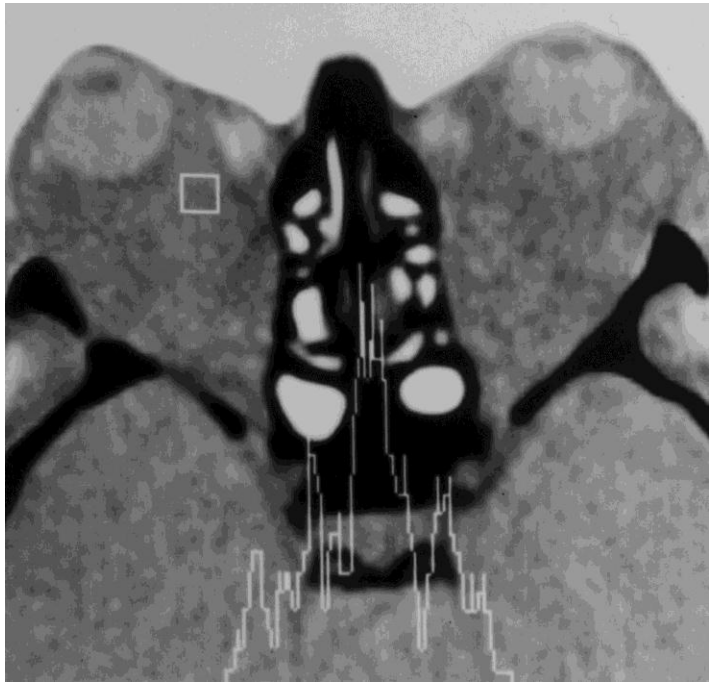




43 pts (26%)

Exophthalmos





36 pts (22%)

Diabetes insipidus

46 pts (28%)

Florence Lachenal
François Cotton
Hélène Desmurs-Clavel
Julien Haroche
Hervé Taillia
Nadine Magy
Mohamed Hamidou
Juan Salvatierra
Jean-Charles Piette
Denis Vital-Durand
Hugues Rousset

Neurological manifestations and neuroradiological presentation of Erdheim-Chester disease: report of 6 cases and systematic review of the literature

J Neurol (2006) 253 : 1267–1277

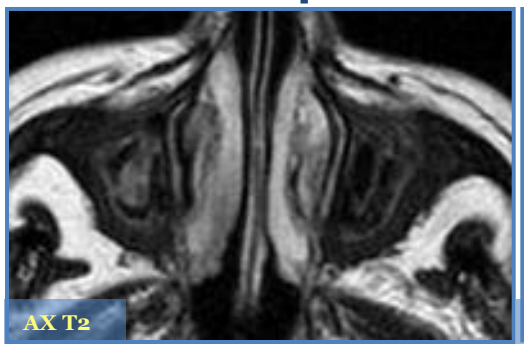
- CNS involvement in 15 to 25 % patients depending on series.
- Clinical symptoms are proteiform: pyramidal syndrom, cerebellar syndrom (sometimes wheelchair), more rarely seizures, headaches, psychiatric or cognitive impairments.

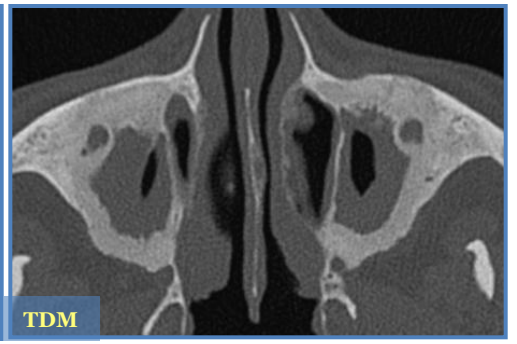
- Important mortality : 9% (6/66 pts)

In our 165 patients series: 60 pts (37%) have CNS, 28 pts (17%) of which have cerebellar involvement

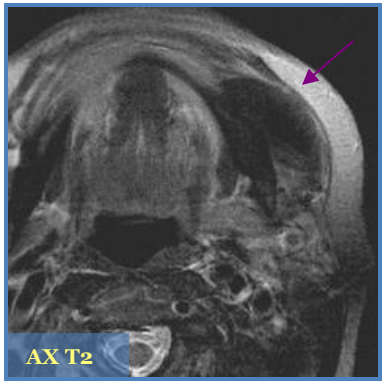
Analyse de l'imagerie SNC de 33 patients avec MEC

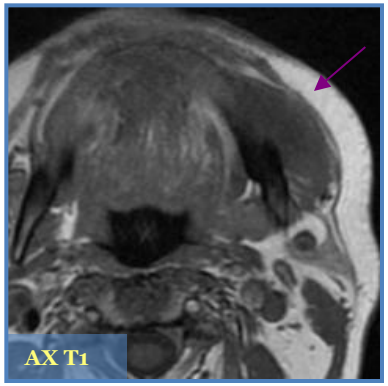
	N	%
Massif facial / Voûte	**24**	**73**
Axe hypothalamo-hypophysaire	15	46
Orbites	9	27
Epaississement des pachyméninges Masses extra-axiales	7	21
Rehaussement nodulaire Masses intra-axiales	5	15
Hypersignal T2 hémisphères cérébelleux	5	15
Infiltration périvasculaire	3	9





Ostéosclérose des parois des sinus maxillaires

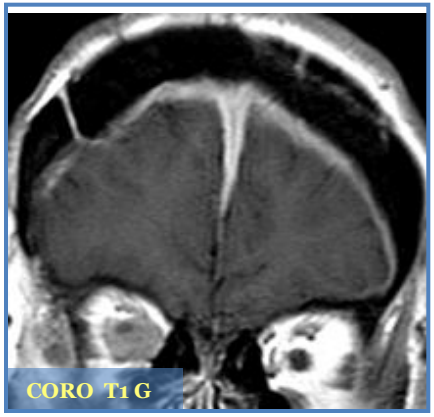




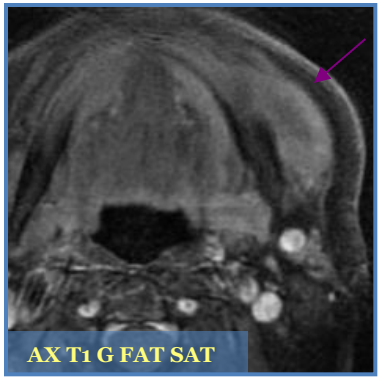
ATTEINTE DES SINUS ET DE LA VOUTE

- **Epaississement des parois des sinus de la face et de la voûte.**
- **Ostéosclérose des parois des sinus maxillaires +++**
- **Parois osseuses en hyposignal T1 et T2.**

Drier, Radiology (2010)



Epaississement de la voûte



Lésion mandibulaire

RESULTATS (n=33)

	N	%
Massif facial / Voûte	24	73
Axe hypothalamo-hypophysaire	15	46
Orbites	9	27
Epaississement des méninges **Masses extra-axiales**	**7**	**21**
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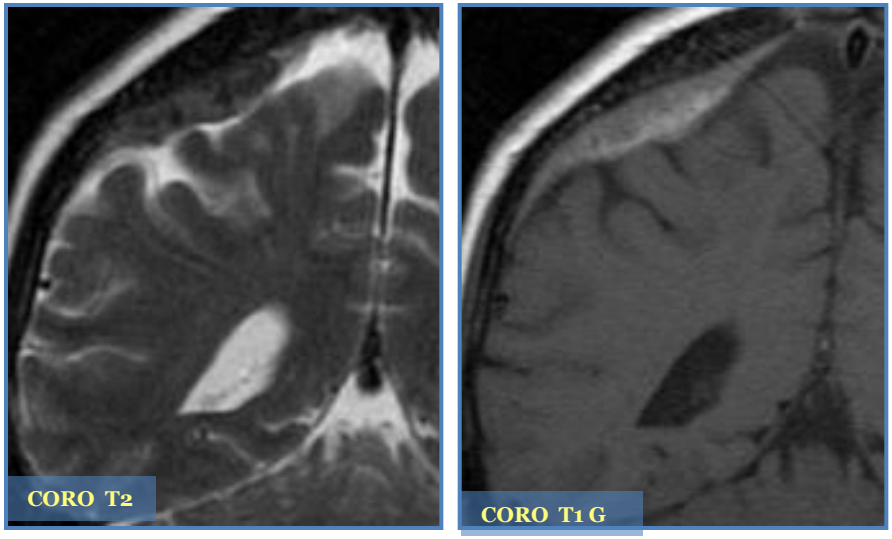
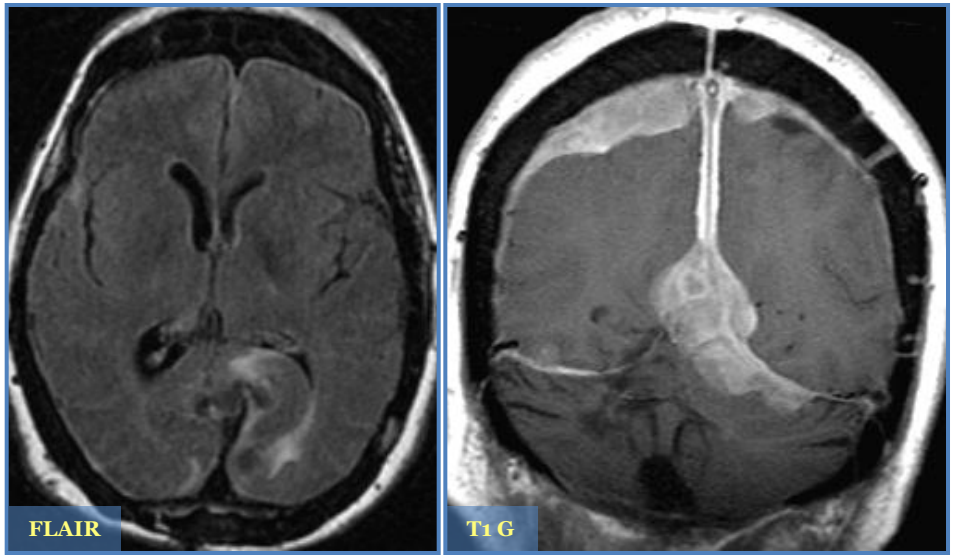


Pachyméninges



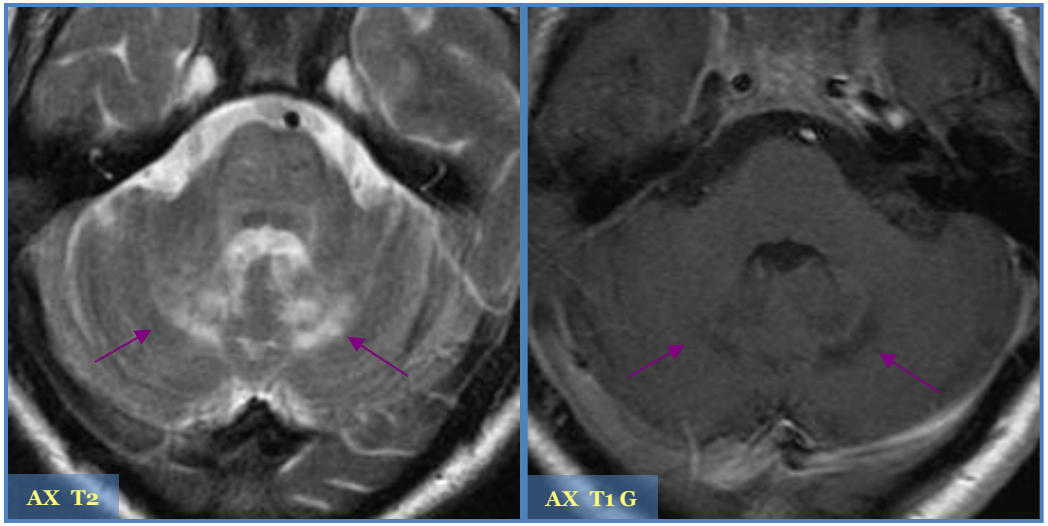
Masses méningées

ATTEINTE DES MENINGES

- Deux types de lésions méningées :
  - épaississement méningé diffus
  - épaississement focal pseudo-méningiomateux
- Lésions en :
  - isosignal T1
  - hyposignal T2
  - se rehaussant après injection.

RESULTATS (n=33)

	N	%
Massif facial / Voûte	24	73
Axe hypothalamo-hypophysaire	15	46
Orbites	9	27
Epaississement des pachyméninges Masses extra-axiales	7	21
Rehaussement nodulaire Masses intra-axiales	5	15
Hypersignal T2 hémisphères cérébelleux	5	15
Infiltration périvasculaire	3	9

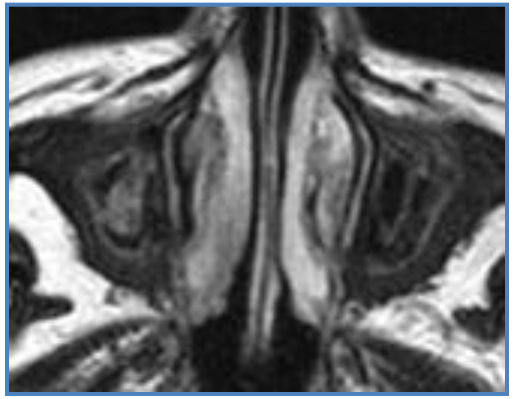


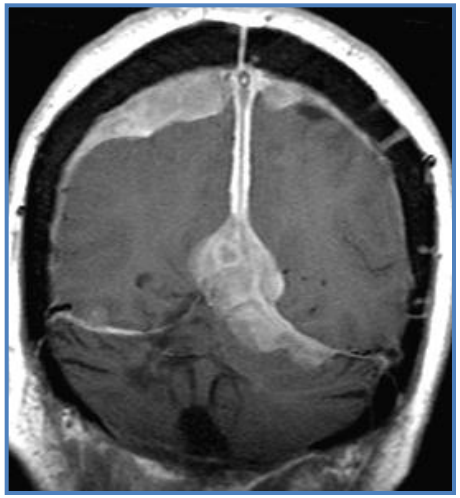
Atteinte des noyaux dentelés

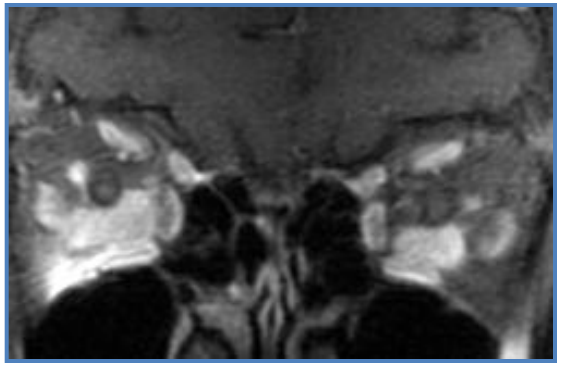
HYPERSIGNAL T2 DES HEMISPHERES CEREBELLEUX

- Lésion d'allure neurodégénérative.
- Atteinte bilatérale et symétrique des noyaux dentelés et de la région péri-dentelée en :
  - iso ou hyposignal T1
  - hypersignal T2
  - ne se rehaussant pas après injection.
- Evolution possible vers l'atrophie.

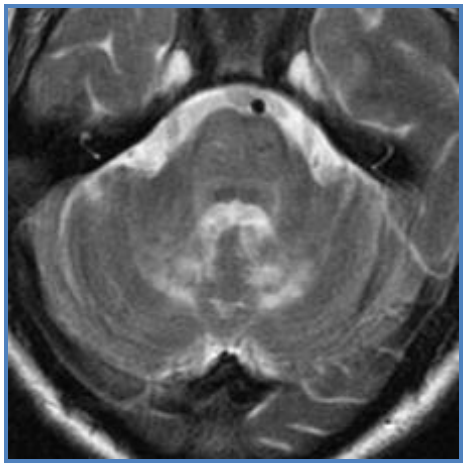
- Lesional associations :
  -Osteosclerosis facial / skull
  -Orbital involvement
  -Meningeal infiltrations

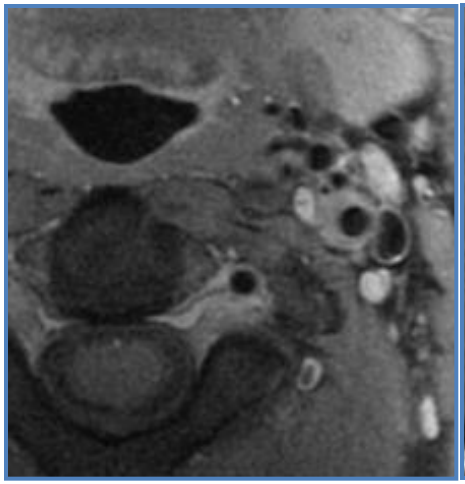


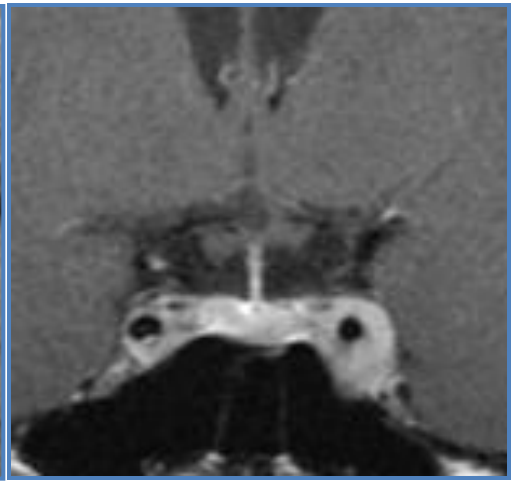




- Dentate nuclei

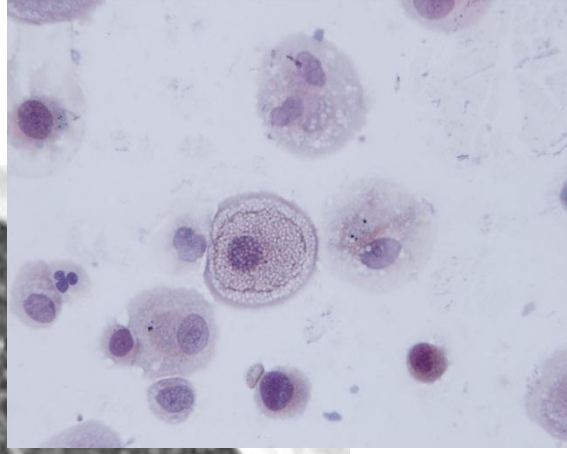


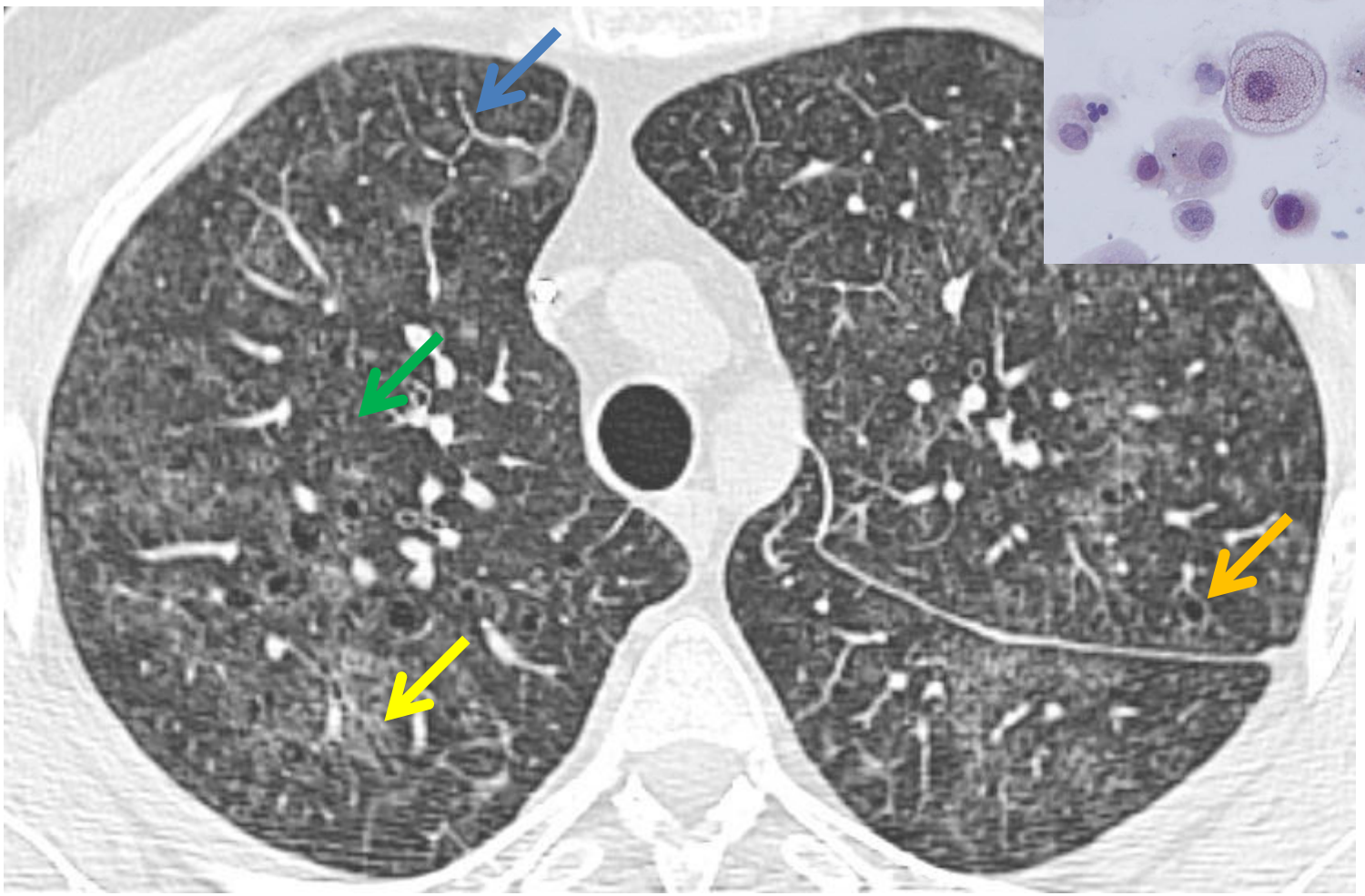




- extra & intracranial peri-vascular sheathing

58 pts (36%)

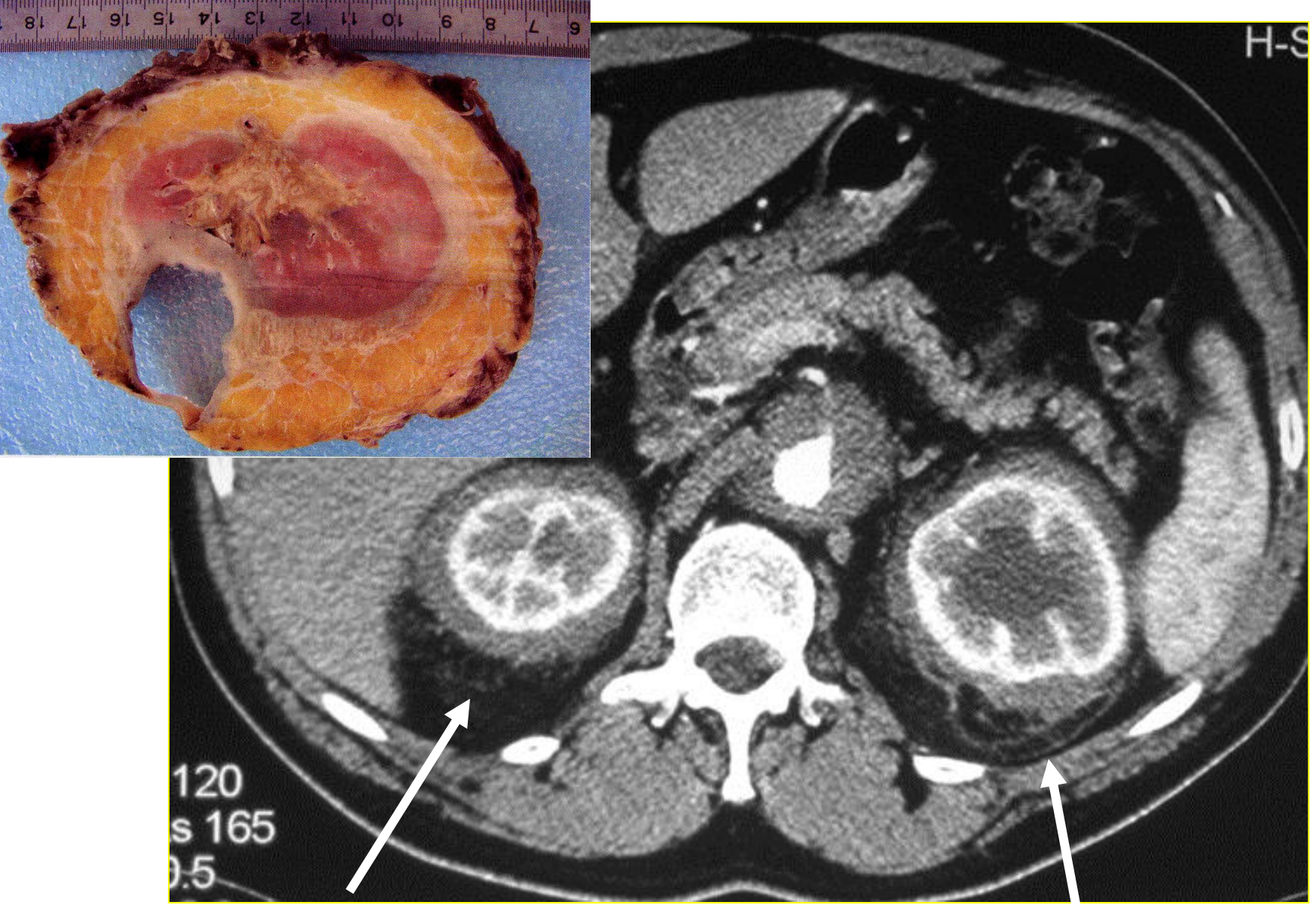




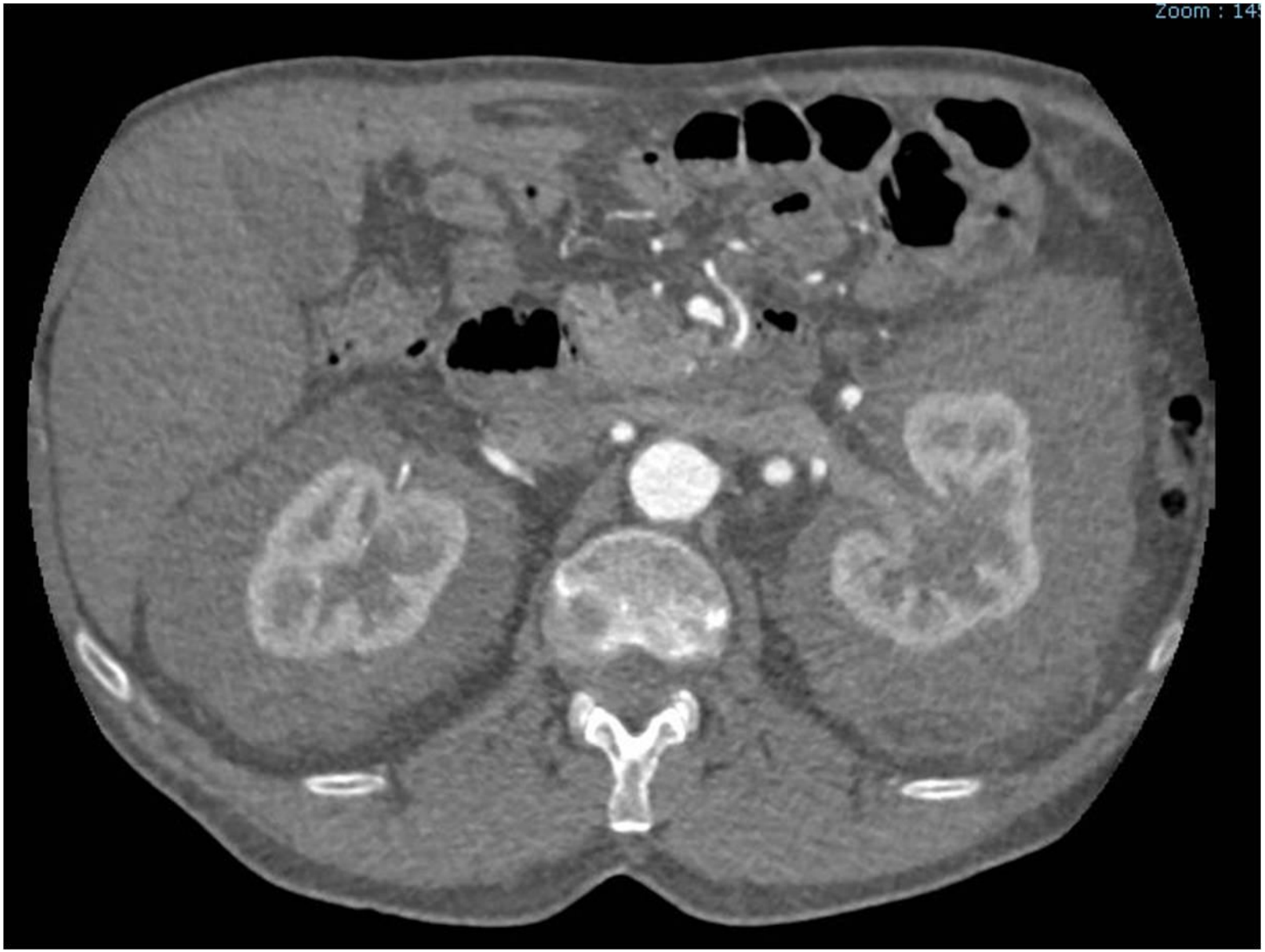
Interlobular septal thickening +++
Centrilobular micronodular opacities
Ground glass opacities
Small areas microcystic lesions

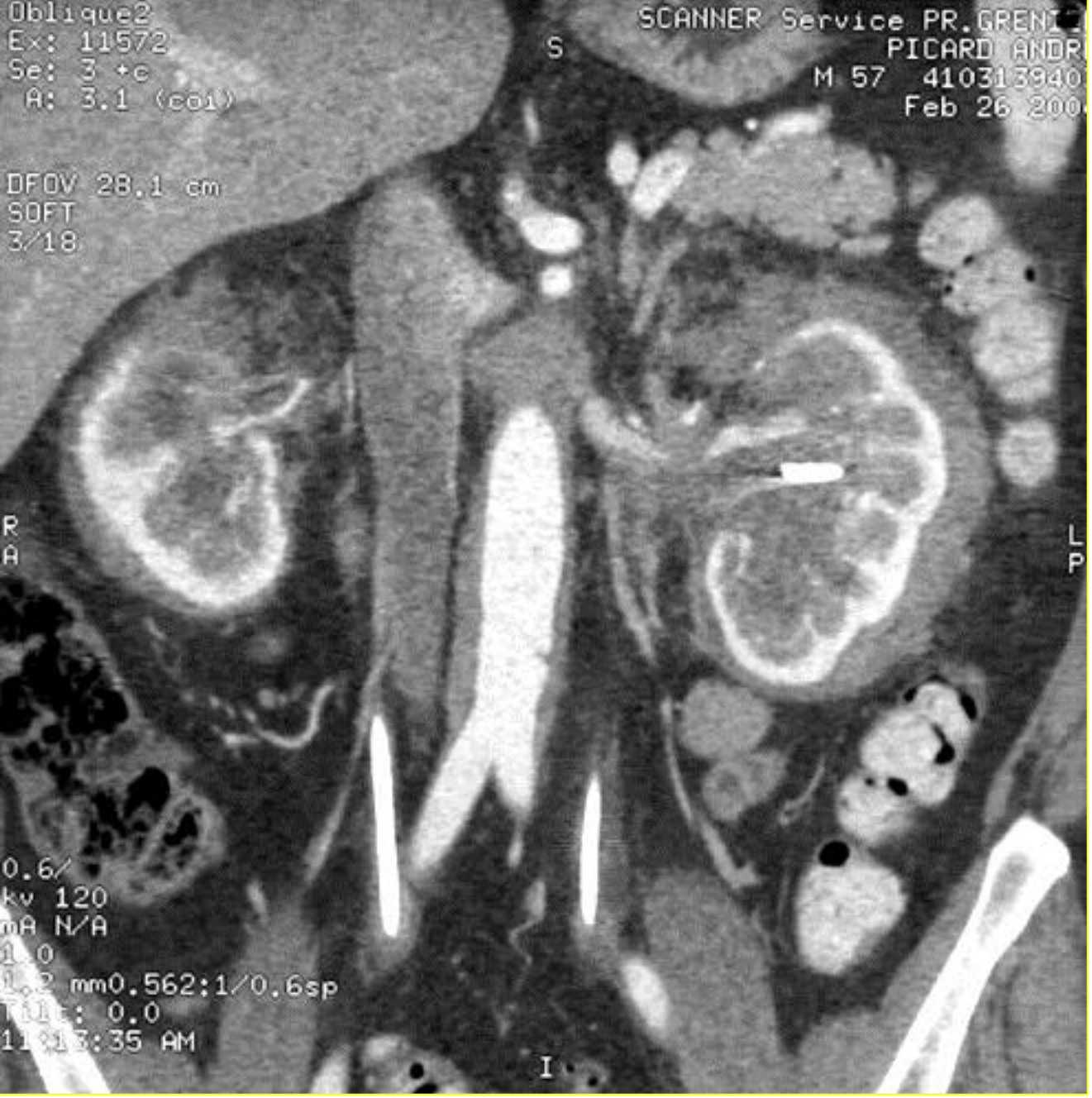
Usually not severe, not a major prognostic factor

Arnaud, Arthritis & Rheumatism, 2010



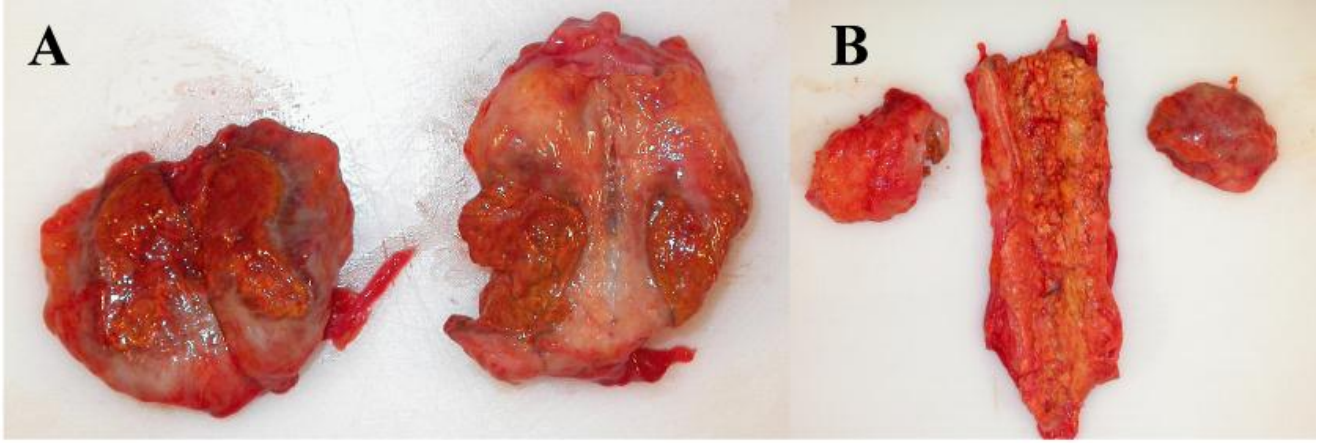
« hairy kidney » aspect with infiltration of the perirenal fat and of the perirenal fascia = 95 pts (58%)


Zoom : 14

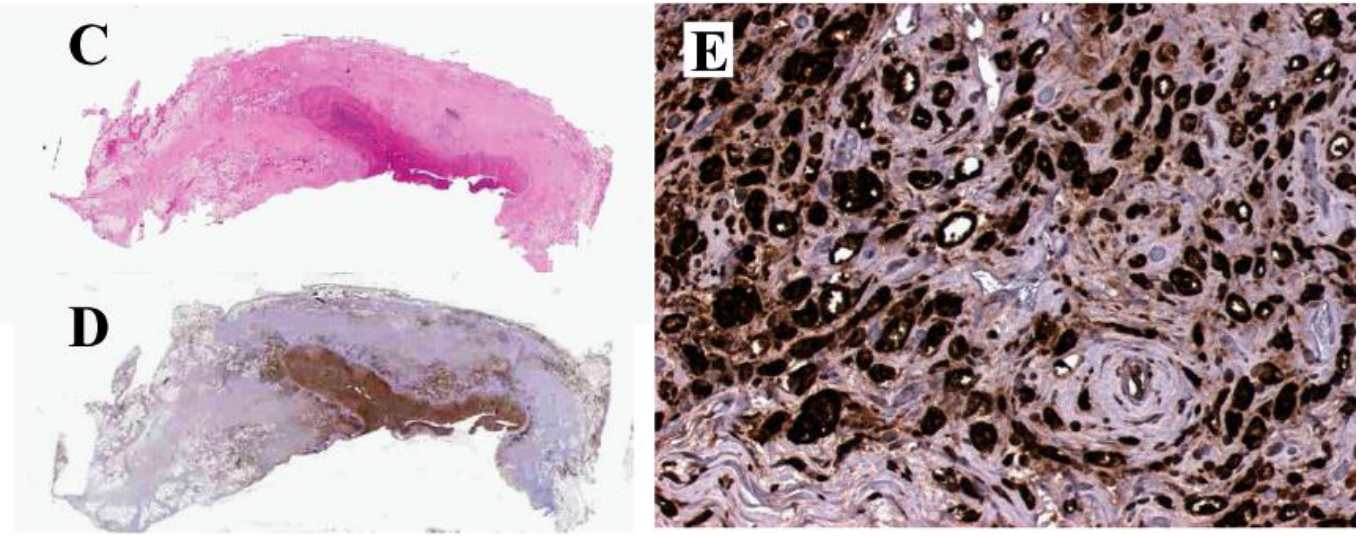


Hydronephrosis

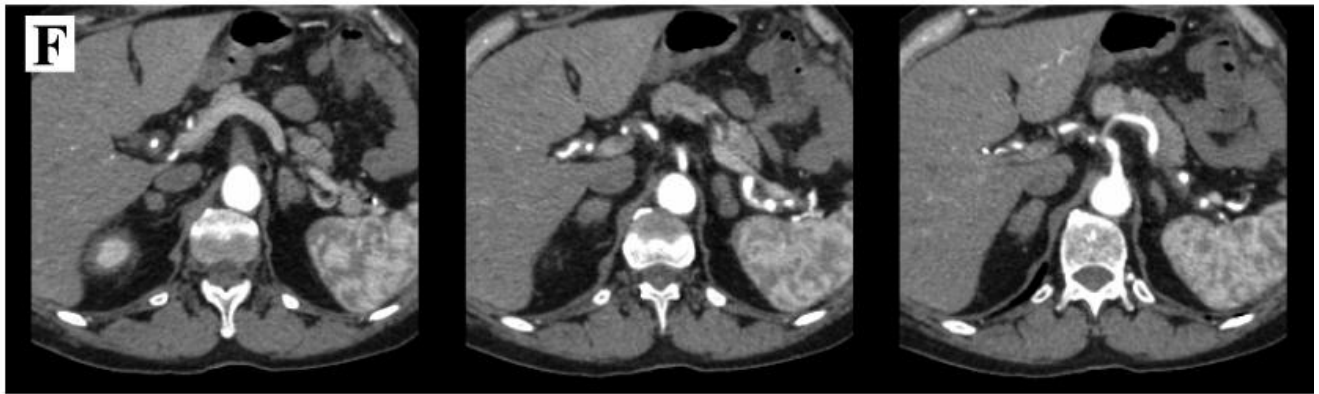
40 pts (25%)



Bilateral Adrenal Infiltration in Erdheim-Chester Disease. Report of Seven Cases and Literature Review



26 pts (17%)



Haroche, JCEM 2007

Atteintes endocriniennes

	N (%)
Insuffisance somatotrope	22/28 (78.6)
Insuffisance testiculaire	26/49 (53.1)
Hyperprolactinémie	26/59 (44.1)
Diabète insipide	19/57 (33.3)
Insuffisance gonadotrope	14/63 (22.2)
Insuffisance thyréotrope	6/63 (9.5)
Hypothyroïdie périphérique	6/63 (9.5)
Insuffisance corticotrope	2/64 (3.1)
Aucune atteinte endocrinienne	1/61 (1.6)

Dysfonction AH

Atteinte des axes dans le même ordre de fréquence que HL ou radiothérapie

Diabète insipide

Inaugural 65% cas

Permanent

Courtillot, JCEM 2016

Evaluation endocrinienne

- **Atteinte hypophysaire**
  - IRM hypophysaire
  - Recherche d'un diabète insipide et de déficits anté-hypophysaires
- **Atteinte gonadique**
  - Échographie ovarienne/testiculaire
  - Information cryoconservation sperme
- **Atteinte thyroïdienne**
  - Échographie thyroïdienne, bilan hormonal
  - Surveillance anticorps anti-thyroïdiens (IFN)
- **Atteinte surrénalienne**
  - TDM surrénalienne
  - Dosage de cortisol, si besoin après test de stimulation

Systématique

Évaluation initiale de la MEC

Suivi endocrinologique
1x /an
car apparition progressive possible

MEC : atteinte cardio-vasculaire

Décrite depuis longtemps…mais longtemps méconnue

- **Infiltration aorte et branches collatérales**
- **Péricarde**
- **Myocarde**

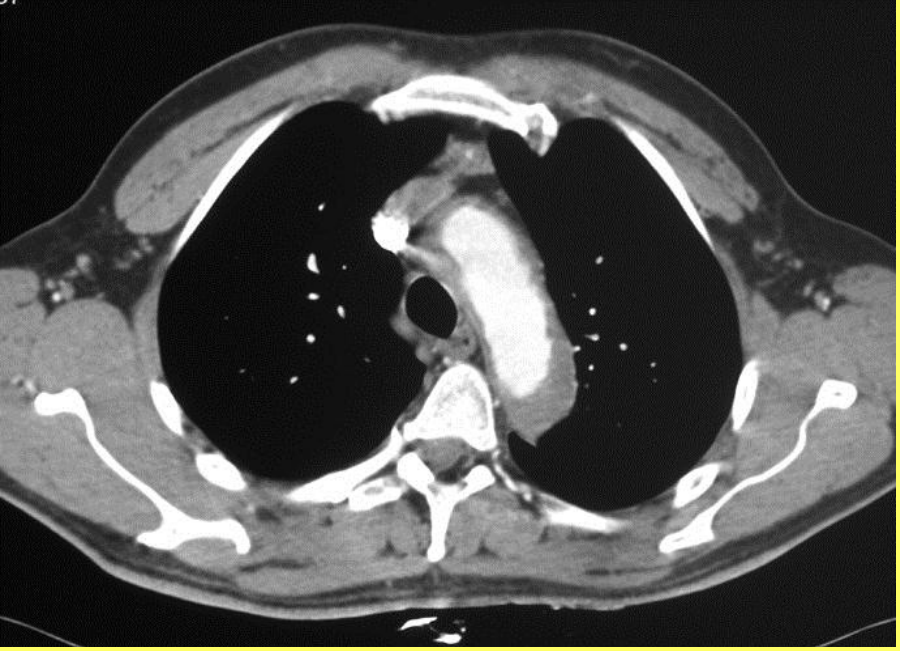
...Et « renominée » récemment : « Coated aorta » Serratrice et al. (2000) *J Rheumatol*

Cardiovascular Involvement, an Overlooked Feature of Erdheim-Chester Disease

Report of 6 New Cases and a Literature Review

Julien Haroche, MD, PhD, Zahir Amoura, MD, Elisabeth Dion, MD, Bertrand Wechsler, MD, Nathalie Costedoat-Chalumeau, MD, Patrice Cacoub, MD, Richard Isnard, MD, Thierry Généreau, MD, Janine Wechsler, MD, Nina Weber, MD, Claire Graef, MD, Philippe Cluzel, MD, Philippe Grenier, MD, and Jean-Charles Piette, MD

Medicine, 2004



Thoracic aorta

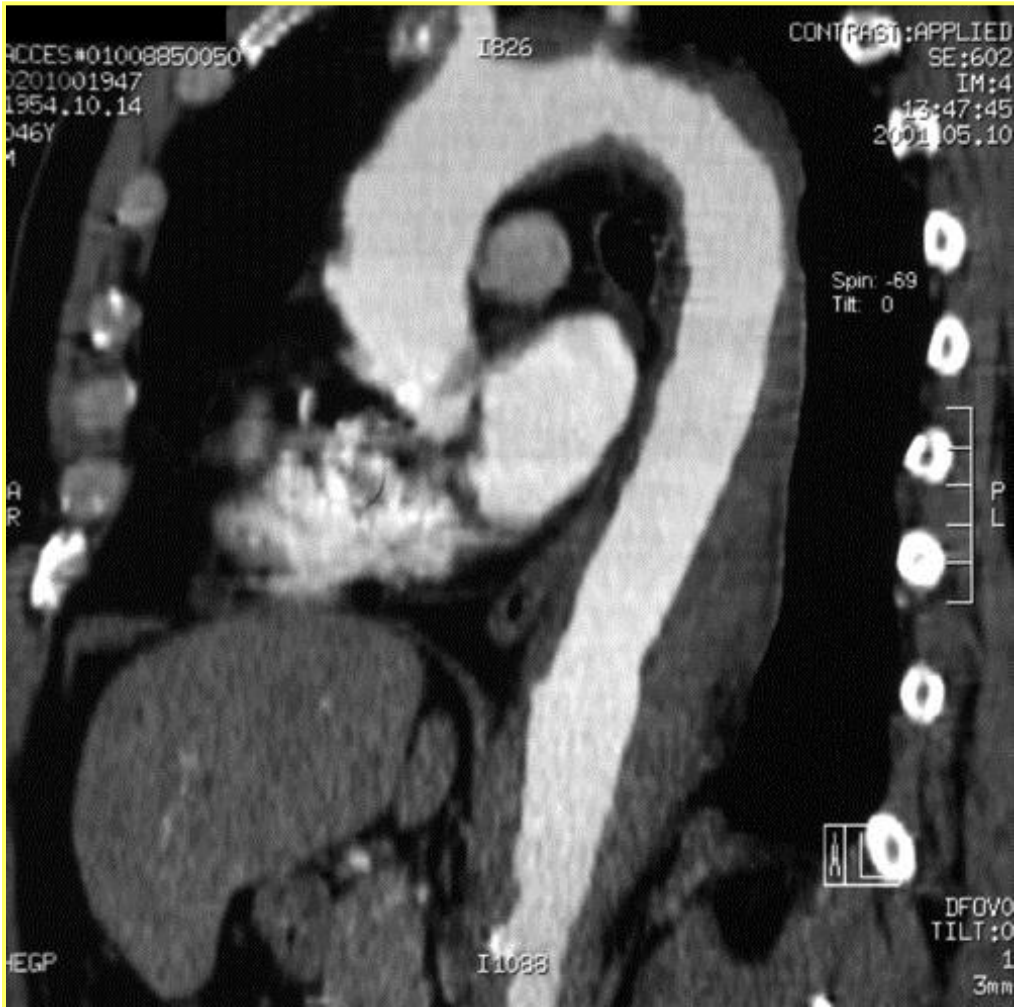
85 pts (57%)

<u>Peri-aortitis</u> =
The most frequent cardiovascular involvement in ECD

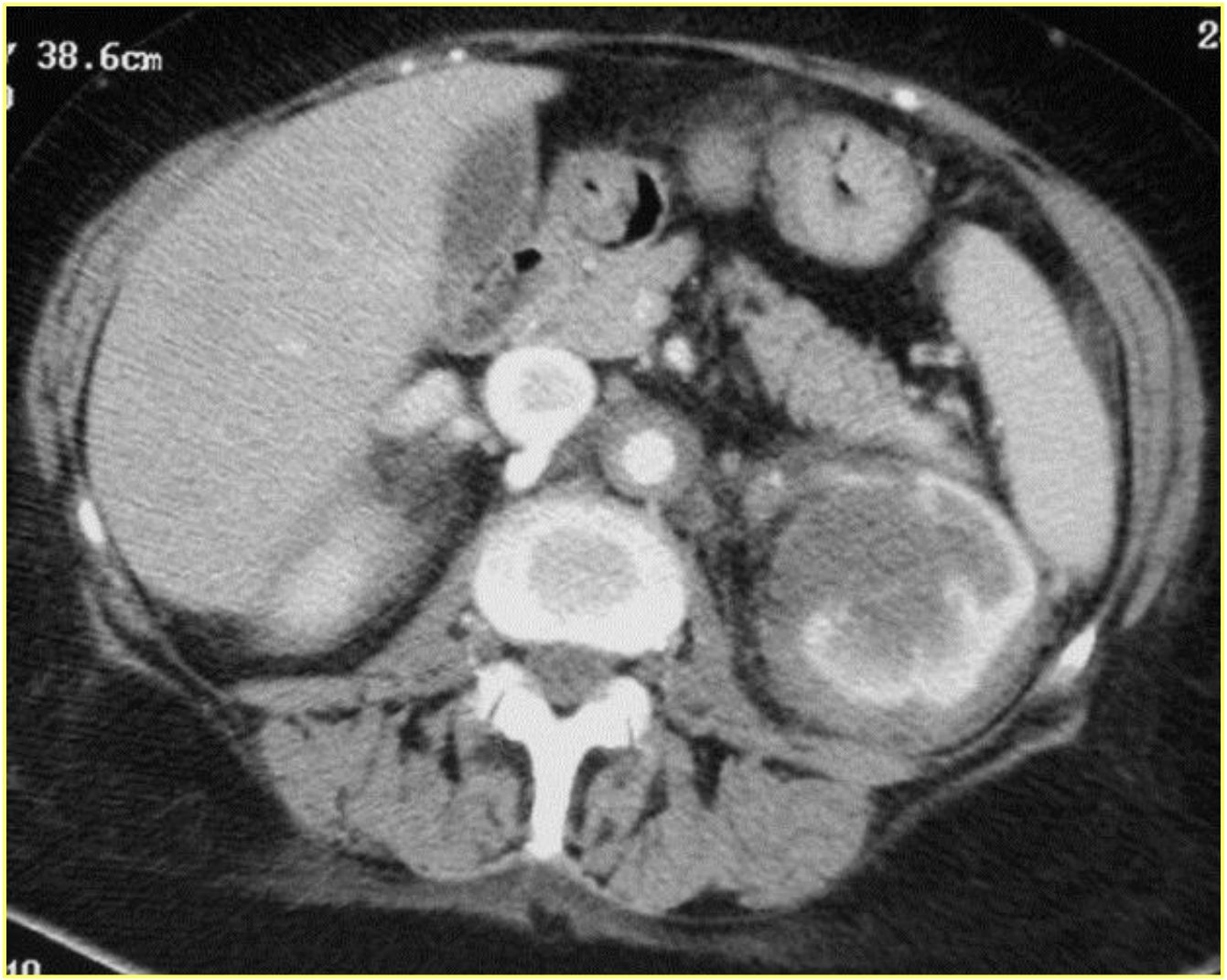
≈ 25% of all published cases

« coated-aorta »

75 pts (46%)



Abdominal aorta 87 pts (57%)



Frequent involvement of aorta branches

- mesenteric superior artery
- celiac trunk
- left sub-clavian artery
- left common carotid artery

Overall little clinical consequences

- renal artery (*stents when reno-vascular hypertension*)

Currently 29 pts (18%) with reno-vascular HT
should be systematically looked for +++

Pericardial involvement : 2nd most frequent

≈ 20% of the published cases

can lead to tamponade (sometimes lethal)

51 pts (31%)

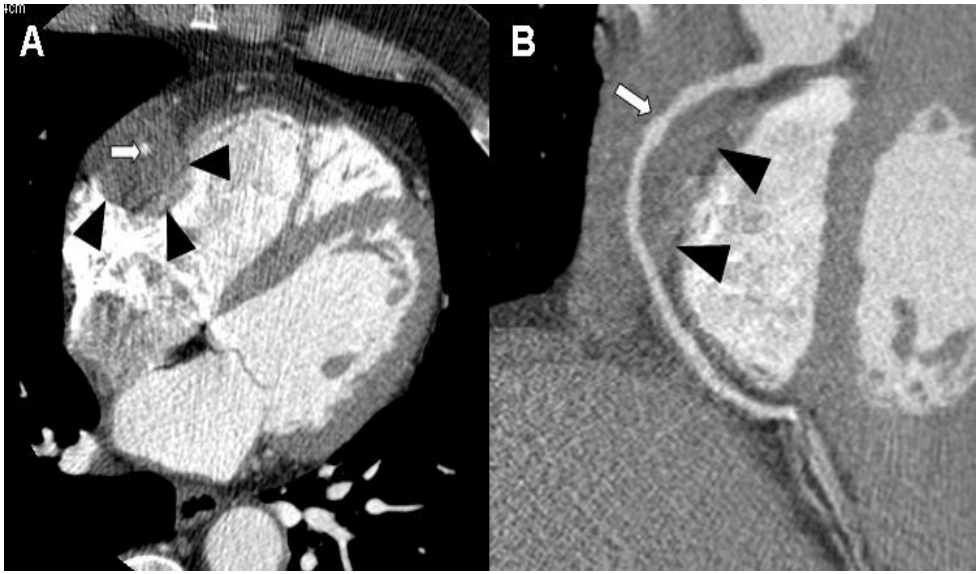
Images in Cardiovascular Medicine

Cardiac Involvement in Erdheim-Chester Disease

Magnetic Resonance and Computed Tomographic Scan Imaging in a Monocentric Series of 37 Patients

Julien Haroche, MD, PhD; Philippe Cluzel, MD, PhD; Dan Toledano, MD; Gilles Montalescot, MD, PhD; Diane Touitou, MD; Philippe A. Grenier, MD; Jean-Charles Piette, MD; Zahir Amoura, MD

Circulation 2009

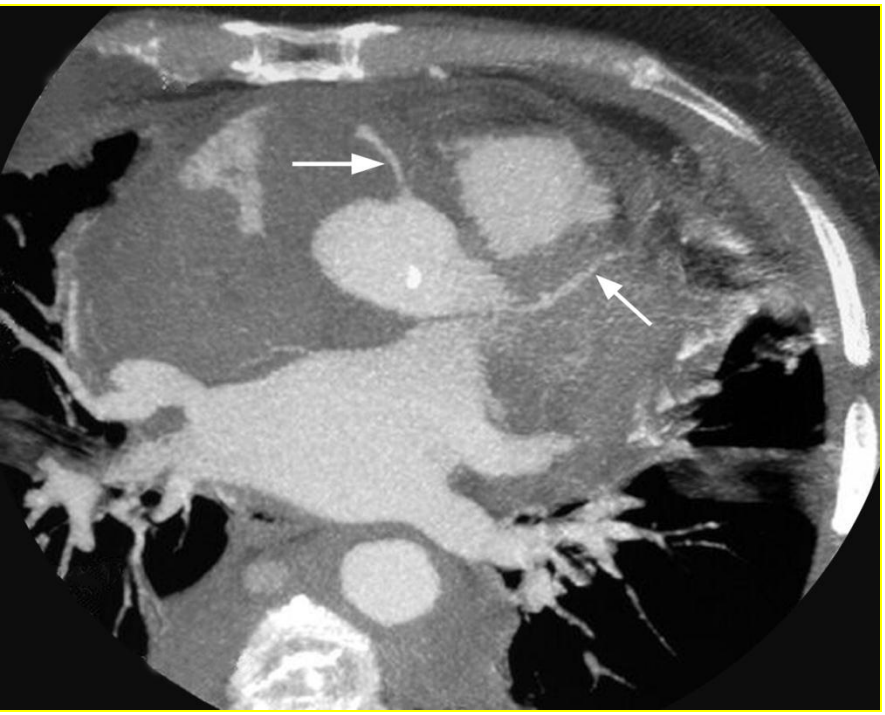


61 pts « pseudo-tumoral » infiltration of the right atrium (37%)

Coronary involvement in ECD

Myocardial infarction in more then 20 pts
(13 personal), fatal in at least 3 cases

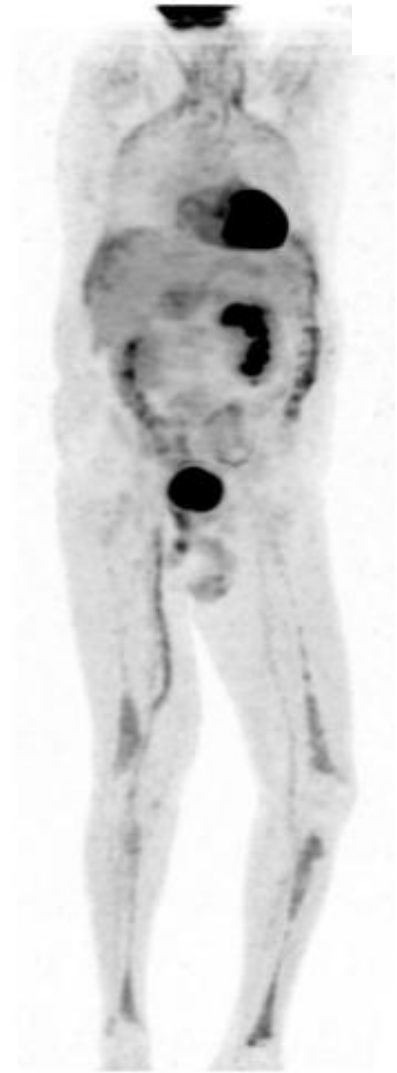
Preferentially Right coronary artery 35 pts (23%)



27 pts (18%) Left coronary

^{18}F-Fluorodeoxyglucose–Positron Emission Tomography Scanning Is More Useful in Followup Than in the Initial Assessment of Patients With Erdheim-Chester Disease

Laurent Arnaud, Zoulikha Malek, Frédérique Archambaud, Aurélie Kas, Dan Toledano, Aurélie Drier, Delphine Zeitoun, Philippe Cluzel, Philippe A. Grenier, Jacques Chiras, Jean-Charles Piette, Zahir Amoura, and Julien Haroche

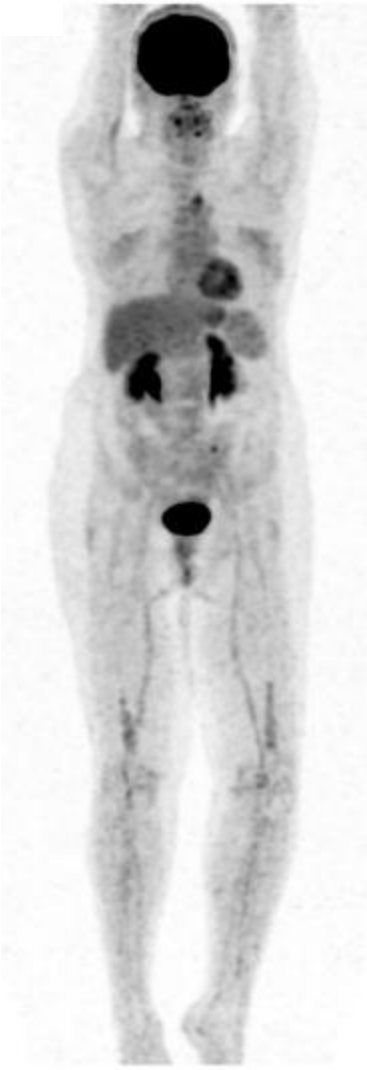


31 patients, follow-up PET in 17 (total of 65 PET)

Sensitivity depends on the type of involvement

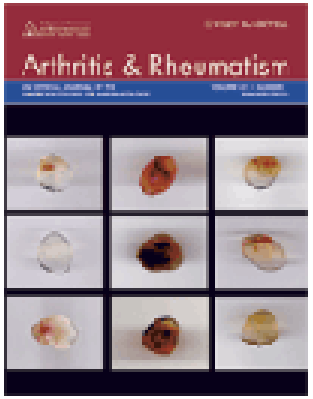
Specificity compared to other imaging modalities is excellent

May best serve in the follow-up of the disease and to assess the therapeutic response



Arthritis Rheum 2009;60:3128–38

Physiopathologie



Immunohistochemical Evidence of a Cytokine and Chemokine Network in Three Patients With Erdheim-Chester Disease

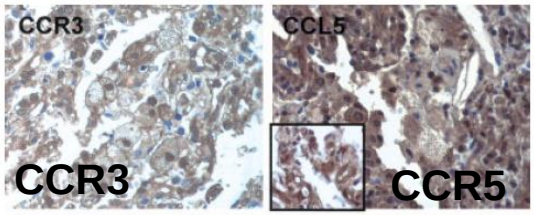
Implications for Pathogenesis

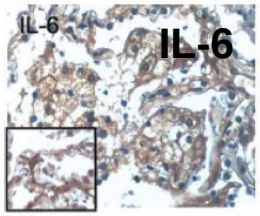
Antonella Stoppacciaro,[1] Marina Ferrarini,[2] Chiara Salmaggi,[2] Cristina Colarossi,[1] Luisa Praderio,[2] Moreno Tresoldi,[2] Angelo A. Beretta,[3] and Maria Grazia Sabbadini[4]

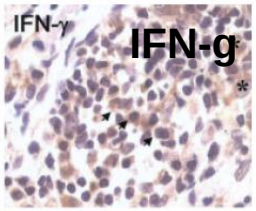
Table 1. Expression of chemokines and chemokine receptors by foamy macrophages in lesions from patients with Erdheim-Chester disease*

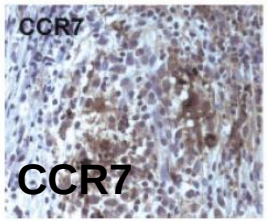
Patient	CD68	CCR1	CCL4	CCR2	CCL2	CCR3	CCL5	CCR7	CCL19	CXCR3	IP-10
1	72	83	69	>90	>90	>90	>90	66	21	>90	15
2	65	>90	>90	>90	>90	>90	>90	79	32	ND	22
3	45	>90	>90	>90	>90	>90	>90	15	12	>90	41

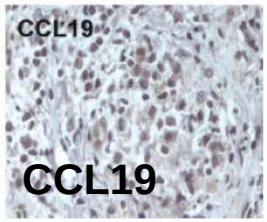
* Biopsy samples of the optic nerve sheath from patient 1, a bone lesion from patient 2, and a pulmonary lesion from patient 3 were evaluated by immunohistochemistry. Values for CD68 are the percentage of CD68+ macrophages in the inflammatory infiltrate (interstitial macrophages in the lung). All other values are the percentage of positive macrophages. The number of positive cells in 10 high-power fields (400×) was determined with the use of a 1-mm^2 optical microscope grid and is reported as the percentage of CD68+ cells, as evaluated in a comparable serial section. IP-10 = inducible protein 10; ND = not done.

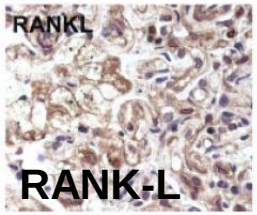


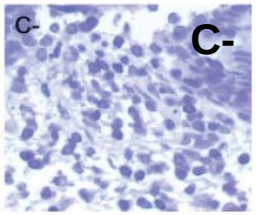






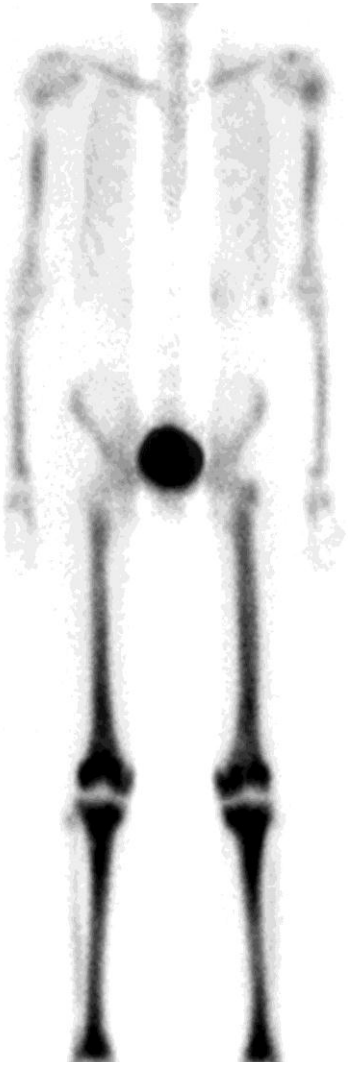


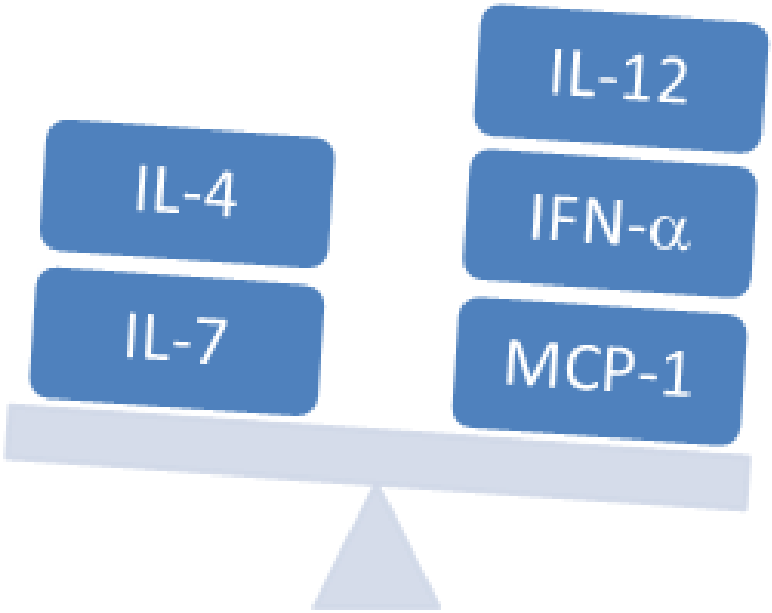




Arthritis Rheum 2006

Identification of
a cytokine « signature »





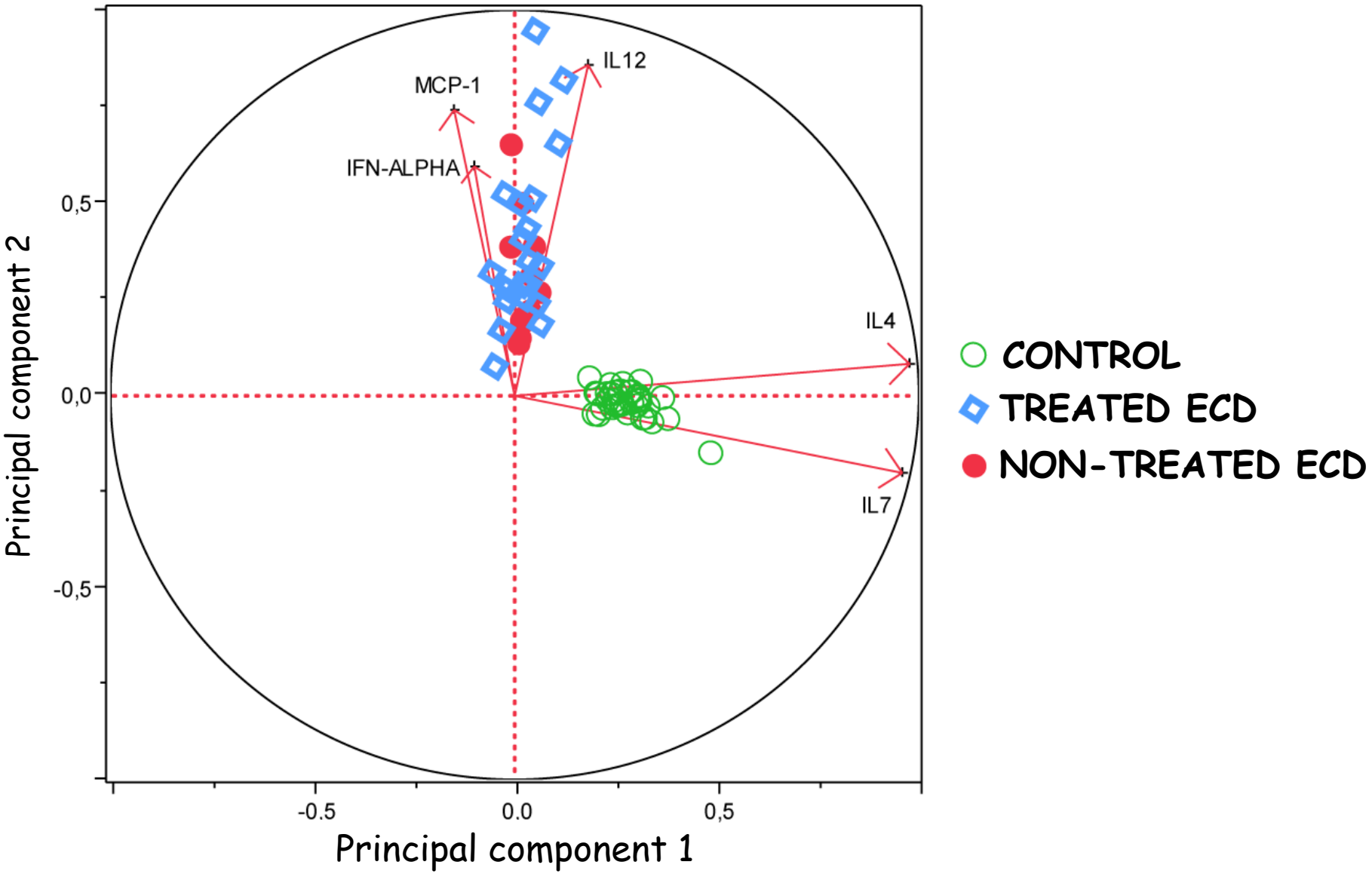
Impaired Th1/Th2 balance
Production of IFN-α (source ?)
Histiocyte recruitment via MCP-1 ?

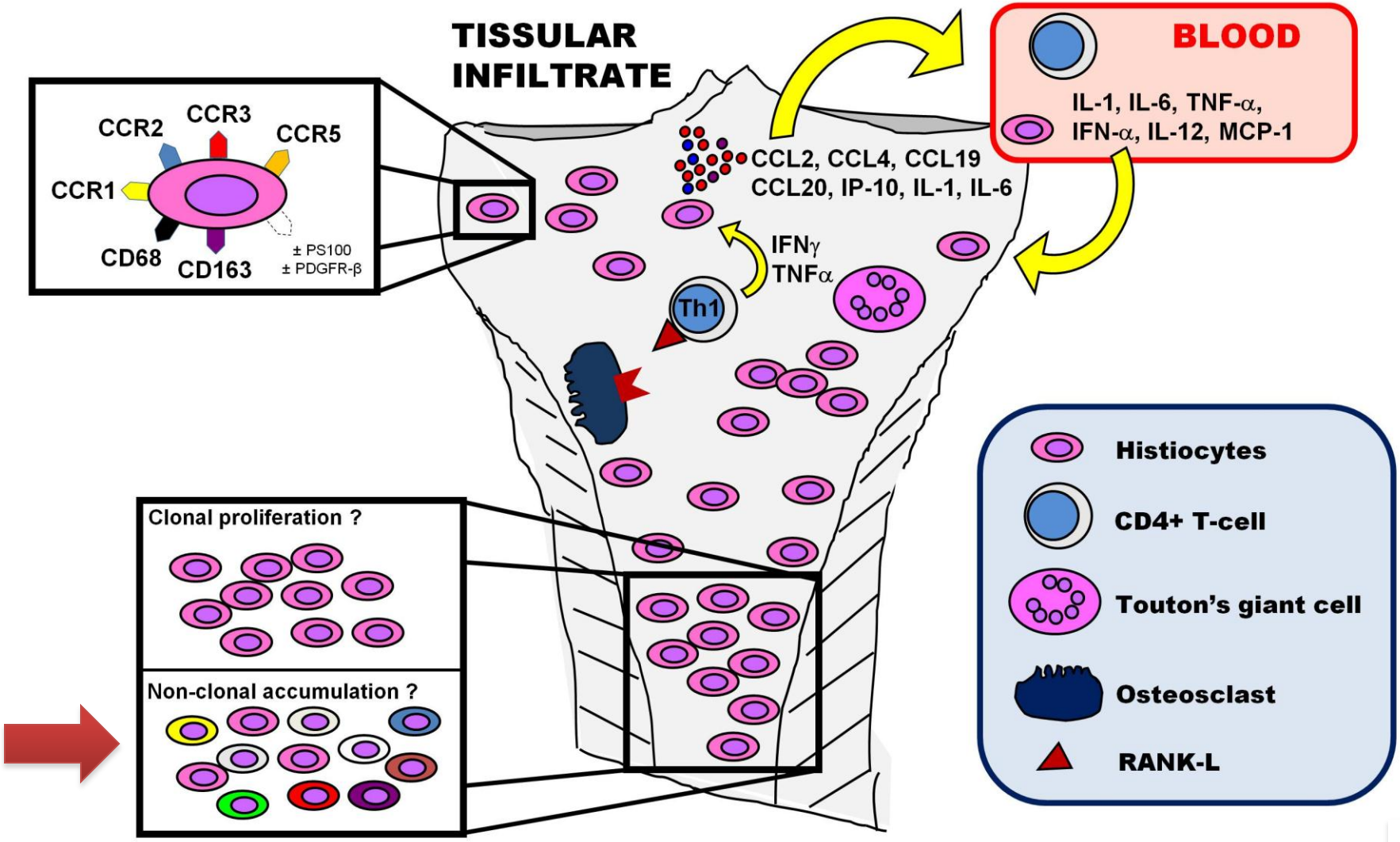
Systemic perturbation of cytokine and chemokine networks in Erdheim-Chester disease: a single-center series of 37 patients

Laurent Arnaud,[1,2] Guy Gorochov,[1-3] Frédéric Charlotte,[1,3] Virginie Lvovschi,[1] Christophe Parizot,[1] Martin Larsen,[2,3] Pascale Ghillani-Dalbin,[1] Baptiste Hervier,[1] Jean-Emmanuel Kahn,[4] Claire Deback,[1] Lucile Musset,[1] Zahir Amoura,[1-3] and Julien Haroche[1,3]

Blood 2011

Principal component analysis




TISSULAR INFILTRATE
BLOOD
IL-1, IL-6, TNF-α, IFN-α, IL-12, MCP-1
CCL2, CCL4, CCL19 CCL20, IP-10, IL-1, IL-6
IFNγ TNFα
Th1
CCR2
CCR3
CCR5
CCR1
CD68
CD163
± PS100
± PDGFR-β
Clonal proliferation ?
Non-clonal accumulation ?
Histiocytes
CD4+ T-cell
Touton's giant cell
Osteosclast
RANK-L

Brief report

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]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Medicine, Brigham & Women's Hospital, Boston, MA; [3]Department of Medicine, Harvard Medical School, Boston, MA; [4]Department of Pathology, Children's Hospital Boston, MA; [5]Department of Pathology, Harvard Medical School, Boston, MA; [6]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA; [7]Department of Medicine, Children's Hospital Boston, MA; [8]Department of Pediatrics, Harvard Medical School, Boston, MA; [9]Center for Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, MA; [10]Department of Pathology, Brigham & Women's Hospital, Boston, MA; [11]Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA; [12]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; and [13]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA

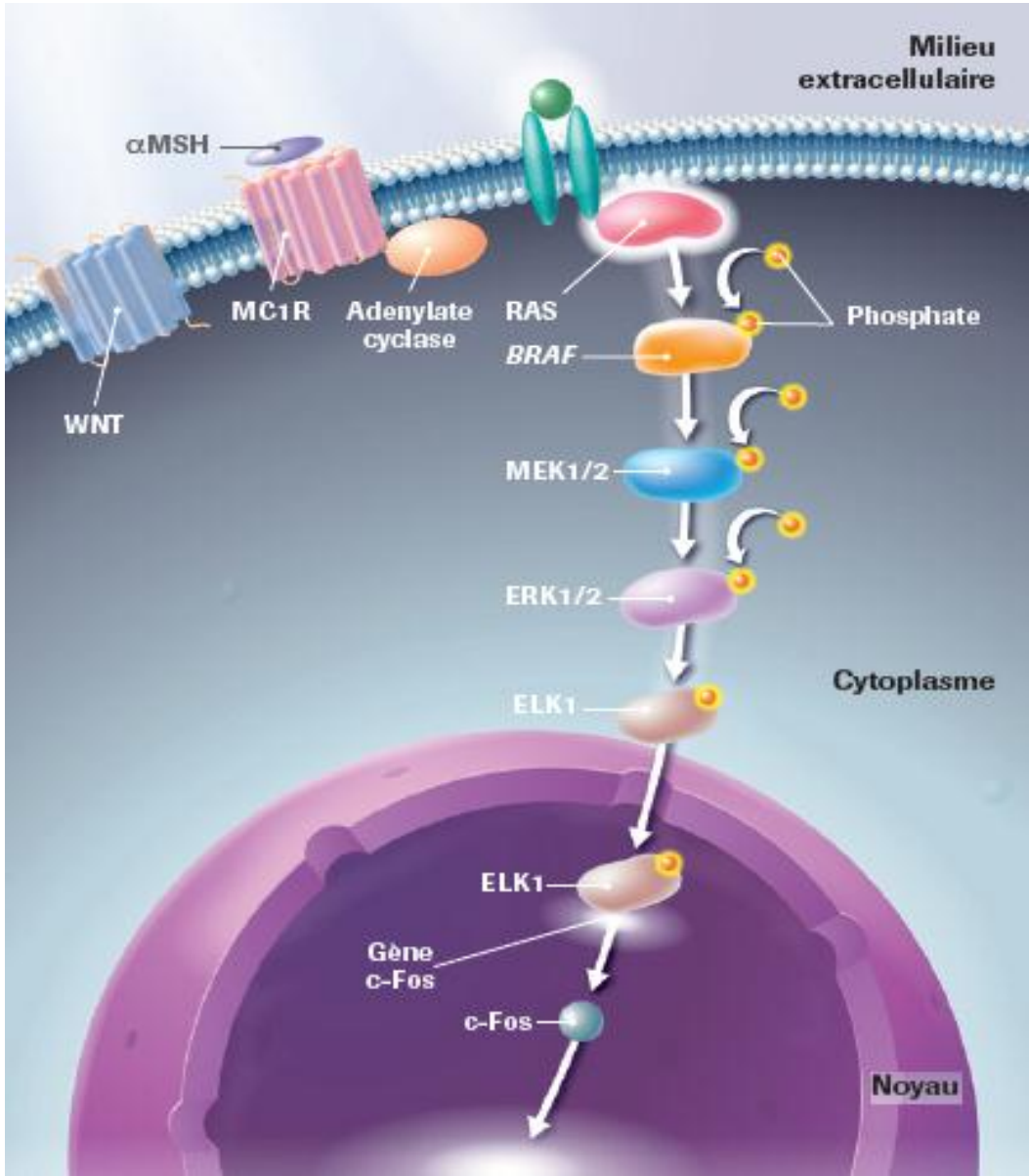
Langerhans cell histiocytosis (LCH) has a broad spectrum of clinical behaviors; some cases are self-limited, whereas others involve multiple organs and cause significant mortality. Although Langerhans cells in LCH are clonal, their benign morphology and their lack (to date) of reported recurrent genomic abnormalities have suggested that LCH may not be a neoplasm. Here, using 2 orthogonal technologies for detecting cancer-associated mutations in formalin-fixed, paraffin-embedded material, we identified the oncogenic BRAF V600E mutation in 35 of 61 archived specimens (57%). TP53 and MET mutations were also observed in one sample each. BRAF V600E tended to appear in younger patients but was not associated with disease site or stage. Langerhans cells stained for phospho-mitogen–activated protein kinase kinase (phospho-MEK) and phospho-extracellular signal-regulated kinase (phospho-ERK) regardless of mutation status. High prevalence, recurrent *BRAF* mutations in LCH indicate that it is a neoplastic disease that may respond to RAF pathway inhibitors. (*Blood*. 2010;116(11):1919-1923)

Looking for BRAF *V600E* mutations

- Histological samples taken from 127 patients with histiocytosis were reviewed
- Detection of BRAFV600 mutations was performed by pyrosequencing of DNA extracted from paraffin embedded samples.
- 46 ECD
- 39 LCH
- 23 Rosai-Dorfman
- 12 Juvenile Xanthogranuloma
- 3 Histiocytic Sarcoma
- 2 Xanthoma disseminatum
- 1 interdigitating dendritic cell sarcoma
- 1 necrobiotic xanthogranuloma

RAS-RAF-MEK-ERK pathway
BRAF V600E activating mutation

- **Mélanome 50 %**
- **Colon 5%**
- **Leucémie Tricho L 100%**
- **Histiocytoses**
  LCH 50-60 %
  ECD 55-70% (PCR digitale)



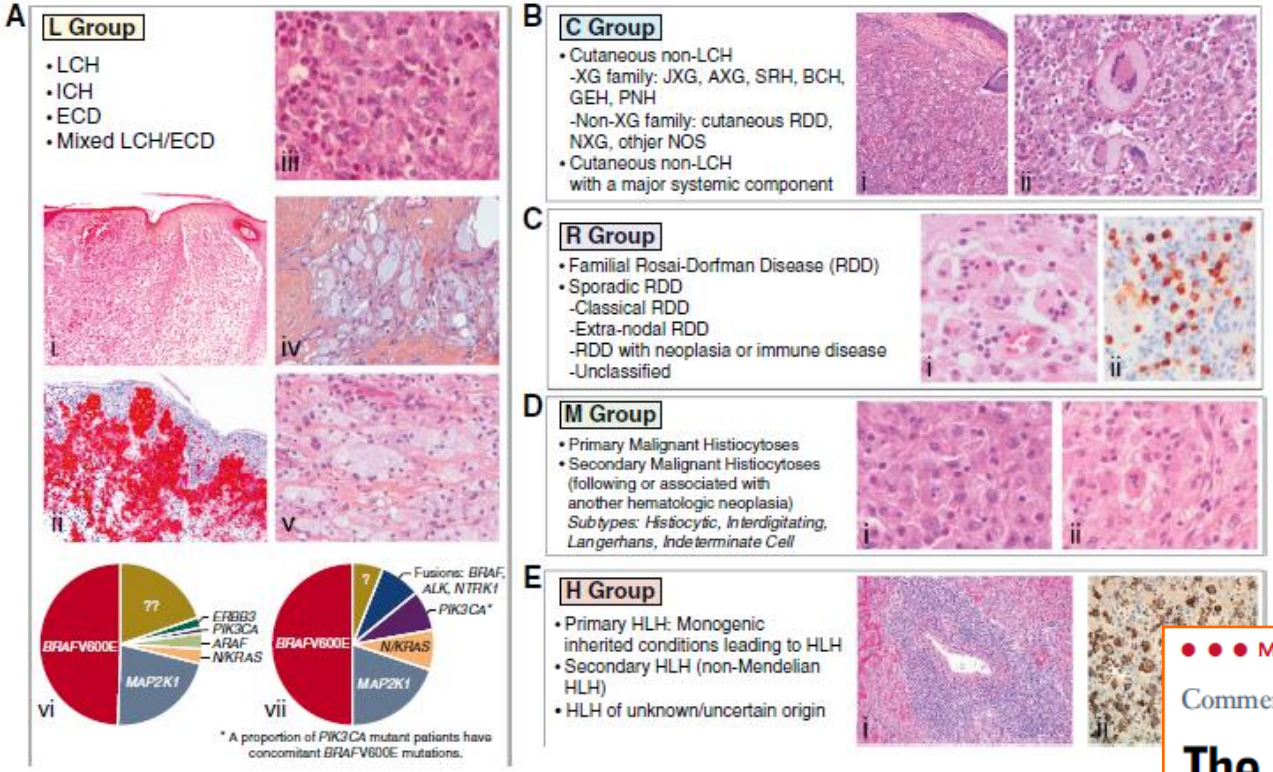
Haroche et al *Blood* 2012; 120: 2700

Classification taking into account molecular alterations

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 • VOLUME 127



MYELOID NEOPLASIA

Comment on Emile et al, page 2672

The histiocytoses: as easy as ABC (or LCMRH)

Démarches Thérapeutiques

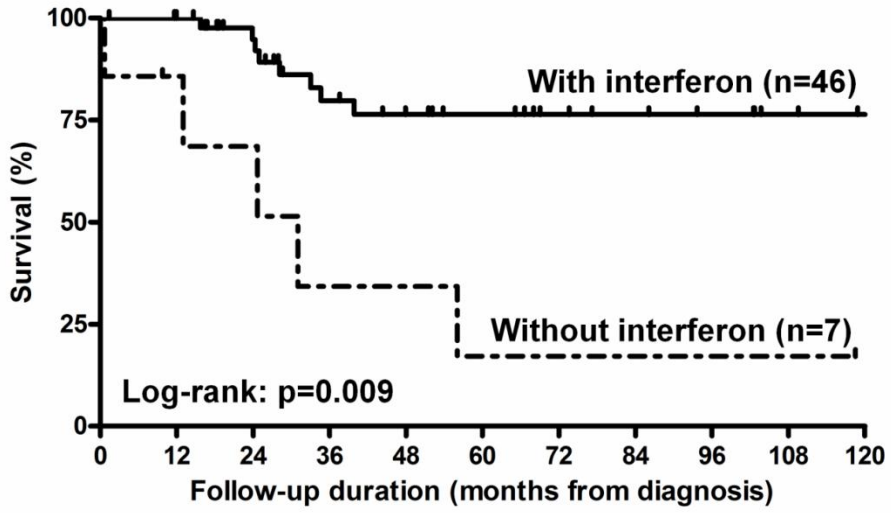
Brief report

BLOOD, 1 NOVEMBER 2005 • VOLUME 106, NUMBER 9

Successful treatment of Erdheim-Chester disease, a non–Langerhans-cell histiocytosis, with interferon-α

Fadi Braiteh, Cynthia Boxrud, Bita Esmaeli, and Razelle Kurzrock

CNS involvement and treatment with interferon-alpha are independant prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients



Numbers at risk

Interferon-alpha	46	43	35	26	22	19	15	13	11	8	6
No interferon-alpha	7	6	5	3	3	2	2	2	2	2	1

Arnaud, Hervier, Haroche, et al. Blood 2011

Clinical and therapeutic predictors of survival in Erdheim-Chester disease (multivariate survival analysis using Cox proportional hazard model).

	Univariate Analysis	Cox multivariate survival analysis†	
	P-value	**HR (95% CI)**	**P-value**
Gender	0.55	-	-
Cardiovascular involvement	0.57	-	-
CNS involvement	**0.10**	**2.51 (1.28-5.52)**	**0.006**
Hypophyseal involvement	0.93	-	-
Paranasal sinus involvement	0.54	-	-
Maxillary involvement	0.23	-	-
Xanthelasma	0.98	-	-
Orbital involvement	0.57	-	-
Pulmonary involvement	0.21	-	-
Retroperitoneal involvement	0.31	-	-
Adrenal involvement	0.53	-	-
Treatment with interferons*	**0.03**	**0.32 (0.14-0.70)**	**0.006**

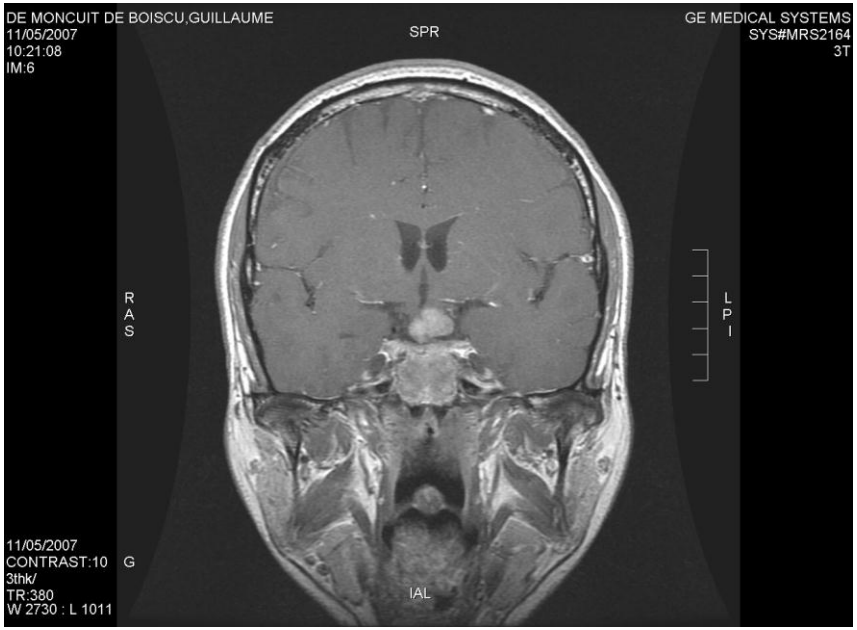
*Interferons: treatment with interferon-alpha and/or PEGylated-interferon alpha. P-values <0.20 in univariate analysis were entered in the multivariate model. HR: hazard ratio, 95% CI: 95% Confidence Interval. †Adjusted for the age at compilation (quartiles of the distribution), the use of corticosteroids or of any other immunosuppressive drugs.

Arnaud, Hervier, Haroche, et al. Blood 2011

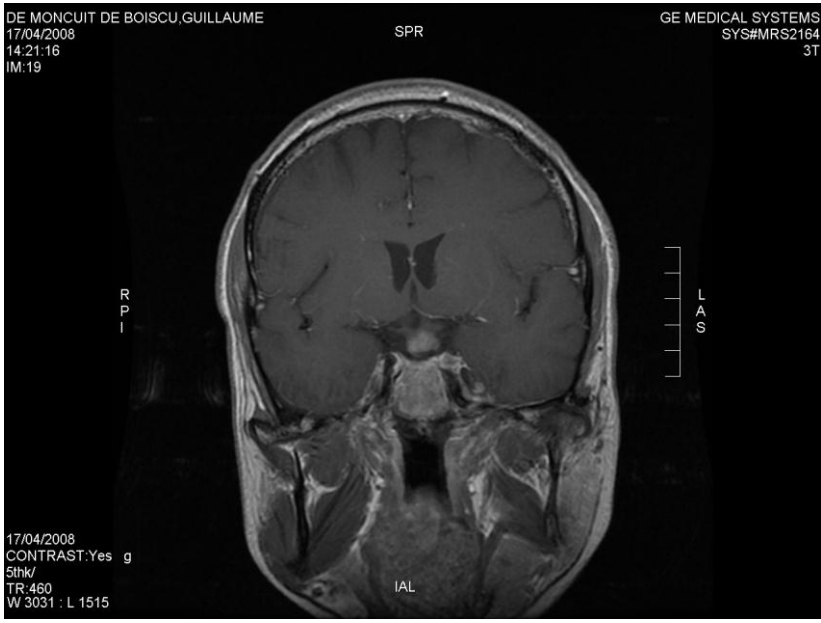
Among our 165 ECD patients (2018)

- Interferon alpha or/and Pegylated (n=113), and - if possible - raise doses to 9M X 3 in case of CNS and cardiac involvements

- Trend to switch to pegylated interferon but problems of dose equivalence



05/2007



04/2008

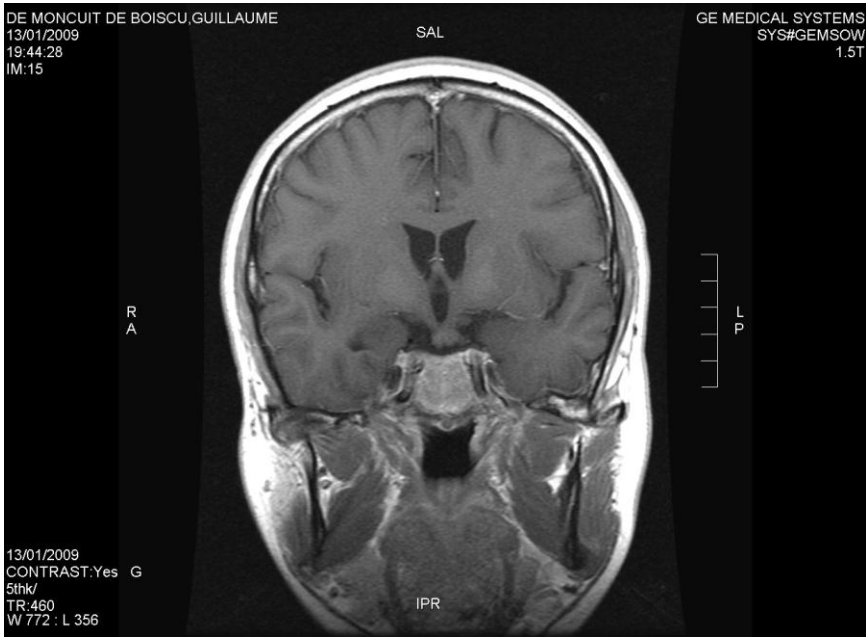
<u>Man, 30-year-old</u>, referred to our institution in october 2006

ECD diagnosed on bone biopsy in september 2002

CNS involvement only with sus and retro-sellar infiltration with diabetes insipidus, hypogonadism and complex partial seizures

Major side effects to vinblastine in 2002

IFN alpha 9 M x 3 per week initiated in October 2006

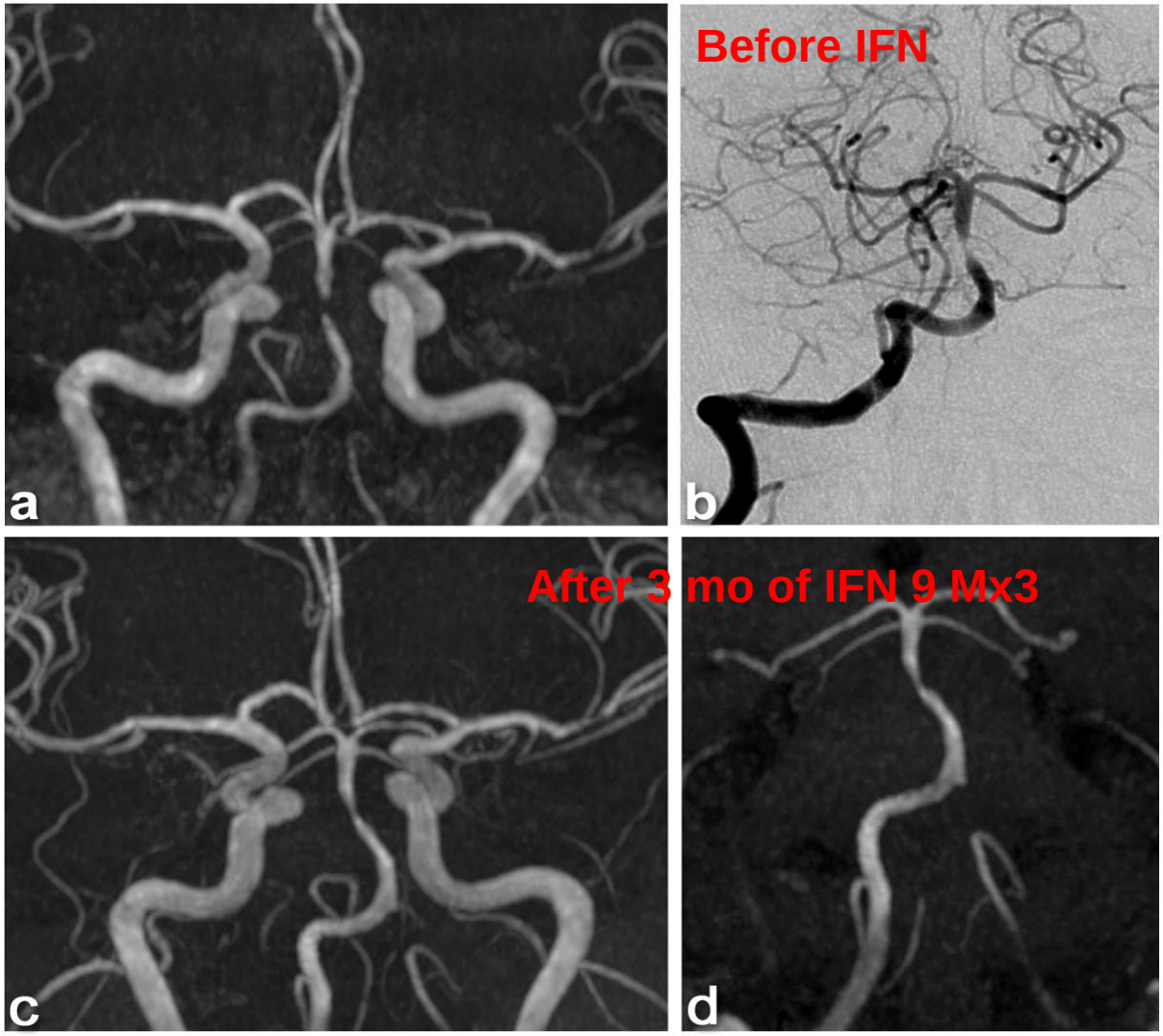


01/2009

60-year-old woman, elevated CRP, recurrent sinusitis, bilateral stenosis of the renal arteries, periaortic infiltration, pericardial effusion and a right atrial tumour

In August 2007, sudden cortical blindness associated with memory impairment.

Cerebral MRI revealed multiple vertebro-basilar ischemic infarcts, due to a severe narrowing of the basilar artery



IFN alpha treatment was initiated and at 3 mo, clinical and biological outcome were favourable. Cardiovascular investigations showed partial regression of atrial infiltration and complete regression of pericardial effusion. Cerebral MRI showed important regression of basilar stenosis (50% versus prethrombotic).

Alternative treatment ?

Anakinra ? *Aouba Blood* 2010

Seems to be efficacious on mild forms of the disease, but no proven efficacy on CNS nor cardiovascular involvements.

12 patients treated, efficacy variable, « mild ECD »

Cohen-Aubart Blood 2016

Cladribine ? a few case reports of efficacy in ECD (exophthalmos), and by analogy with treatment of other histiocytoses (LCH, RDD). How many pulses ?

Tyrosine kinase inhibitors ? Overall failure

Tocilizumab ? Only one patient

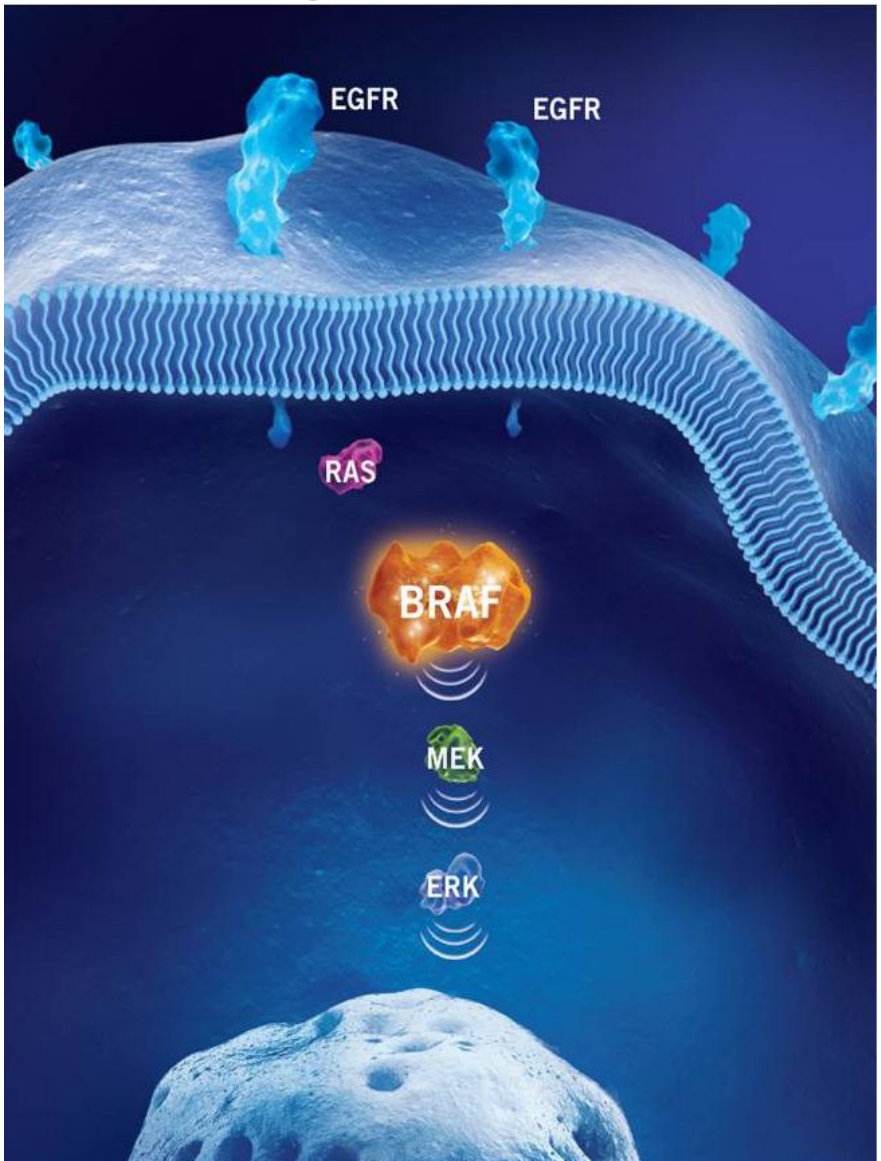
Infliximab ? Currently 16 patients, various therapeutic responses

Dagna JCO 2012

Sirolimus Blood 2015

RAS-RAF-MEK-ERK pathway
BRAF V600E activating mutation

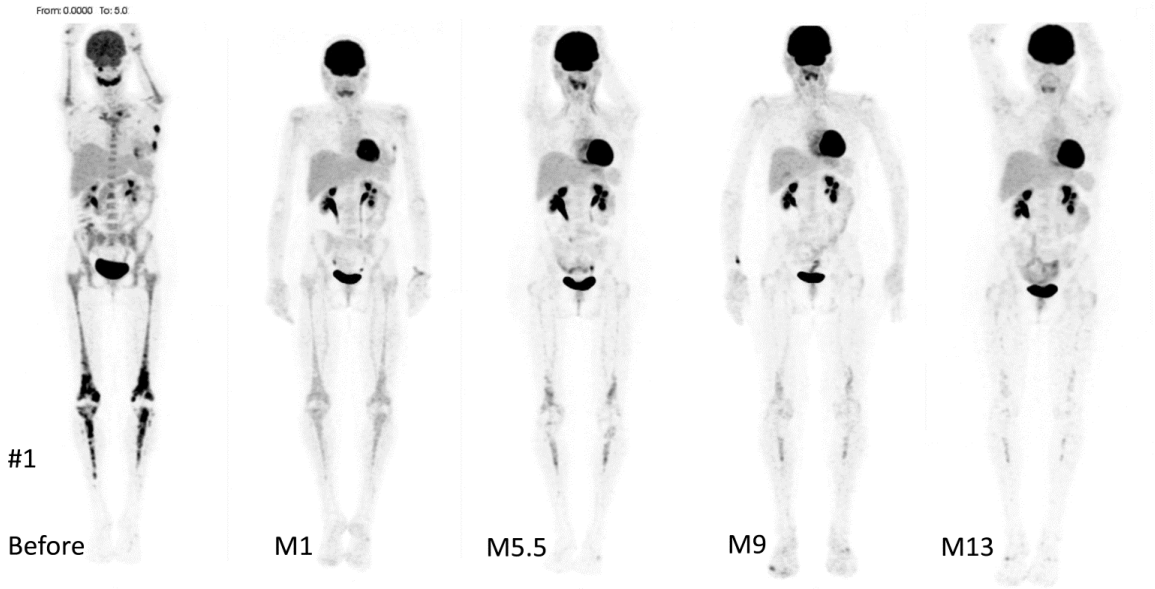
- **Melanoma 80 %**
- **Colon 5%**
- **Hairy cell L 100%**
- **Histiocytoses**
  - **LCH 50-60 %**
  - **ECD 55-70%**



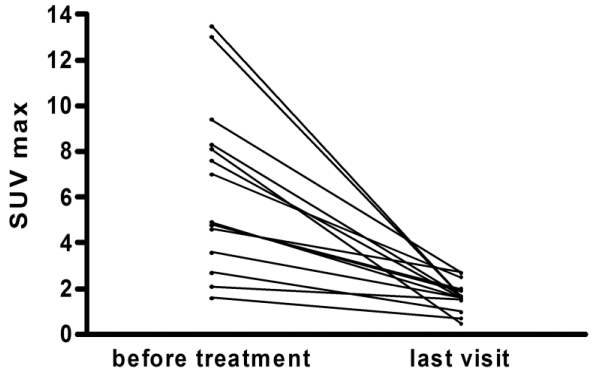
Haroche et al Blood 2012; 120: 2700

Reproducible and sustained efficacy of targeted therapy with Vemurafenib in Eight patients with BRAFV600E mutated Erdheim-Chester disease

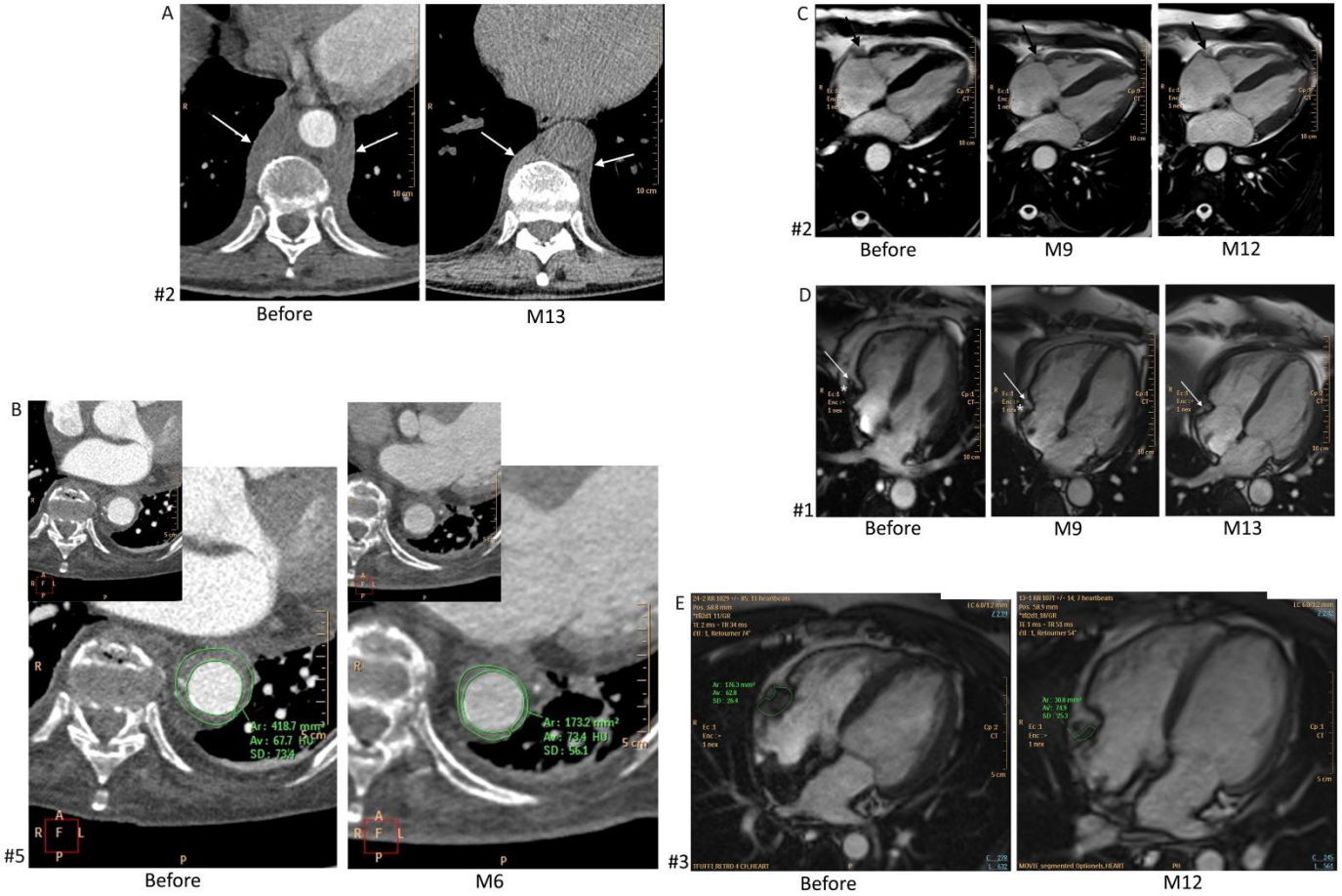
A



B



Haroche et al J Clin Oncol, 2015



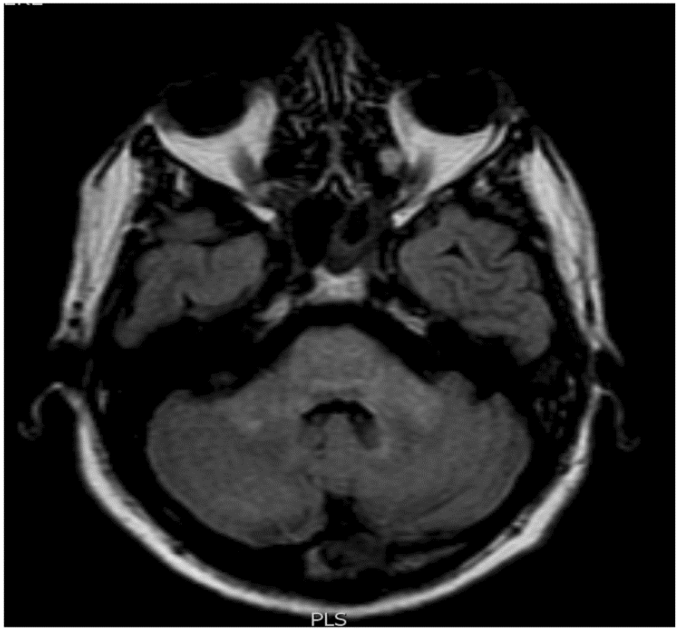
•All patients were PMR at M6 of vemurafenib, and the median SUVmax reduction was 63.5 % (range: 41.3 - 86.9)

•Evaluation of cardiac and aortic infiltrations showed that 7 patients had a partial response, and 1 was in stable disease according to RECIST criteria

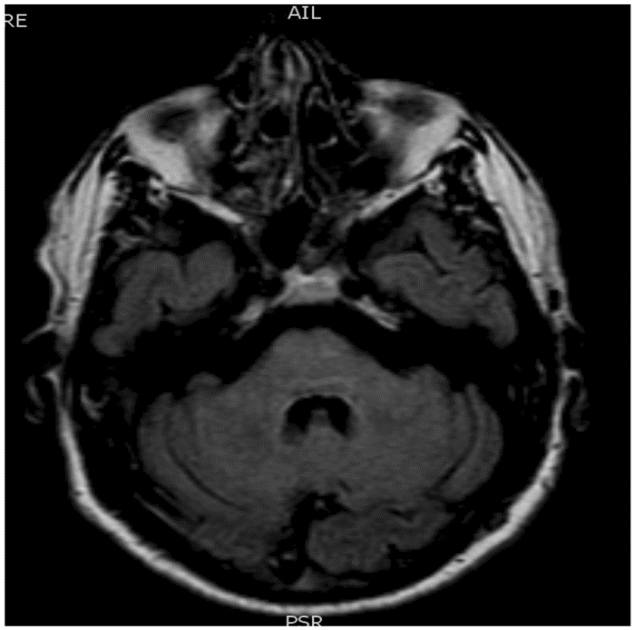
•Persistent response to vemurafenib, with a median follow up of 10.5 months (range: 6-16)

Haroche et al J Clin Oncol, 2015

#4



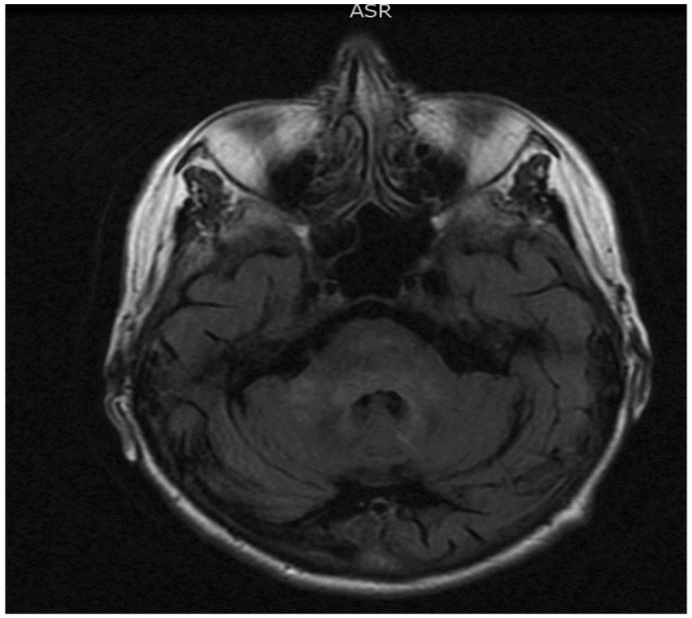
Before



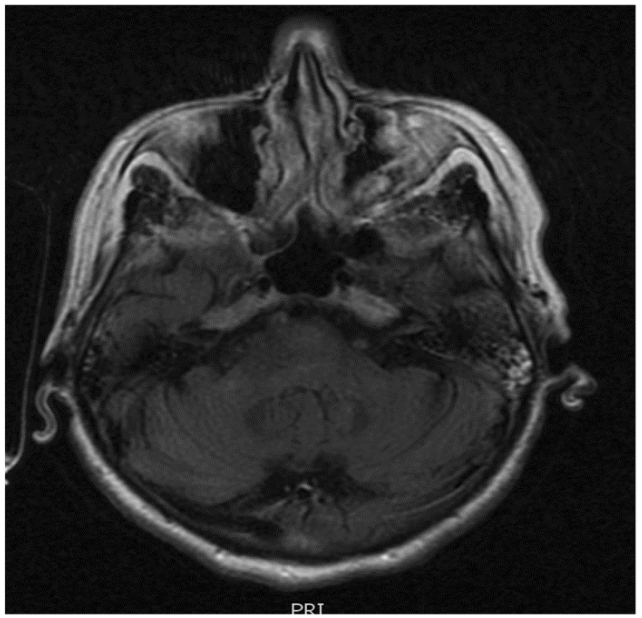
M9

Neurologic regression

#5



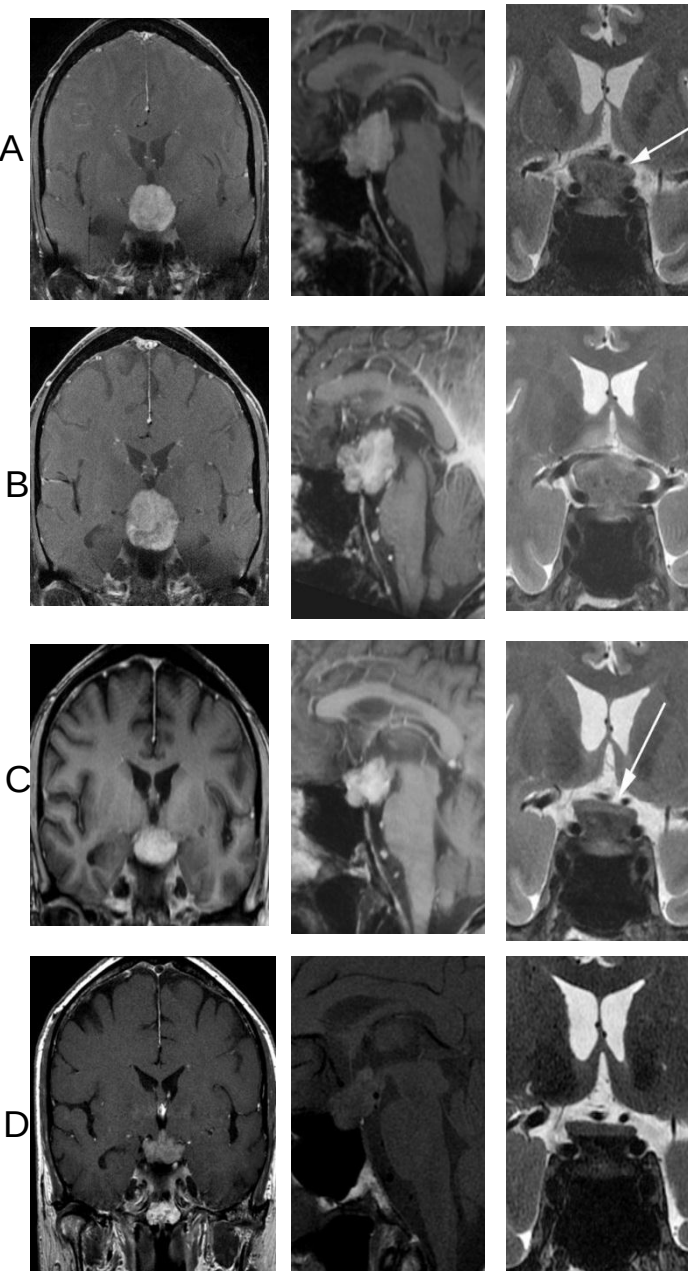
Before

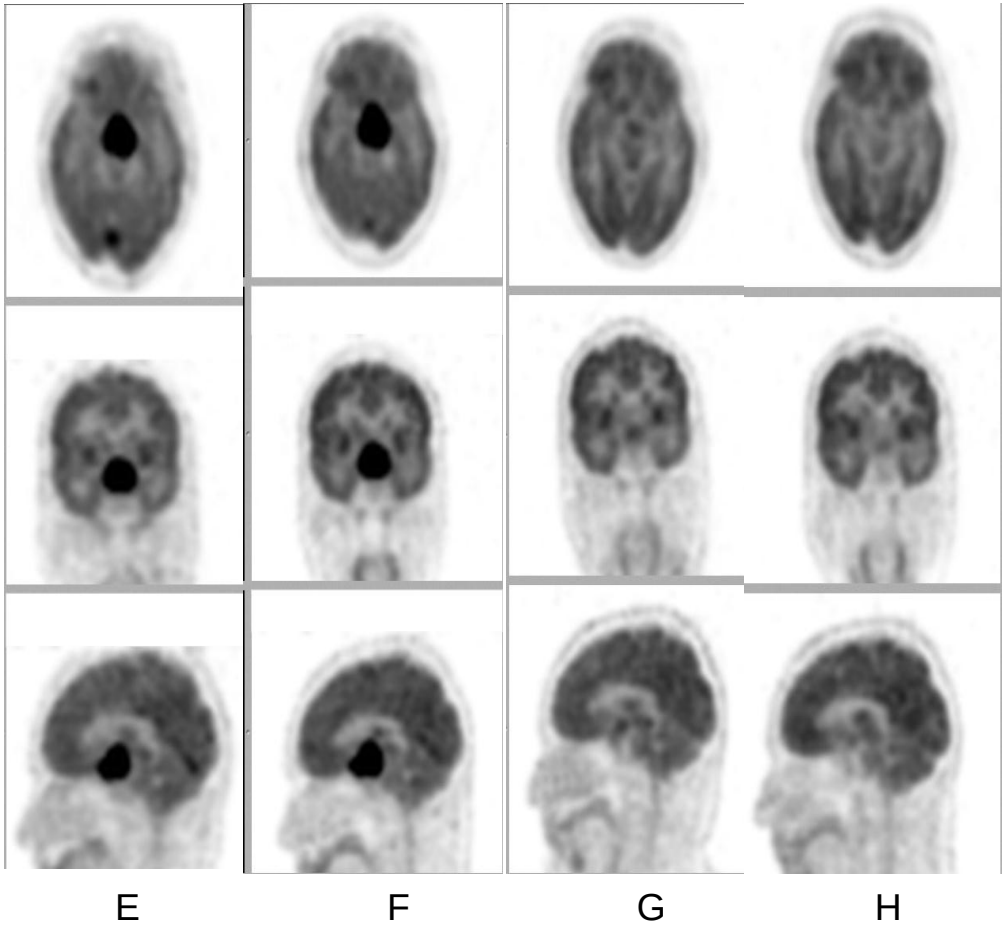


M6

Haroche J Clin Oncol 2015

Marked efficacy of vemurafenib in suprasellar Erdheim-Chester disease

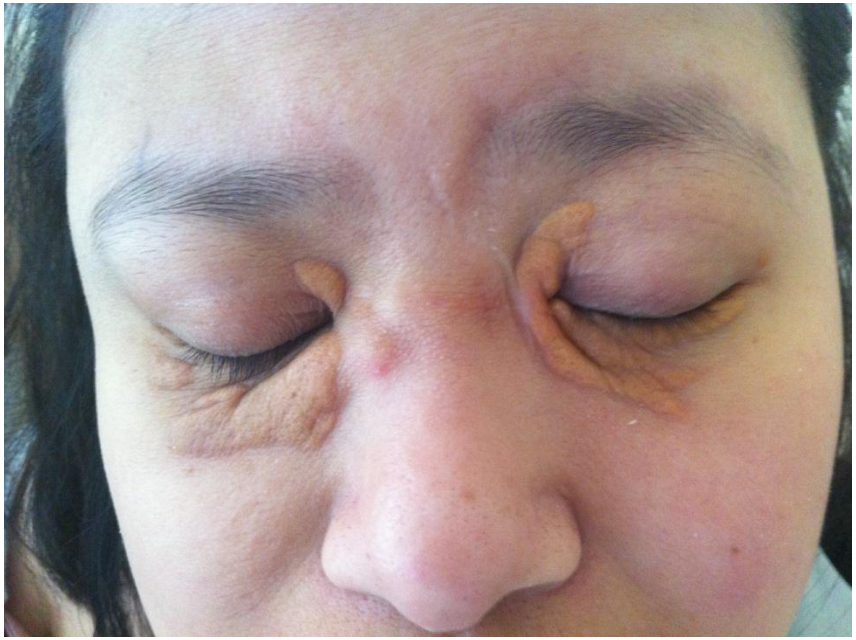




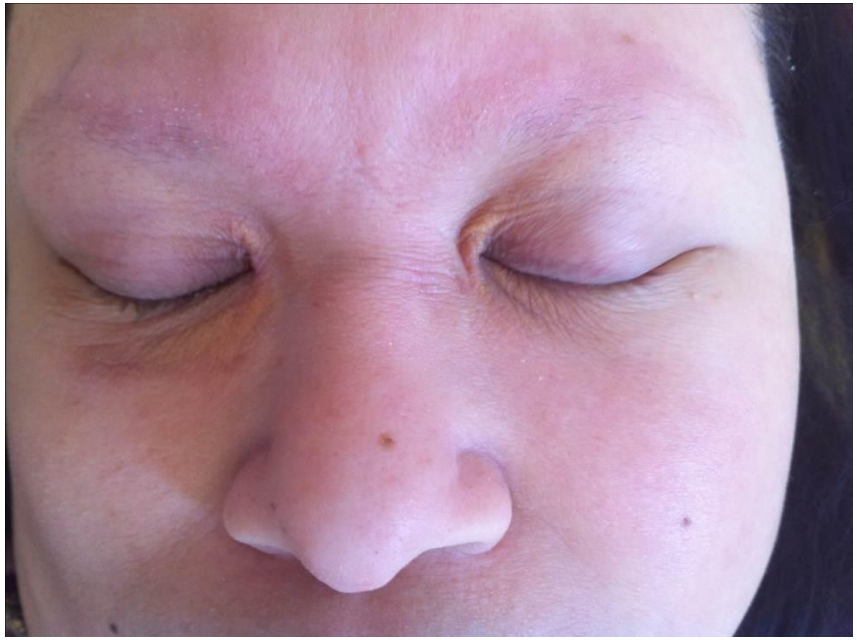
PET at M4 : total disappearance of suprasellar and lung hypermetabolism

Cohen-Aubart, Neurology 2014

Xanthelasma



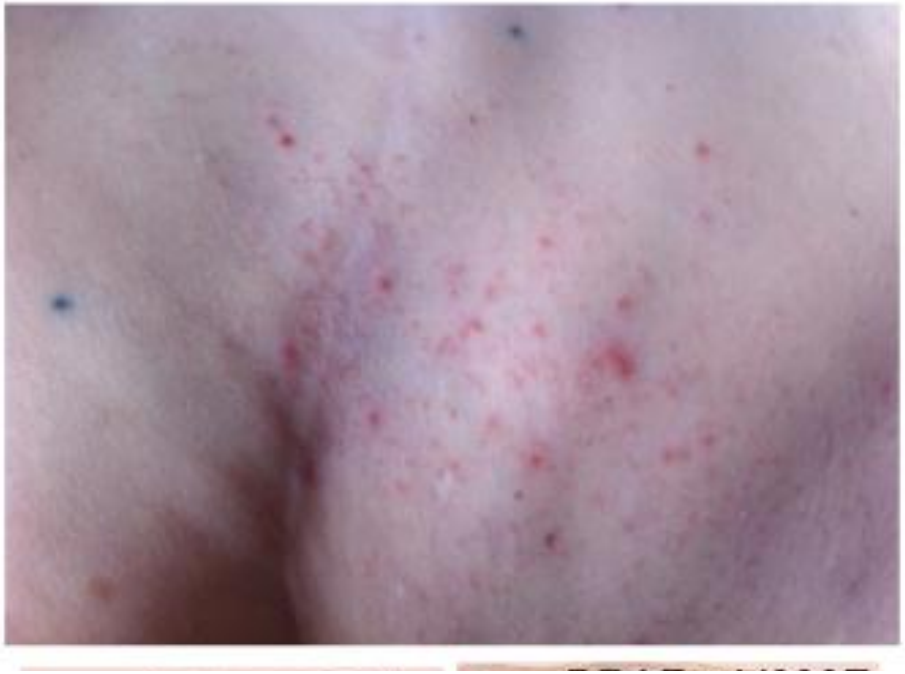
M0

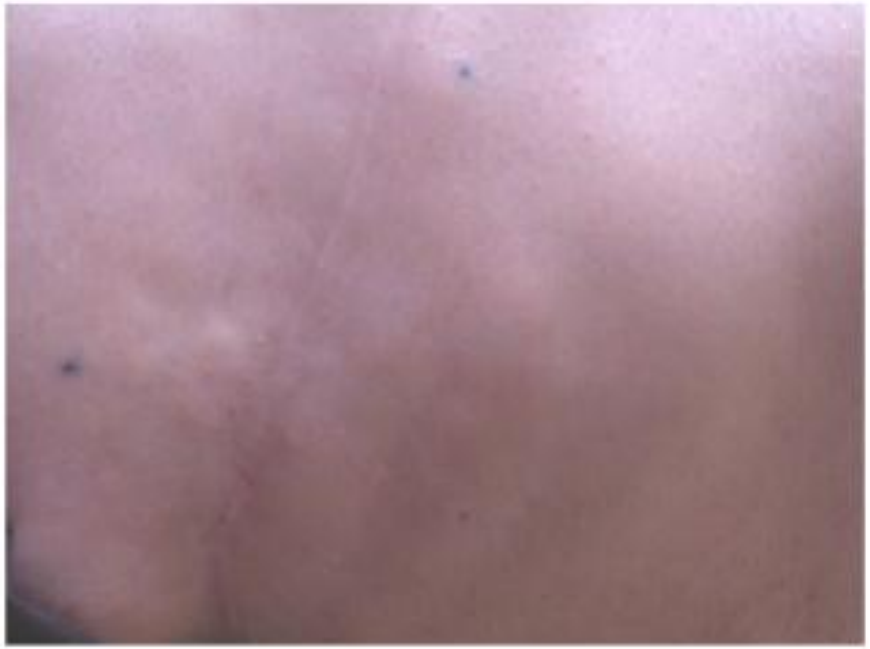


M12

Haroche J Clin Oncol 2015

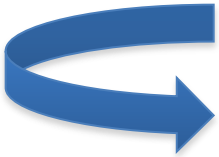
LCH skin





BRAF inhibition 2012-2018

- MSKCC: Basket Trial: 18 histiocytoses (mainly ECD) published in *NEJM* august 2015, close to 40 pts currently
- Italy: 10 pts treated by Augusto Vaglio (Parma)
- Italy: Lorenzo Dagna (Milano) : 10 - 15 pts
- Israel: 5 pts treated
- Germany at least 1 patient (ICU)
- Norway: 2 cases
- Sweden: at least one case with CNS
- EU group & Jean Donadieu LCH children **50** VMF
- Houston Group : 5 – 10 LCH children pts
- PITIE-SALPETRIERE : 90 patients (Mai 2018)



> 200 patients worldwide adults & children with ECD, ECD + LCH and

Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study)

Table 1. Clinical characteristics of treated patients

	Vemurafenib* (n = 50) or dabrafenib (n = 1)	Cobimetinib (n = 15)
Sex	15 females and 36 males	3 females and 12 males
Age at diagnosis, median (range), y	57 (17-72)	56 (34-71)
BRAF^{V600E}	49 (96)	10† (67)
BRAF WT	2† (4)	5 (33)
Mixed histiocytosis (ECD + LCH)	15 (29)	5 (33)
CNS	26 (51)	9 (60)
Cerebellar	15 (29)	7 (47)
Lung	18 (35)	6 (40)
Vascular	39 (76)	12 (80)
Heart	38 (75)	10 (67)
Xanthelasma	19 (37)	3 (20)
Diabetes insipidus	23 (45)	5 (33)
Retroperitoneal fibrosis	33 (65)	11 (73)
Bones	44 (86)	13 (87)
Previous treatments		
Anakinra	6 (12)	2 (13)
Interferon-α	36 (71)	11 (73)
Deaths	5 (10)	0
Targeted treatments‡		
Vemurafenib/dabrafenib, n	51	12
Cobimetinib, n	12	15

En Mai 2018: 90 pts histiocytose ont reçu une thérapie ciblée dans le service

Cohen-Aubart, *Blood* 2017

BRAF inhibitors = analysis of 51 treated patients until June 2016

PET evaluation of efficacy (M6 *or M3* if M6 was not available)

n= 48 (3 interruption before 3 months because of intolerance)

- 2 worsening (the 2 WT *BRAF* patients)
- 4 stable
- 35 partial metabolic remission
- 7 complete metabolic remission

Cohen-Aubart, *Blood* 2017

MEK inhibitors : 15 treated patients

3 patients prematurely stopped the treatment (*before efficacy evaluation*)

- 1 severe rhabdomyolysis (combo)
- 1 severe nausea/diarrhea (cobi alone)
- 1 severe allergic reaction (cobi alone)

Efficacy evaluation in 12 patients

- 8 under combotherapy : 5 PMR and 3 CMR

Cohen-Aubart, *Blood* 2017

- 4 under cobi alone : 2 PMR and 2

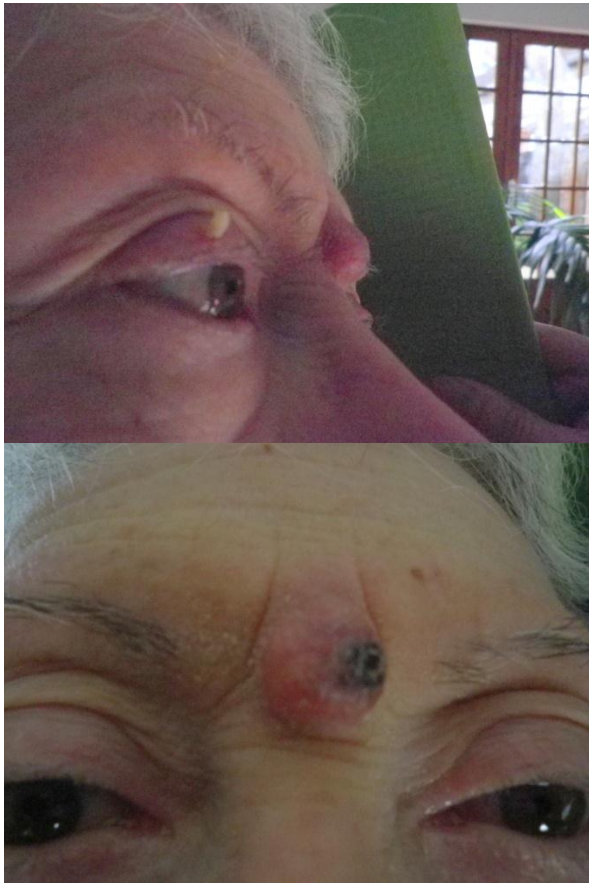
Table 2. Side effects of BRAF and MEK inhibitors

	Vemurafenib, n (%)	Cobimetinib, n (%)
Photosensibility, pilar keratosis	16 (32)	—
Acne rash	—	8 (53)
DRESS	2 (4)	
DRESS-like*	1 (2)	—
Cutaneous allergy	1 (2)	1 (7)
Spinocellular carcinoma	4 (8)	—
Basocellular carcinoma	3 (6)	—
Melanoma	1 (5)	—
Actinic keratosis	2 (4)	—
Bowen disease	1 (2)	—
Multiple nevi	3 (6)	—
Eyelid keratoacanthoma	1 (2)	—
Nausea, vomiting	1 (2)	4 (27)
Arthralgia	7 (14)	
Renal vasculitis	1 (2)	—
Tuberculosis	1 (2)	—
Deep vein thrombosis	1 (2)	—
Neutropenia	1 (2)	—
Scotoma and syncope	1 (2), combination therapy; ophthalmic examination was normal, and electrocardiogram and electrophysiological studies were also normal	
QT prolongation, torsade de pointes and cardiac arrest	1, treatment was resumed after ICD implantation (2)	—
Gastric cancer	1 (no RAF or RAS mutation) (2)	—
Cardiac failure	1 case, reversible when the dose was tapered (2)	—
Hypertriglyceridemia	1 (2)	—
Depressive episode	1 (2)	—
Rhabdomyolysis	—	4 (27)
Sarcoidosis-like disease	3 (6)	—

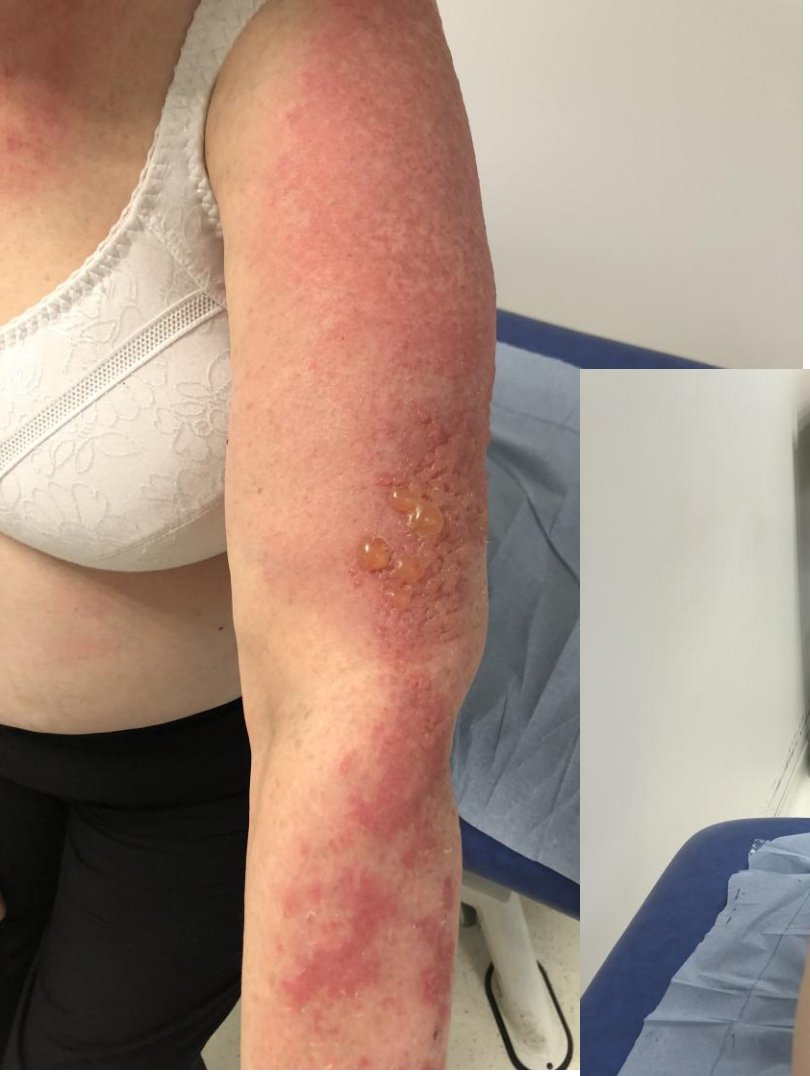
Et depuis 2016: + 3 mélanomes; un adéno K pancréatique muté KRAS; 2 pancréatites; 2 SMD

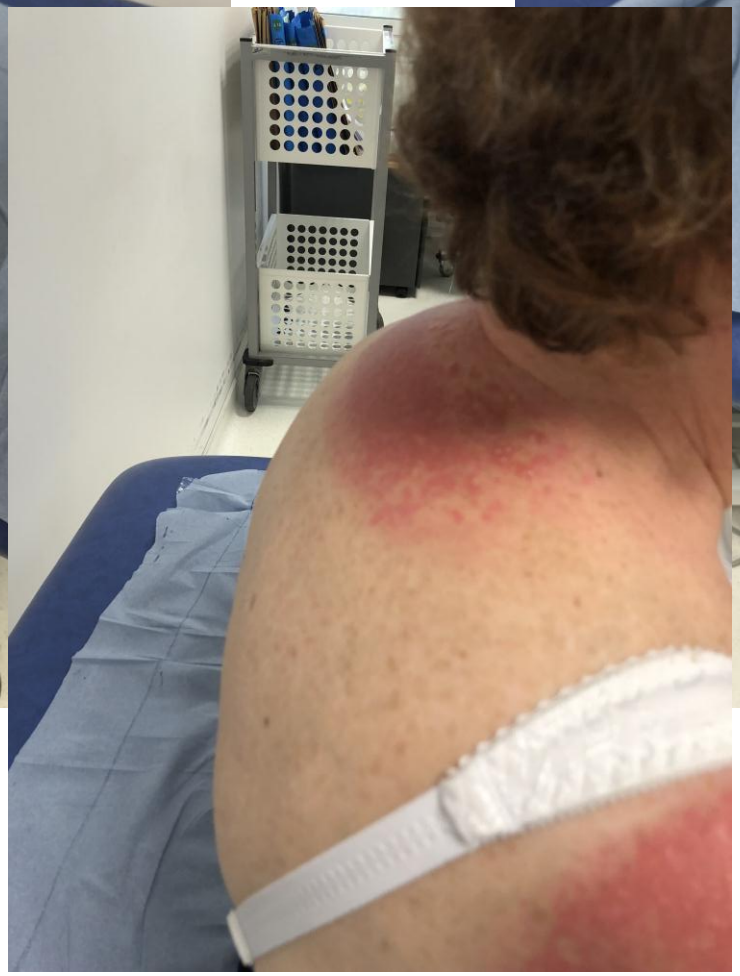
Cohen-Aubart, *Blood* 2017

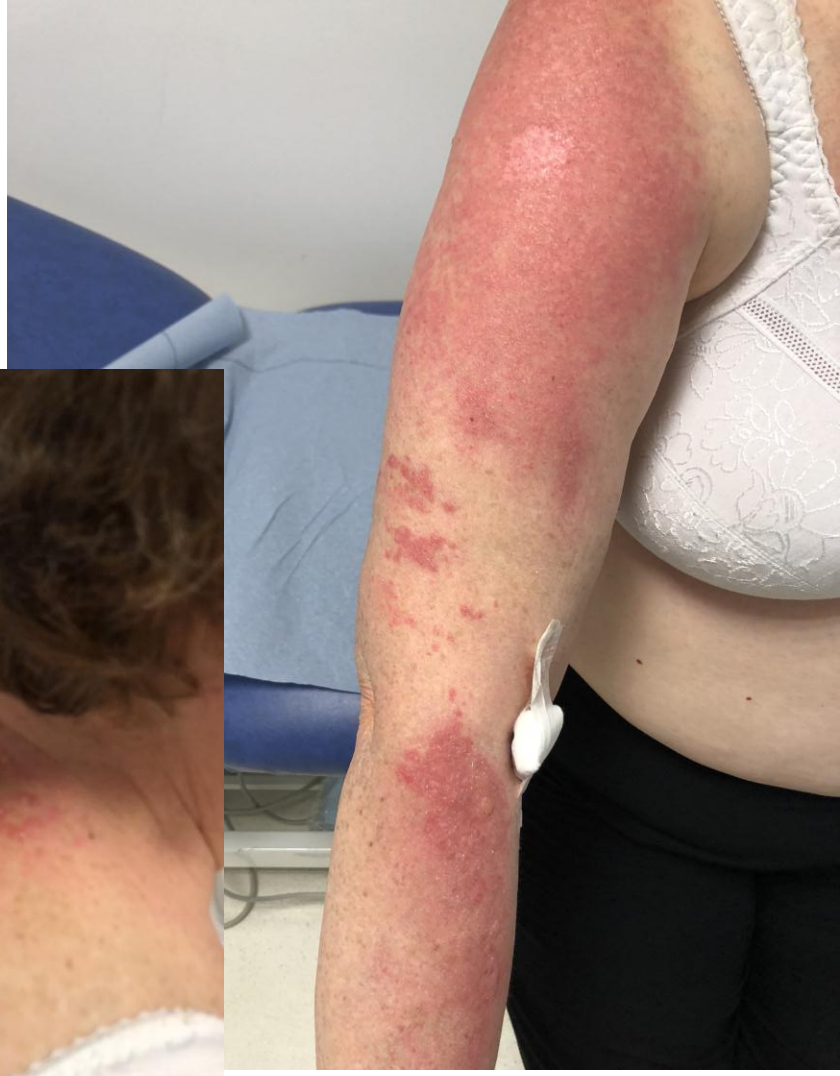
Infiltrant squamous cell carcinoma requiring surgery and radiotherapy (treatment discontinuation)



J Clin Oncol 2015





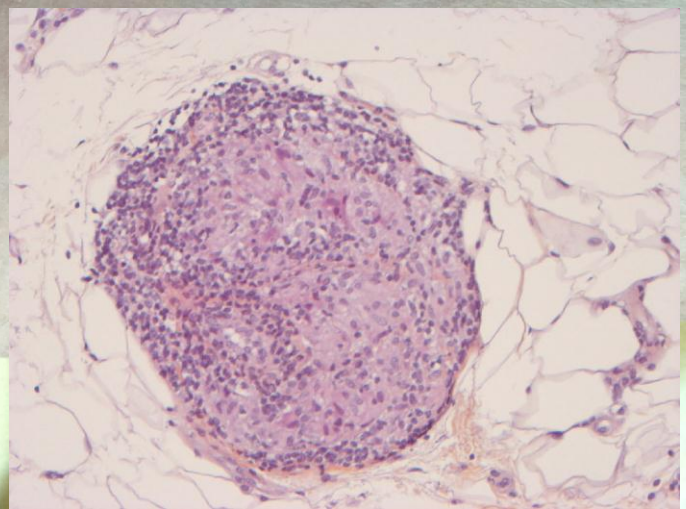


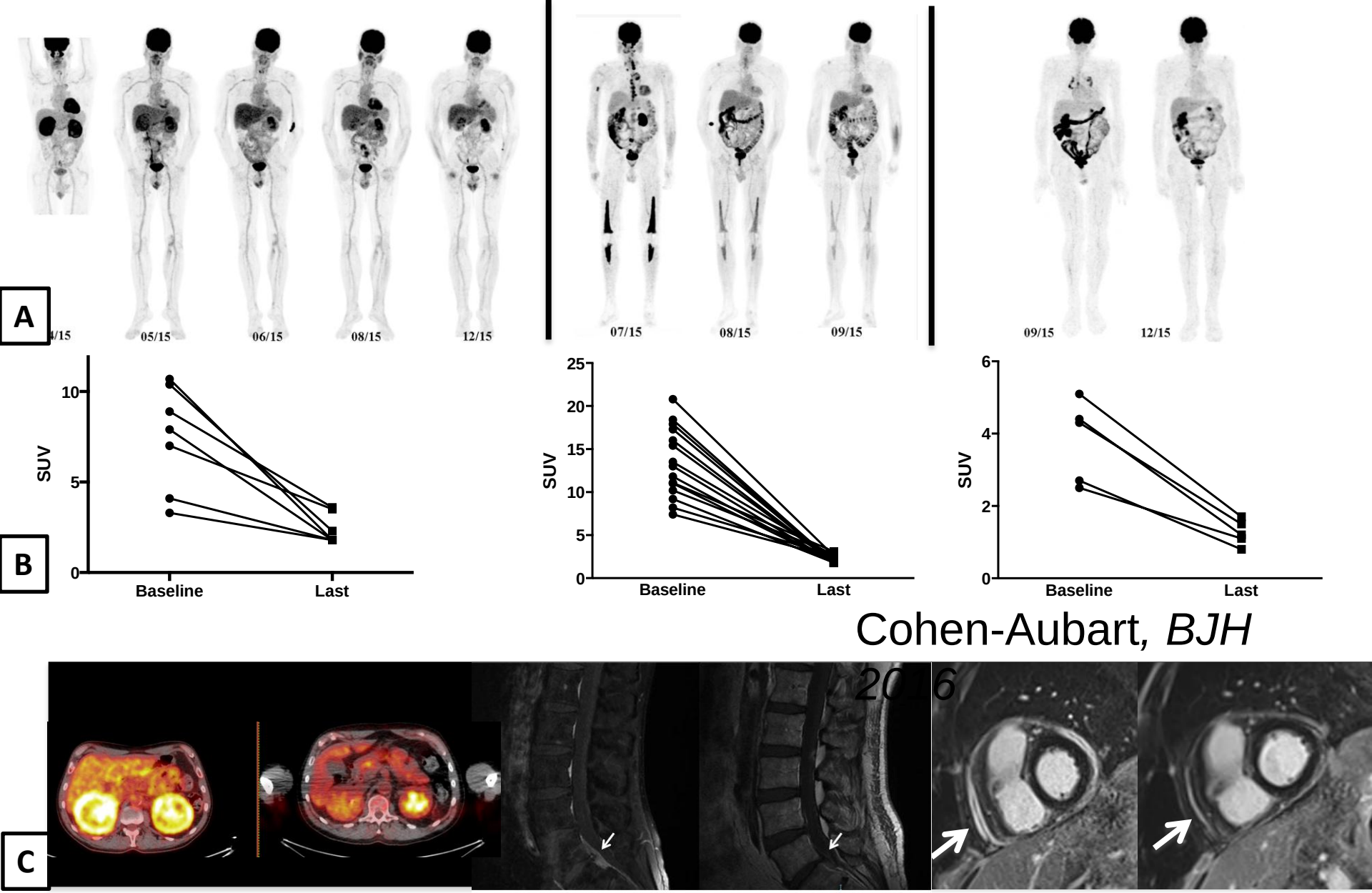
6/6/2018

Erdheim-Chester + HL J1-C18 VEMURAFENIB

AcSé VEMU

Sarcoidosis under vemurafenib

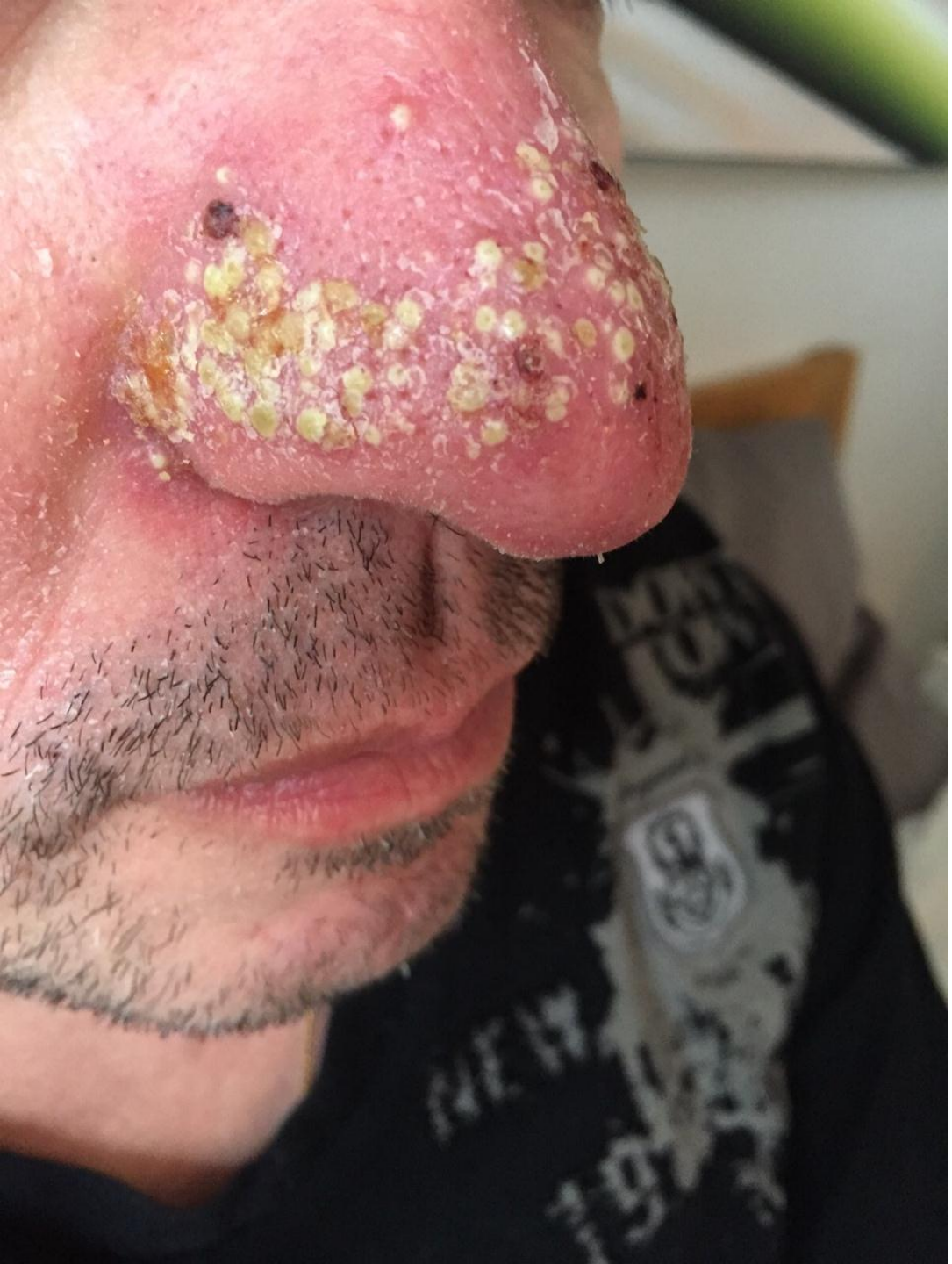




Cohen-Aubart, *BJH* 2016

Patient 1 Patient 2 Patient 3

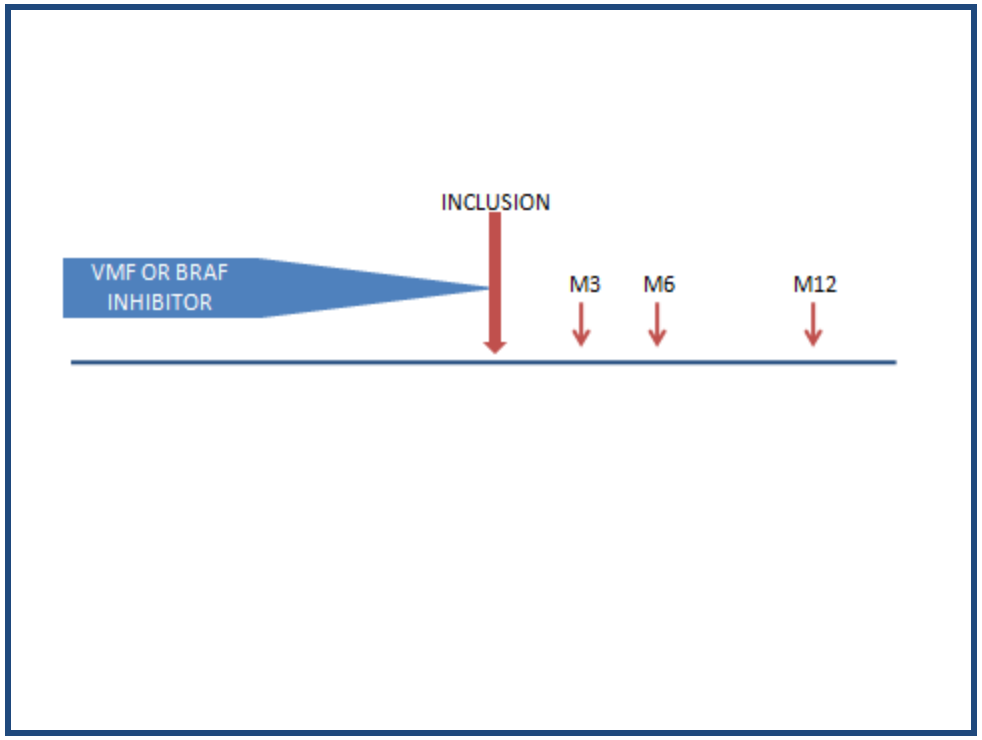
MEK inhibition (MSKCC & Paris) after 2015



Severe acneic rash under cobimetinib

LOVE STUDY

*A multi-center study of the **L**ong-term **O**utcome after **V**emurafenib / BRAF inhibitors interruption in **E**rdheim-chester disease*

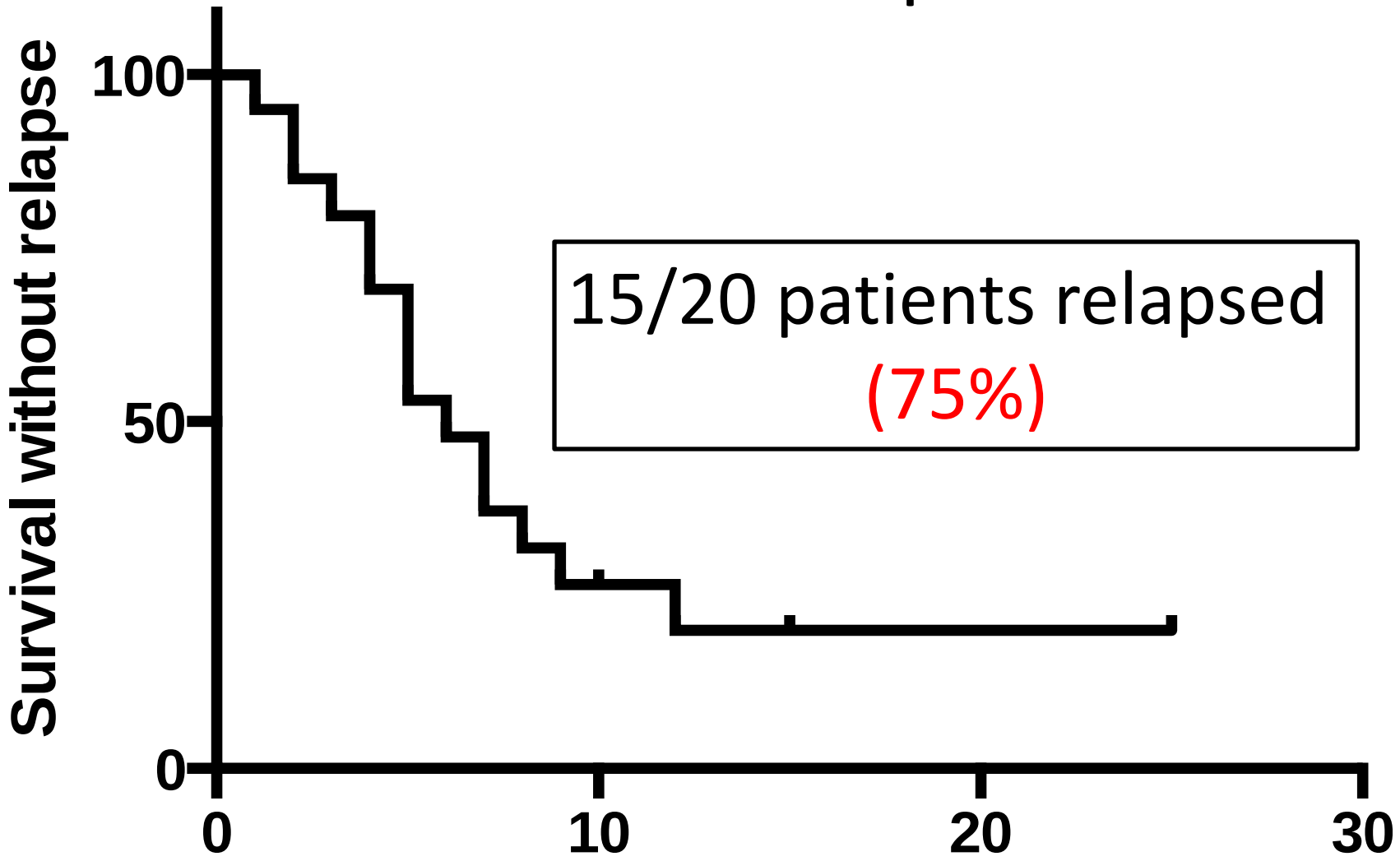


To evaluate the outcome after vemurafenib or other BRAF inhibitors interruption in ECD with 18 FDG PET scanner

NCT02089724

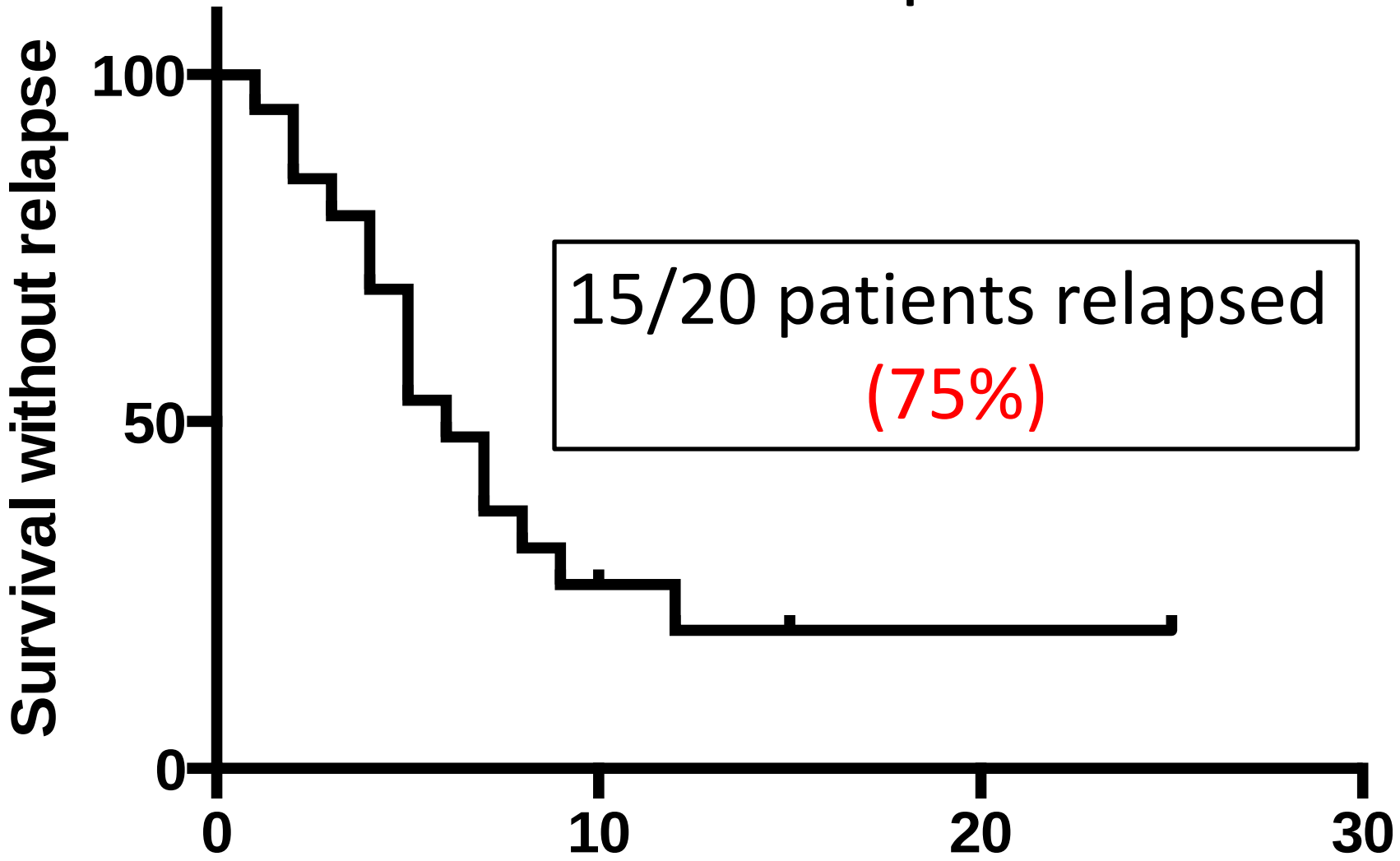
This study is a phase 2, non-randomized open label trial. Patients will be included after having received at least 6 months of induction therapy (either vemurafenib at least 480 mg / day, or other BRAF inhibitor)

The *LOVE* study : relapses after treatment interruption



Cohen-Aubart, *Blood* 2017

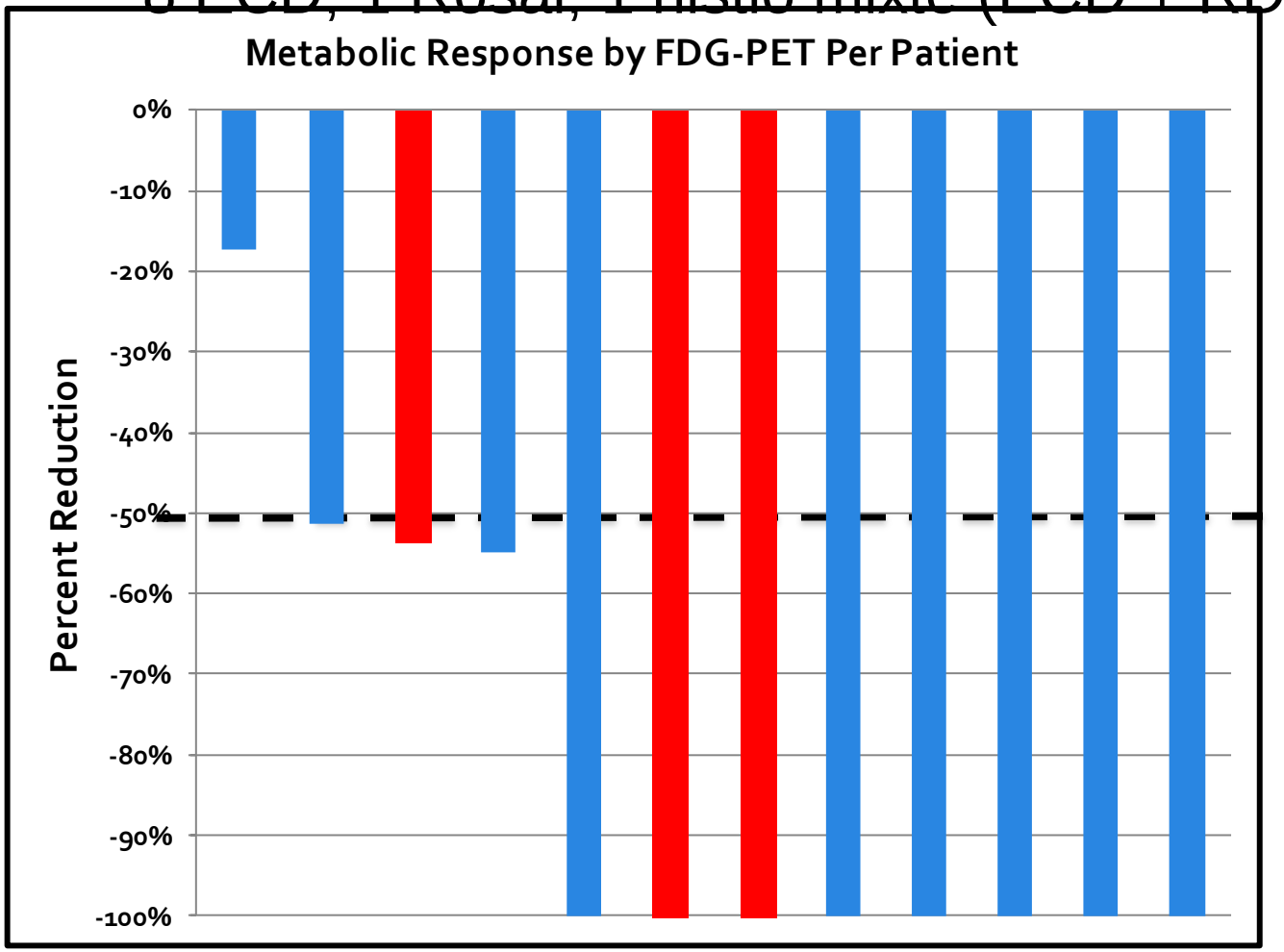
The *LOVE* study : relapses after treatment interruption



Cohen-Aubart, *Blood* 2017

Résultats *interim* de l'essai COBI/12 patients (E Diamond, MSKCC)

8 ECD, 1 Rosai, 1 histio mixte (ECD + RDD), 1 LCH



***BRAF*V600E**

***BRAF*-V600 WT**

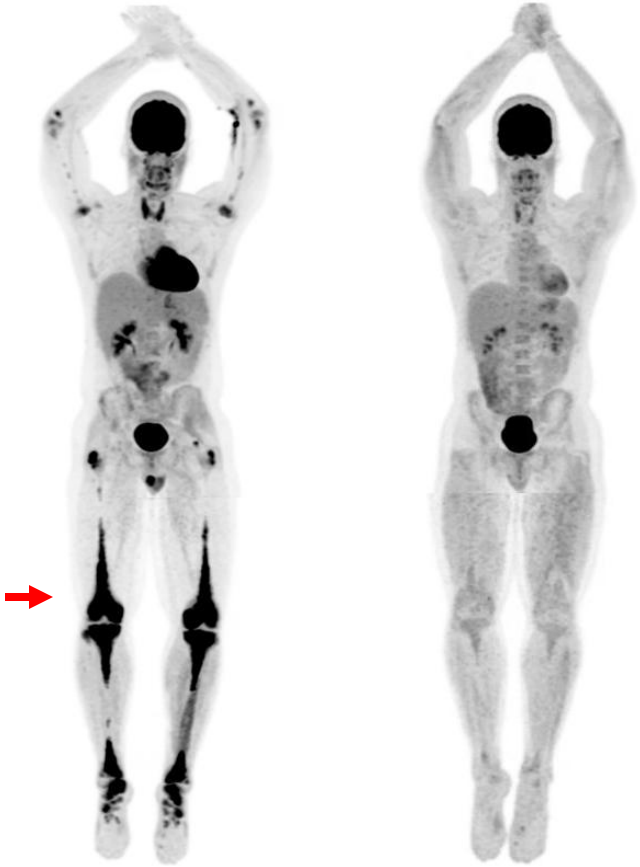
- **8 Complete Response**
- **3 Partial Response**
- **1 Stable Disease**

Partial Metabolic Response

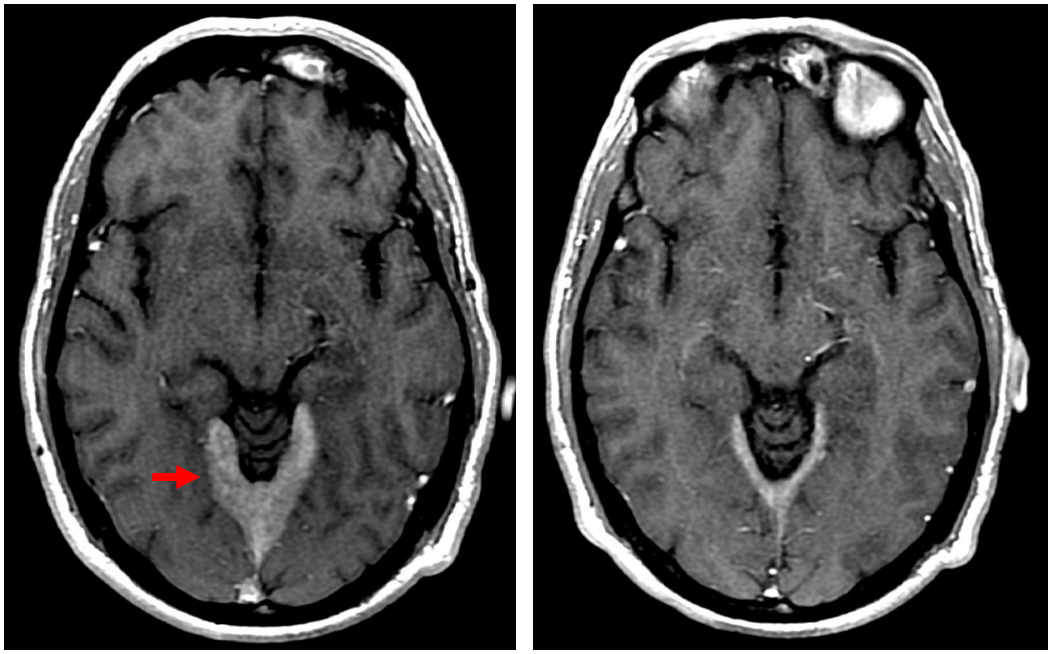
- **Response Rate: 92%**
- **Clinical Benefit: 100%**

Primary Endpoint: Metabolic Responses

CNS/cardiac/bone+ ECD (*BRAF*V600E)



Baseline **Cobimetinib**

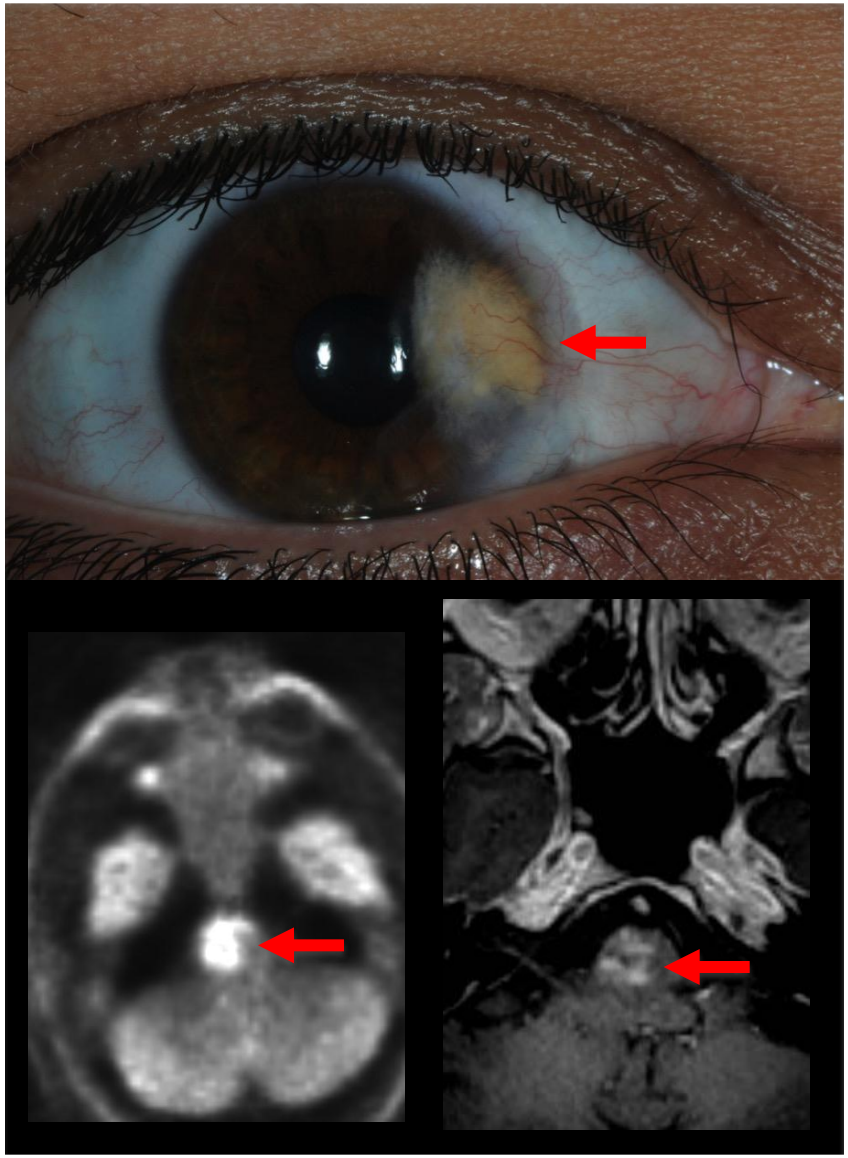


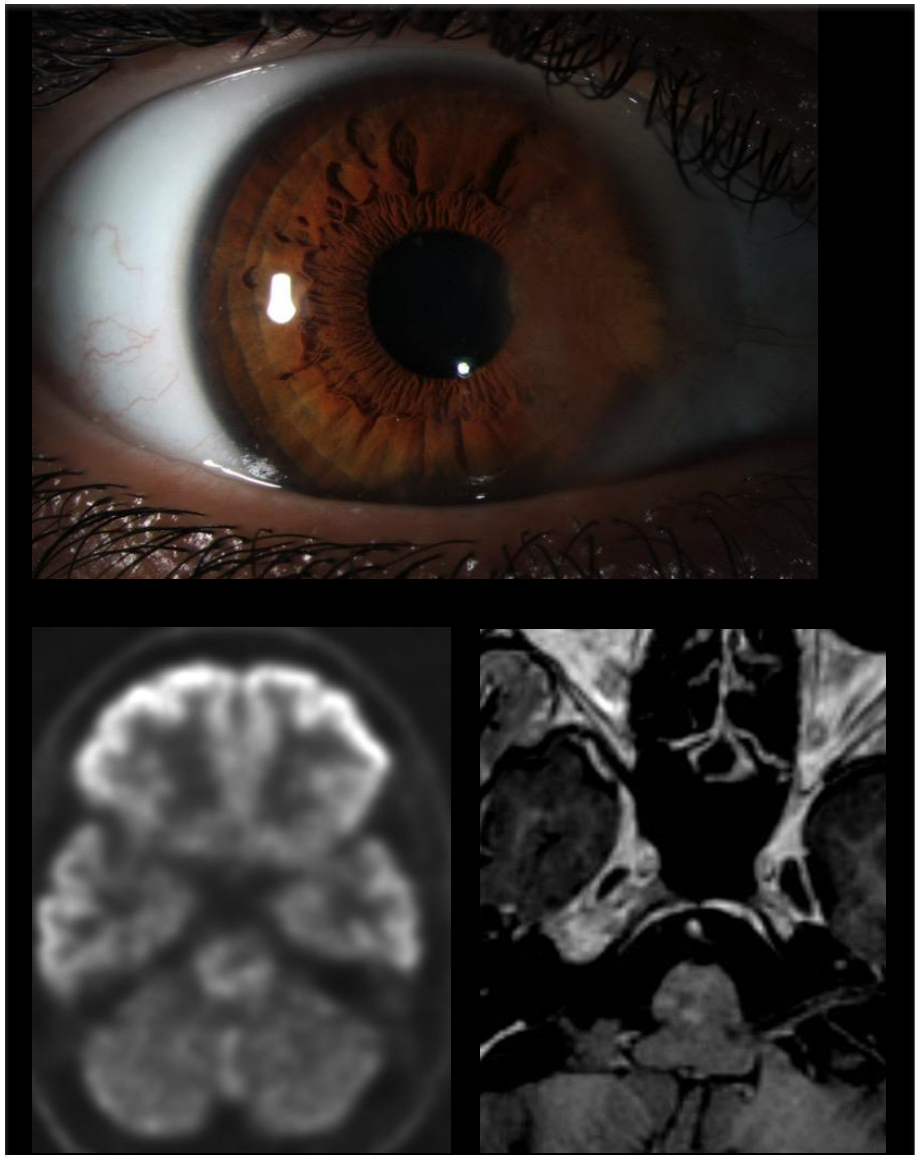
Baseline **Cobimetinib**

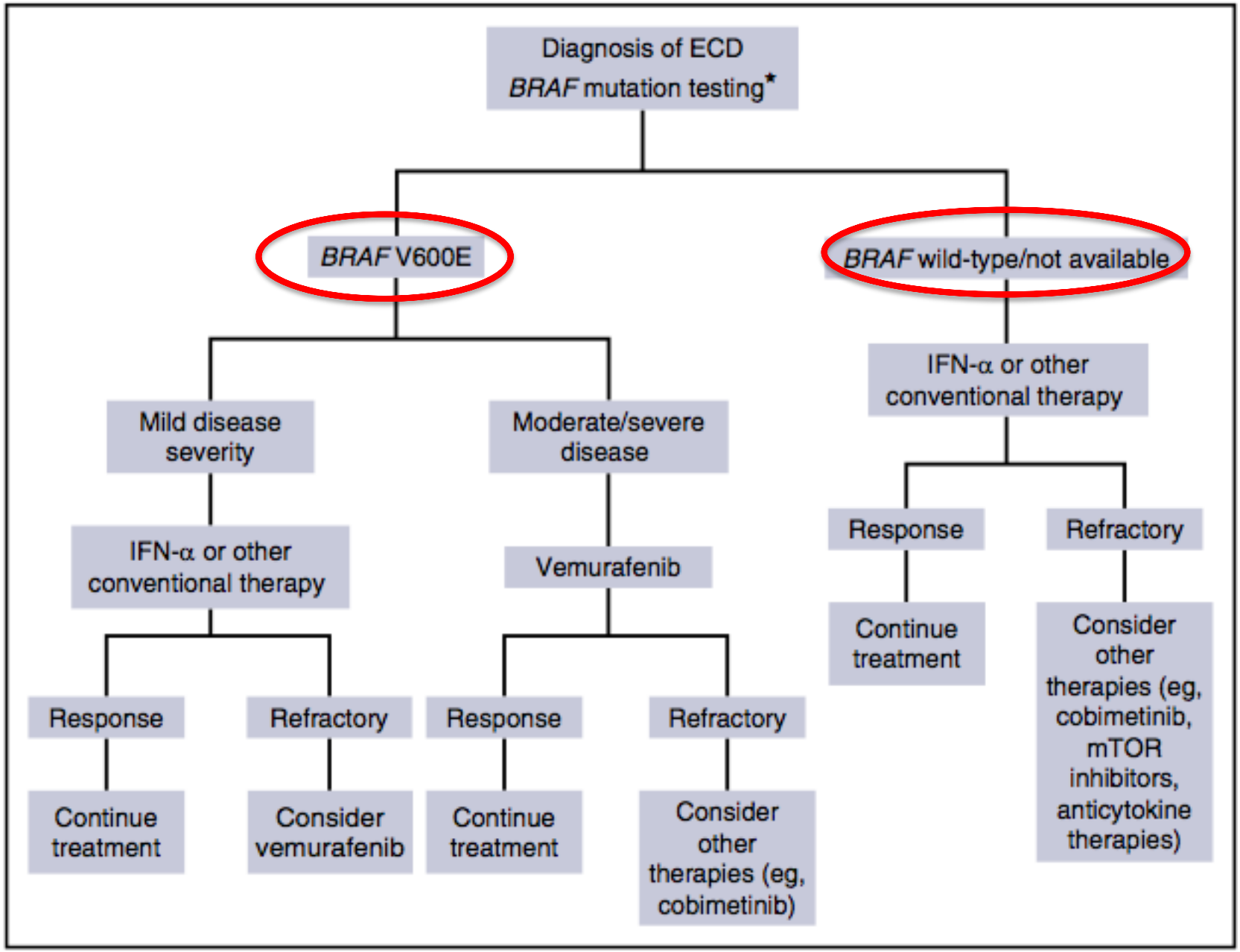
Brainstem-ocular RDD (mutation unknown)

Baseline

Cobimetinib

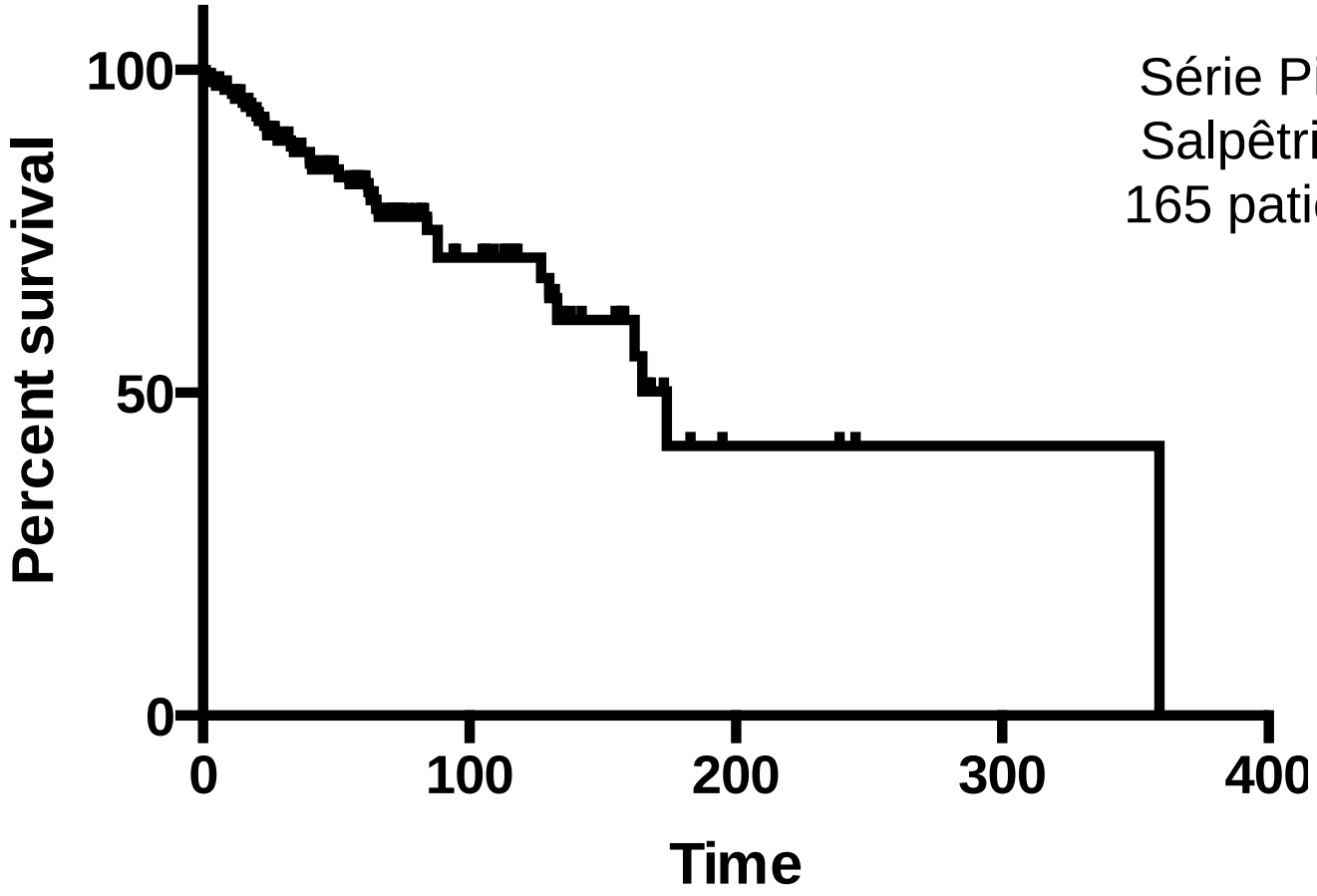






Vaglio & Diamond, *Blood* 2017

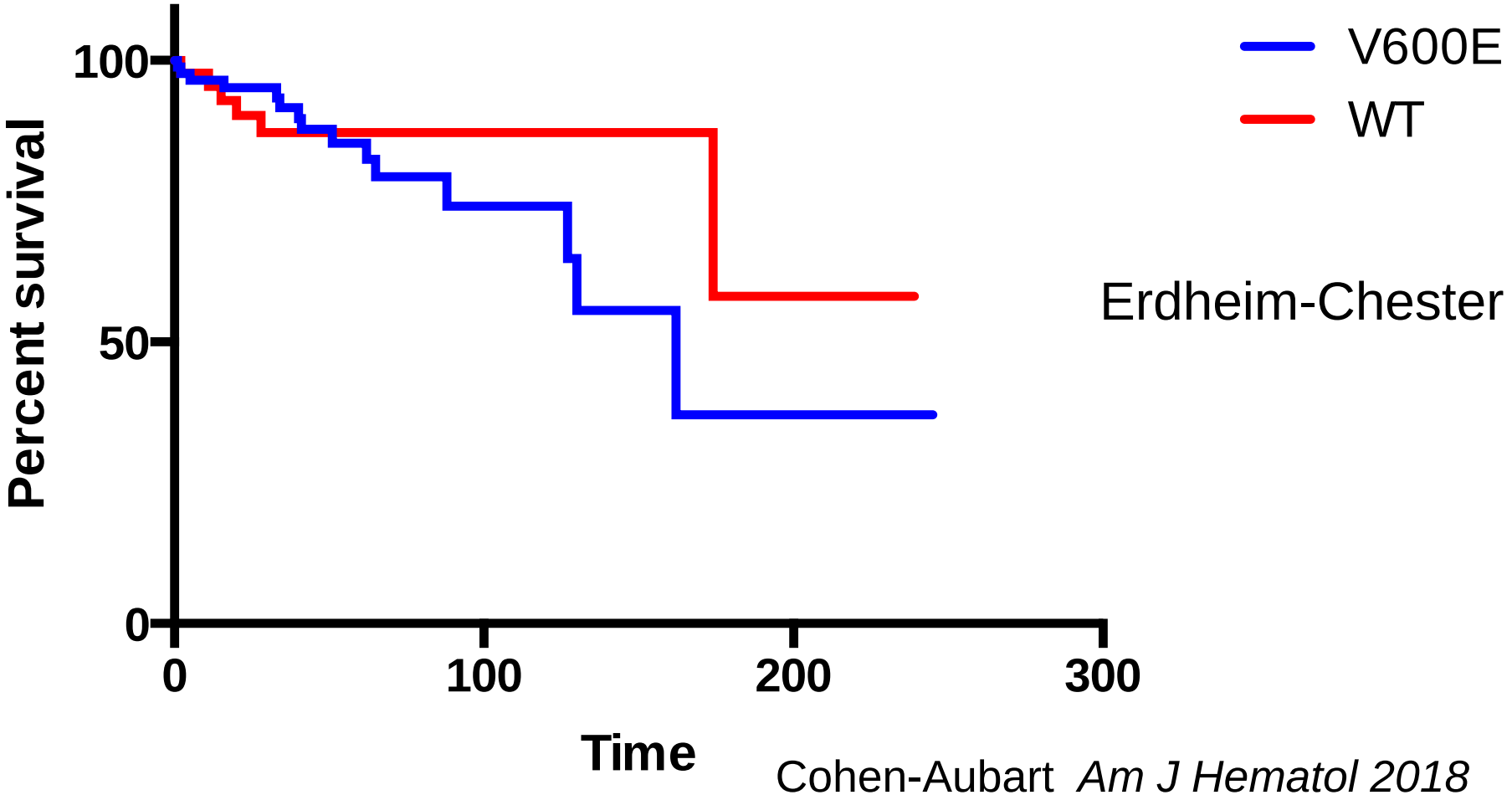
Global survival (median : 162 months)



In 2016 prognosis of ECD is better than in « older series »
published in 1996 & 2004 ≈ 60% death at 3 yrs

Cohen-Aubart *Am J Hematol 2018*

No difference of survival V600E / WT (p = 0.32)



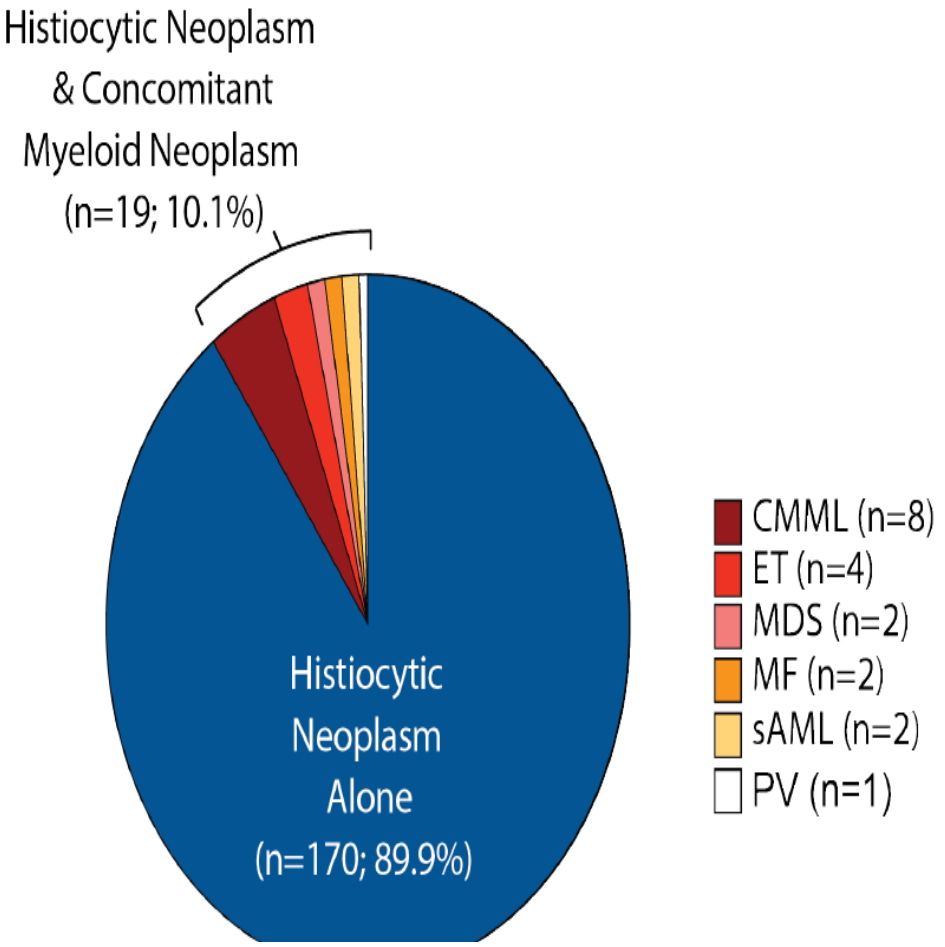
Cohen-Aubart *Am J Hematol 2018*

Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the *BRAF*^{V600E} mutation

Baptiste Hervier,[1-3] Julien Haroche,[1-3] Laurent Arnaud,[1-3] Frédéric Charlotte,[2,4] Jean Donadieu,[5] Antoine Néel,[6] François Lifermann,[7] Carles Villabona,[8] Bruno Graffin,[9] Olivier Hermine,[10] Aude Rigolet,[1,2] Camille Roubille,[11] Eric Hachulla,[12] Thierry Carmoi,[13] Maud Bézier,[14] Véronique Meignin,[14] Marie Conrad,[15] Laurence Marie,[16] Elise Kostrzewa,[17] Jean-Marie Michot,[18] Stéphane Barete,[19] Valerie Taly,[20] Karine Cury,[19] Jean-François Emile,[21,22] and Zahir Amoura,[1-3] on behalf of the French Histiocytoses Study Group

BLOOD, 14 AUGUST 2014 • VOLUME 124, NUMBER 7

23 LCH + ECD



Diagnosis

7 before (4 years [1-22])

6 simultaneously

6 after (1 year [1-4])

Papo, *Blood*

High prevalence of myeloid neoplasms in adults with non–Langerhans cell histiocytosis

Patient	Histiocytosis	Sex	Age	Mutationnal status histiocytosis	Haematological disease	Mutationnal status MPN/MDS
#1	ECD, LCH, RDD	M	64	*BRAF* WT	MPN (MF)	*JAK2* p.V617F
#2	ECD	M	60	*BRAF*V600E	MPN (ET)	*CALR*
#3	ECD, LCH	M	56	*BRAF*V600E	MPN (ET)	*JAK2* p.V617F *TET2* X95X
#4	ECD	M	73	*BRAF* WT	CMML	*JAK2* p.V617F NRAS G12S *TET2* L7[illegible]X5[illegible] *U2AF*
#5	ECD	M	68	*BRAF*V600E	MPN (PV), AML	*JAK2* p.V617F
IFN	ECD	M	73	*BRAF* WT	MPN (MF)	*CALR*
#7	ECD	M	71	*BRAF*V600E	CMML	*ASXL1* Q592X
#8	ECD, RDD	M	71	*BRAF* WT	CMML	-
#9	ECD	M	63	*BRAF*V600E	MPN (ET)	*JAK2* p.V617F
#10	ECD, LCH	M	51	*BRAF* WT	MDS	-
#11	ECD, LCH	F	83	*BRAF*V600E	MDS	-
#12	ECD	M	52	*MAP2K1* p.K57N	MPN (ET)	*JAK2* p.V617F
#13	ECD	M	66	*NRAS* p.Q61R	CMML	*NRAS* p.Q61R
#14	ECD	M	73	*BRAF*V600E	CMML	*JAK2* p.V617F *IDH2* R140Q
#15	ECD	F	64	*BRAF*V600E	CMML	*NRAS* p.G12D *ASXL1* 1Q733X
#16	ECD	M	75	*BRAF*V600E	CMML	
#17	ECD	M	55	*BRAF*V600E	MDS	-
#18	ECD	M	78	*BRAF*V600E	CMML	*ASXL1* 1A733X *TET2* Q904X *TET2* Q321X *TET2* N1387S
#19	ECD, LCH	M	70	*BRAF*V600E	AML	*IDH2*R140Q *TP53*N131K

JAK2 V617F 36,8%

BRAF V600E 63,2%

MH 31,5 %

MAP2K1

NRAS

CALR

NRAS

TP53

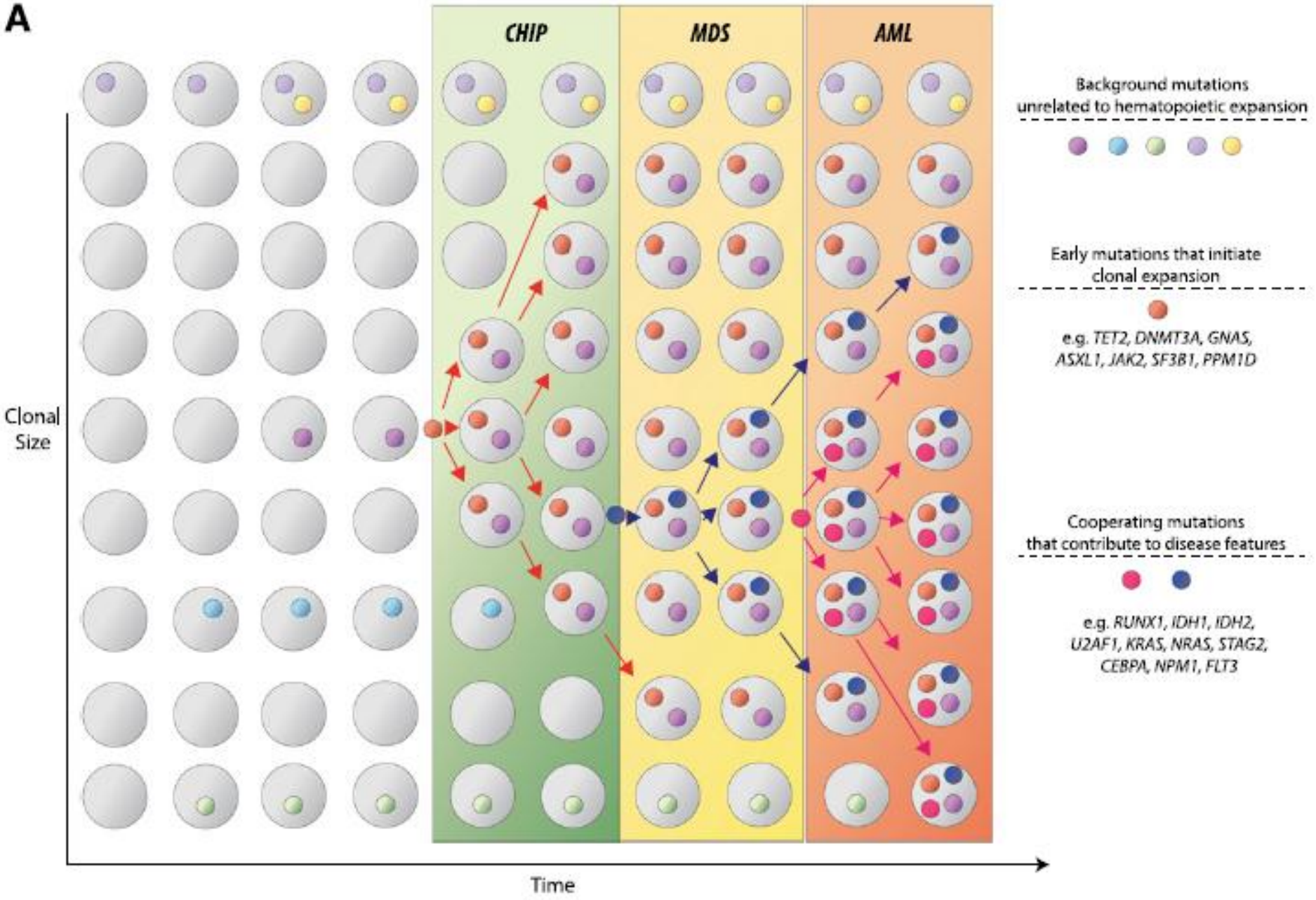
ASXL1

TET2

NRAS p.Q61R

U2AF1

IDH2


A
CHIP
MDS
AML
Clonal Size
Time
Background mutations unrelated to hematopoietic expansion
Early mutations that initiate clonal expansion
e.g. TET2, DNMT3A, GNAS, ASXL1, JAK2, SF3B1, PPM1D
Cooperating mutations that contribute to disease features
e.g. RUNX1, IDH1, IDH2, U2AF1, KRAS, NRAS, STAG2, CEBPA, NPM1, FLT3

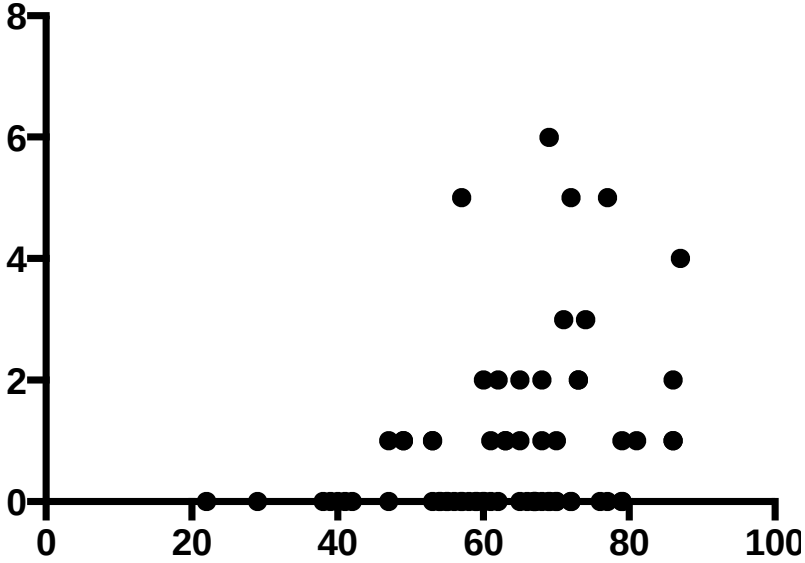
Hématopoïèse clonale de signification indéterminée (CHIP)

Depuis fin 2016 analyse 121 myélogrammes / Erdheim-Chester et formes mixtes
+ 31 myélogrammes de suivi sous thérapies ciblées

Analyse en NGS d'un panel de 36 gènes myéloïde + caryotype

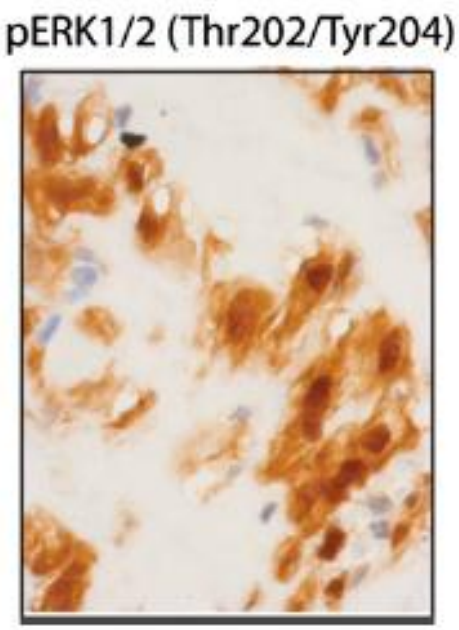
Gènes les plus fréquemment mutés : *TET2*, *ASXL1*, *DNMT3A* et *NRAS*

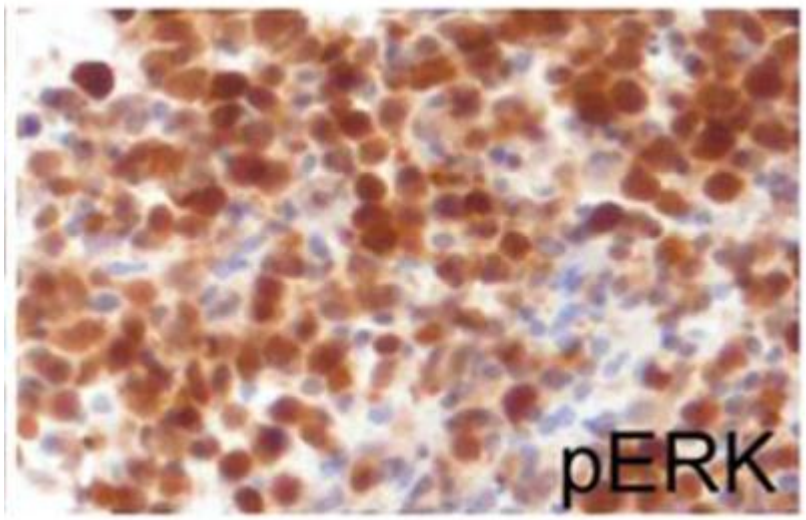
Hématopoïèse clonale augmentée de 40% par rapport à une

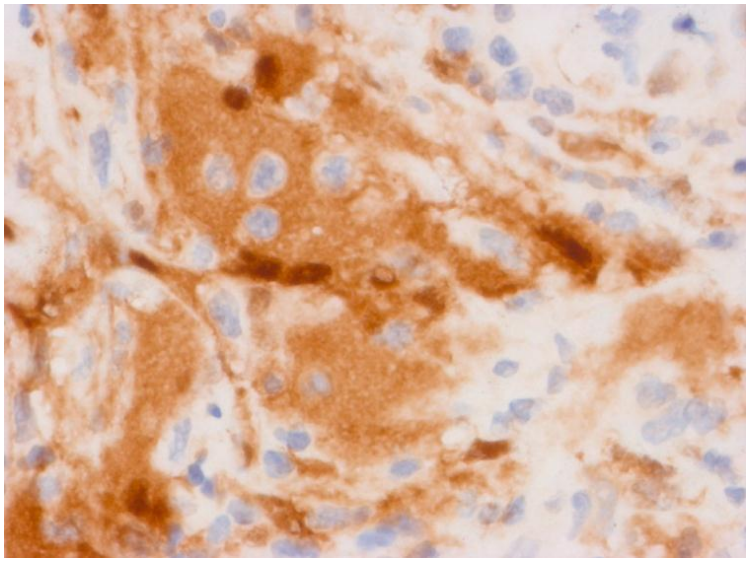


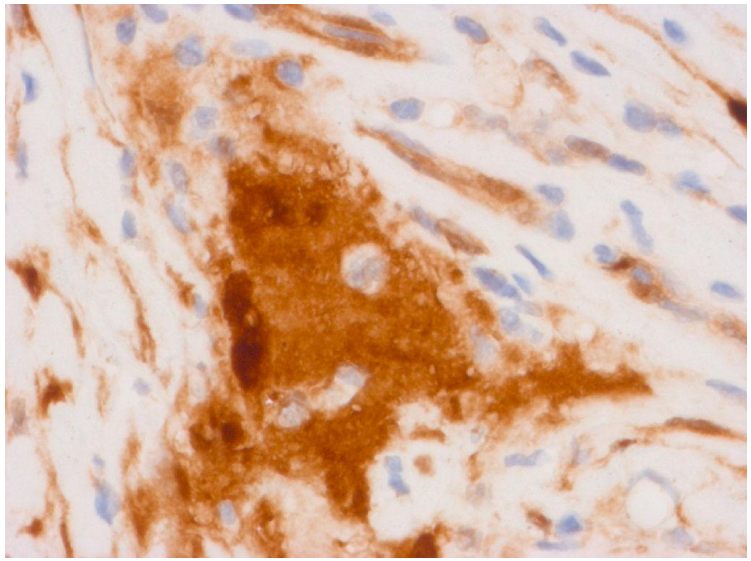
ASH 2017, SFH 2018

Au bout du bout









Media Release

Basel, 07 November 2017

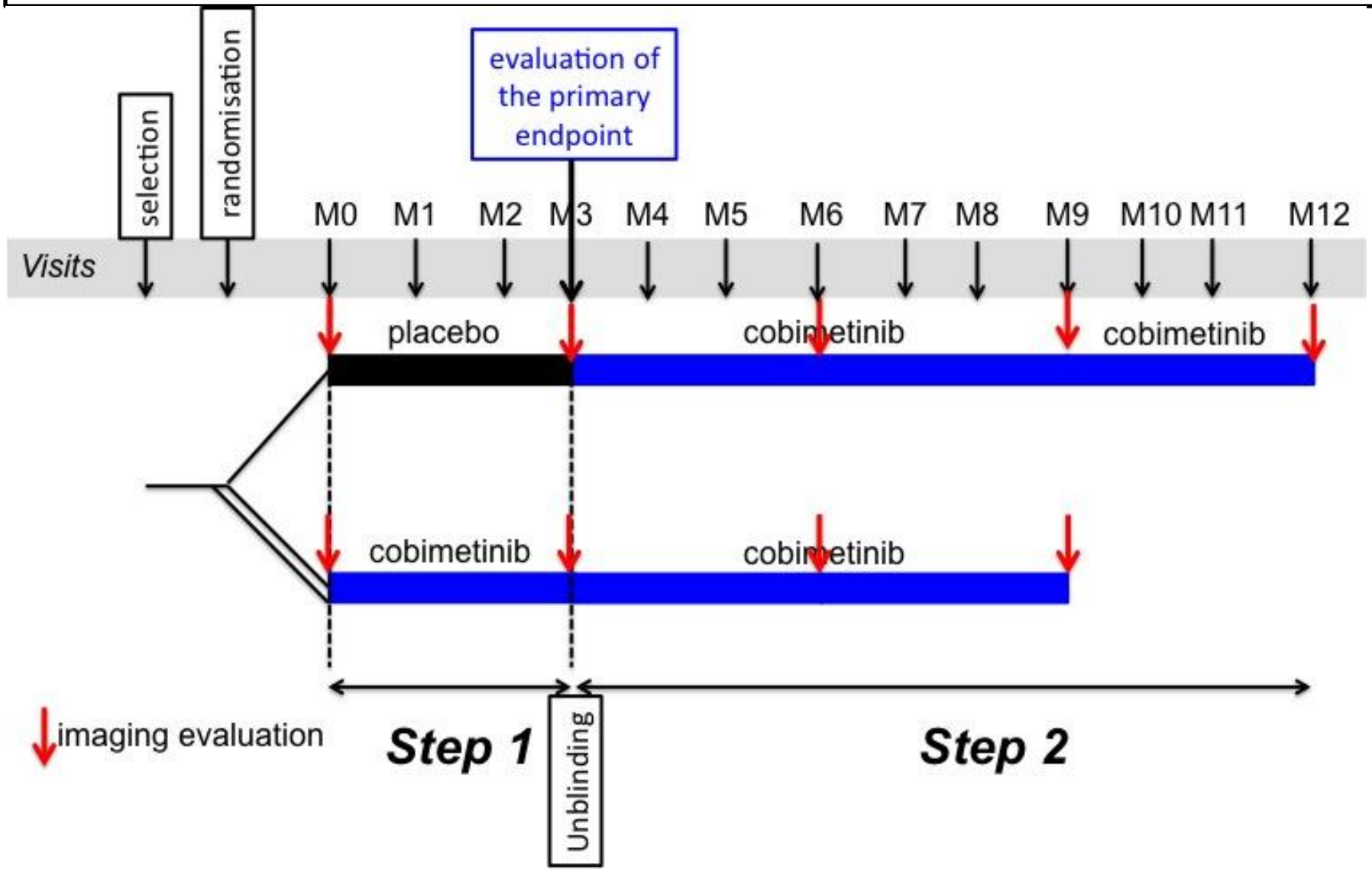
FDA approves Zelboraf (vemurafenib) for Erdheim-Chester disease with BRAF V600 mutation

- **Zelboraf is the first FDA-approved treatment for Erdheim-Chester disease (ECD), a rare blood disease**
- **Approval based on data from a basket study, which enrolls participants across multiple diseases based predominantly on genetic profile**

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that the US Food and Drug Administration (FDA) has approved Zelboraf® (vemurafenib) for Erdheim-Chester disease (ECD) with BRAF V600 mutation. ECD is a rare, serious blood disease characterized by the abnormal multiplication of certain white blood cells called histiocytes, which can invade normal tissues and organs in the body.[1]

The approval is based on data from the Phase II VE-BASKET study. Basket studies use an innovative clinical trial design that helps collect data faster and may accelerate the development of medicines for diseases with high unmet need. Instead of enrolling people based primarily on their disease or its location, basket studies match a disease's underlying genetic profile to the mechanism of action of the medicine.

" Cobimetinib for *BRAF*-wild-type histiocytoses : a randomized, placebo-controlled, double blind study"
PHRC National 2017 Etude COBRAH



Patient (1950) : LCH + RDD + ECD

Dyspnea,
Pl Effusion

↓

RDD

Skin lesions

↓

LCH

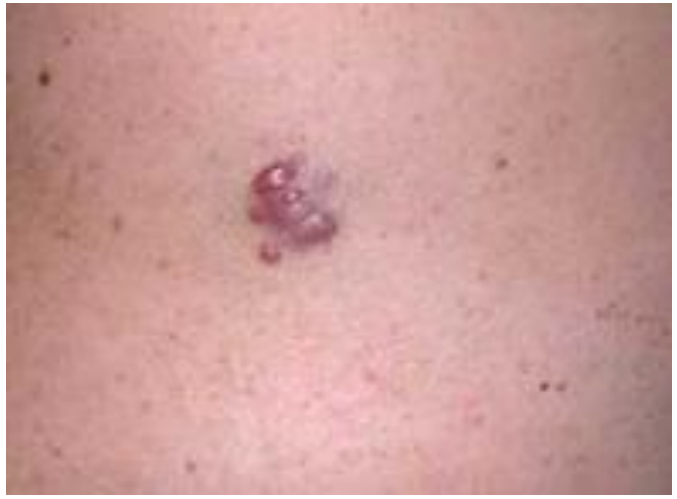
Pericardial thickening
Aortitis
Retroperitoneal fibrosis

ECD

12/08

pleurodesis

08/09



Histiocytoses: emerging neoplasia behind inflammation

Julien Haroche, Fleur Cohen-Aubart, Barret J Rollins, Jean Donadieu, Frédéric Charlotte, Ahmed Idbaih, Augusto Vaglio, Omar Abdel-Wahab, Jean-François Emile, Zahir Amoura

Histiocytoses are disorders characterised by inflammation and the accumulation of cells derived from the monocyte and macrophage lineages, which results in tissue damage. Although they are often considered rare disorders with protean clinical manifestations, considerable advances in the understanding of their genetics have led to increased clinical recognition of these conditions, and fuelled further insights into their pathogenesis. In this Review, we describe insights into the cells of origin, molecular pathology, the most common histiocytic disorders, including Langerhan Dorfman disease. With the discovery of recurrent mutatio mTOR–AKT pathways in some of these histiocytoses, our un concept of a primary inflammatory condition to that of a clon development of effective mechanism-based therapeutic strate

Introduction

Chester, Christian, Destombes, Dorfman, Erdheim, Hand, Hashimoto, Langerhans, Letterer, Nezelof, Pritzker, Rosai, Schüller, Siwe... This list of doctors—whose names are often used in eponyms for the numerous histiocytic disorders—reflects 150 years of research on a group of orphan diseases. For decades, these diseases were mainly classified as Langerhans cell and non-Langerhans cell histiocytoses. In 2010, a major breakthrough came with the discovery of recurrent *BRAF* mutations in Langerhans cell histiocytosis,[1] which were later also found in Erdheim-Chester disease.[2] This finding paved the way for a revised classification of histiocytic disorders,[3] which incorporates their histology, phenotype, and molecular alterations, as well as clinical and imaging characteristics. Histiocytoses are now categorised into five groups with an emphasis on targetable mutations of the mitogen-activated protein kinase (MAPK) pathway. As many subtypes of histiocytoses have already been described[3] with a wide range of clinical manifestations and histologies, we specifically focus on key aspects and new findings relating to the most frequent histiocytic disorders in this Review.

Review

Conclusions (I)

- HL et MEC souvent associées, groupe L de la nouvelle classification = néoplasie myéloïde inflammatoire
- Réserver les thérapies ciblées aux formes graves: Cœur et ou SNC chez l'adulte
- Ne pas traiter une atteinte cutanée isolée: discuter en RCP
- Effets secondaires fréquents et parfois graves
- *BRAF*^{V600E} n'a pas d'influence sur la survie des patients avec une MEC (≠ HL pédiatrique)
- Interferon-alpha et les thérapies ciblées (BRAF et/ou MEKi) améliorent la survie dans la MEC.
- Vemurafenib / FDA approval pour MEC le 6 Nov 2017 (en Europe ODD pour MEC depuis 2016), *en moins de 5 ans*

Conclusions (II)

- LOVE Study : 75% Erdheim-Chester et formes mixtes rechutent

Cohen-Aubart, *Blood* 2017

- Pas de résistance aux inhibiteurs de BRAF dans la MEC ou formes mixtes après plus de 5 ans, pas de résistance aux inhibiteurs de MEK même si recul seulement de 2 ans
- Effet suspensif: ne guérit pas les patients; rechute à l'arrêt
- Quelle est la place des COMBOTHERAPIES dans la MEC et histiocytoses mixtes ?
- PHRC COBIMETINB vs Placebo dans histiocytoses BRAF WT (Fleur Cohen-Aubart)

Merci

Fleur Cohen-Aubart
Zahir Amoura
Tous les internes

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Les patients
Kathy Brewer and the ECD global alliance
Histiocyte Society