Centre de Référence
des Syndromes hyperéosinophiliques

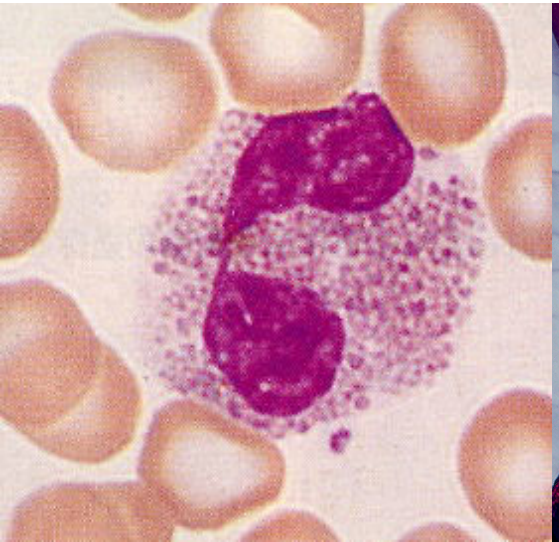
HOPITAL FOCH

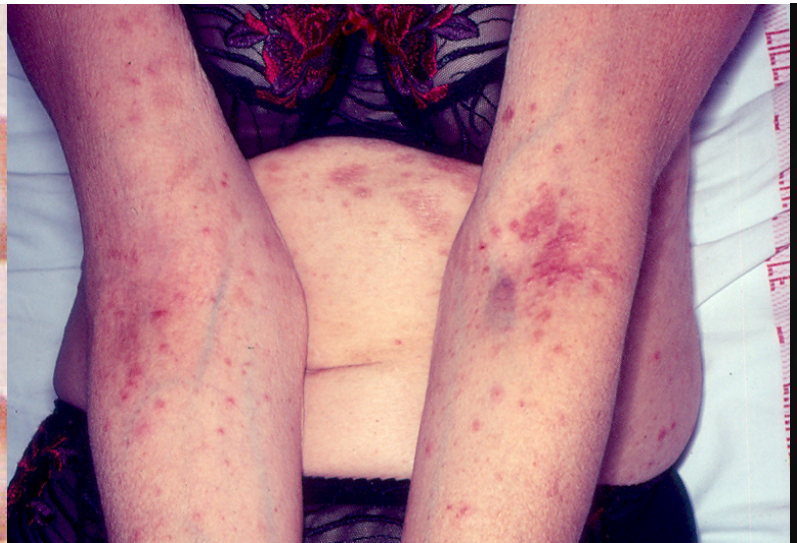
Les différents variants de SHE

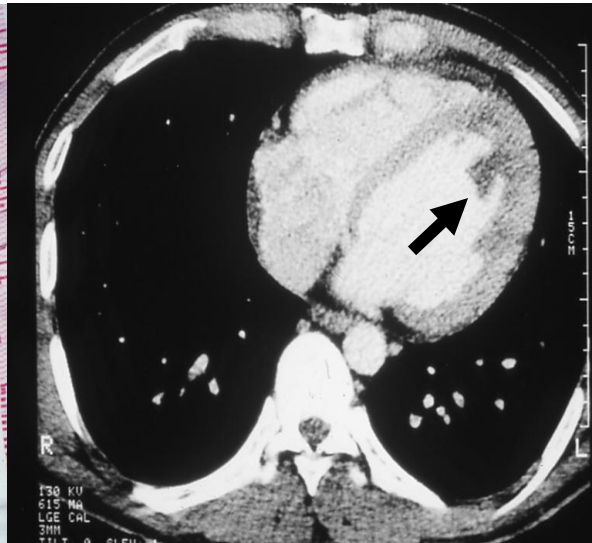
Matthieu GROH

Médecine Interne, Hôpital Foch

CEREO-Centre de Référence des Syndromes Hyperéosinophiliques







Centre de Référence
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Plan

1. *Généralités*
2. *SHE clonaux*
3. *SHE lymphoïdes*
4. *SHE réactionnels*
5. *Maladies à éosinophiles localisées à un organe*
6. *Hyperéosinophilies de signification indéterminée*

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Classification des SHE (1)

Entité	Définition
Éosinophilie sanguine	PNE> 0,5 G/L
Hyperéosinophilie (HE)	PNE> 1,5 G/L à deux reprises à un mois d'intervalle OU Eosinophilie tissulaire définie par: - Infiltrat médullaire >20% - Infiltrat médullaire jugé extensif par le pathologiste - Dépôts de granules des éosinophiles
Atteinte d'organe attribuable aux éosinophiles	**Dysfonction d'organe imputable à toxicité des éosinophiles** - Fibrose - Thrombose - Atteinte cutanée associée - Atteinte neurologique associée - Autre **Documentation histologique**
Syndrome hyperéosinophilique (SHE)	**Hyperéosinophilie** ET **Atteinte ou dysfonction d'organe attribuable aux éosinophiles** ET **Exclusion des autres causes pouvant mener à l'atteinte d'organe**

1. Valent, J Allergy Clin Immunol 2012

Classification des SHE (2)

Proposed terminology	Proposed abbreviation
Hereditary (familial) HE	HE_{FA}
HE of undetermined significance	HE_{US}
Primary (clonal/neoplastic) HE†	HE_{N}
Secondary (reactive) HE†	HE_{R}

1. *Valent, J Allergy Clin Immunol 2012*

Classification des SHE (2)

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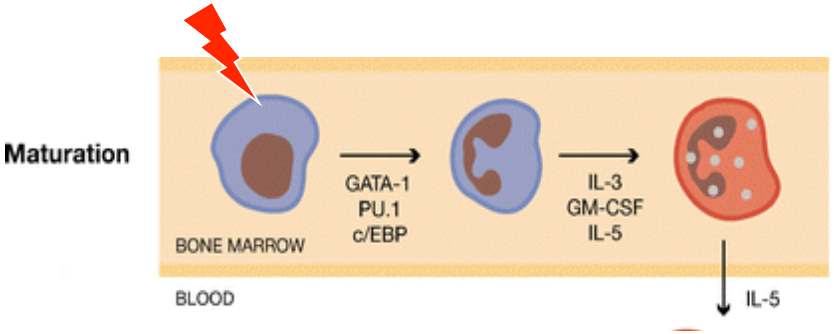

Hyperéosinophilies clonales

Néoplasies myéloïdes avec HE constante:

- ✓ Délétion FIP1L1-PDGFRA
- ✓ Translocation PDGFRA
- ✓ Translocation PDGFRB
- ✓ Translocation PCM1-JAK2
- ✓ Translocation FLT3

Néoplasies myéloïdes avec HE inconstante

- ✓ LMC BCR-BL
- ✓ Mutation JAK2 V617F (PV et TE)
- ✓ Mastocytoses systémiques cKIT
- ✓ LAM4-Eo
- ✓ SMD-Eo

Néoplasies myéloïdes avec HE inconstante et anomalie génétique non récurrente

- ✓ Critères d'exclusion: LAM, SMP,
- ✓ Présence d'autre(s) anomalie(s): T8, isochromosome 17, anomalie NGS

1. *Valent, J Allergy Clin Immunol 2012*
2. *Reiter, Blood 2016*

Classification des SHE (2)

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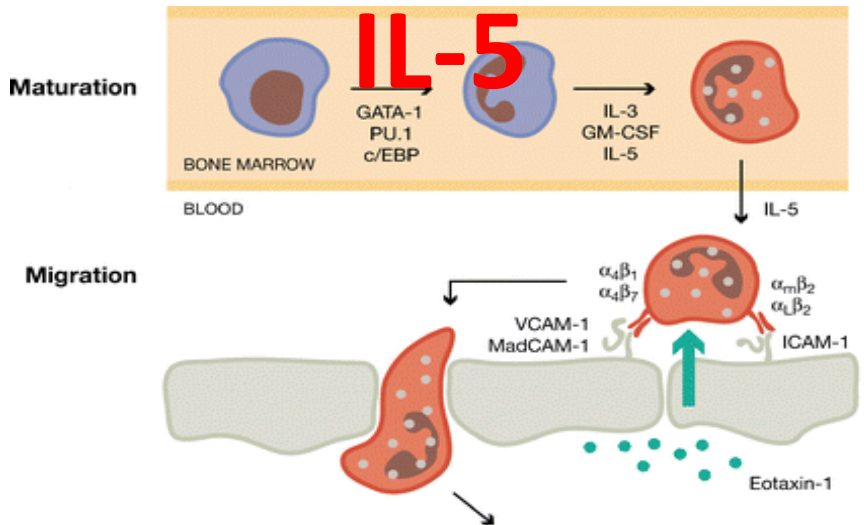


Hyperéosinophilies réactionnelles

Causes fréquentes :

- ✓ Réactions médicamenteuses
- ✓ Helminthiases
- ✓ Atopie *(PNE < 1,5G/L)*

Causes rares :

- ✓ ABPA
- ✓ Virales (VIH1, HTLV1)
- ✓ Maladies auto-immunes (PB, PR, GEPA, MICI)
- ✓ Cancers solides
- ✓ SHE lymphoïde (3-4+; 3+4+7-; 3+4-8-TCRab)
- ✓ Lymphomes (Hodgkin, lymphomes T)
- ✓ Mastocytose

1. *Valent, J Allergy Clin Immunol 2012*
2. *Kahn, Front Med 2017*

Classification des SHE (3)

LEUCÉMIES CHRONIQUE À PNE

HE/SHE Secondaires Lymphoïdes (10-20%)
LT sanguin de phénotype anormal producteur d'IL-5

HE/SHE clonaux (10-15%)
1- LCE, dont FIP1L1-PDGFRA+++
2-Autres

HE/SHE idiopathiques (50 à 70%)

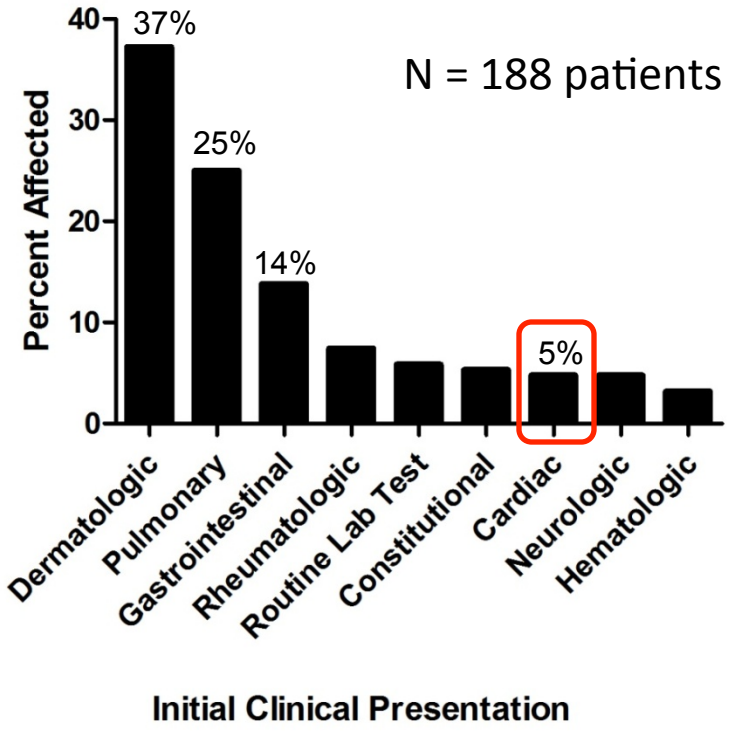
Eosinophilie familiale

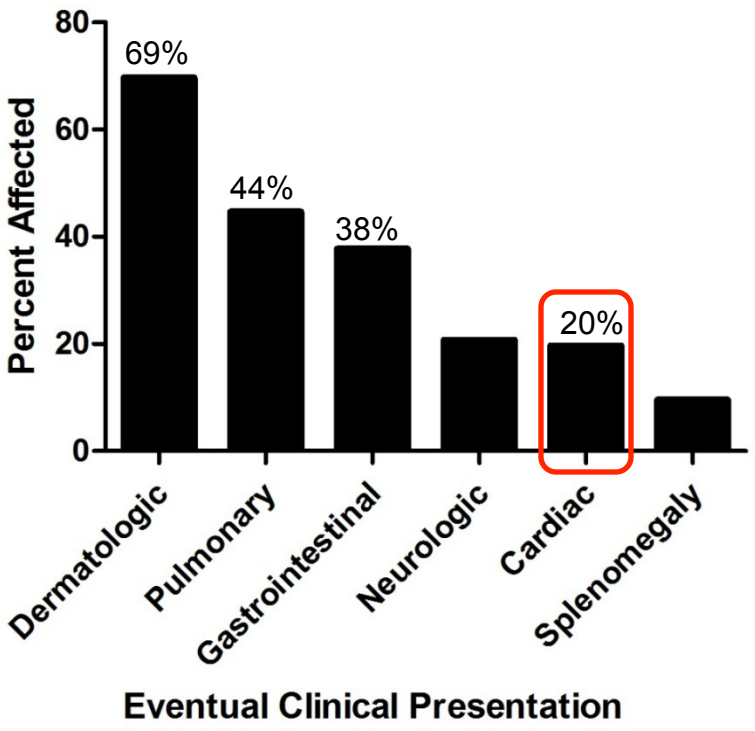
Syndromes de chevauchements et Maladies à PNE restreintes à un organe

- MICI
- PCE-PAE-Bronchiolite PNE
- GEPA
- EGID
- Maladies dermatologiques

Manifestations cliniques des SHE

Sex-Ratio 1♀ / 1♂





Ogbogu, J Allergy Clin Immunol 2009

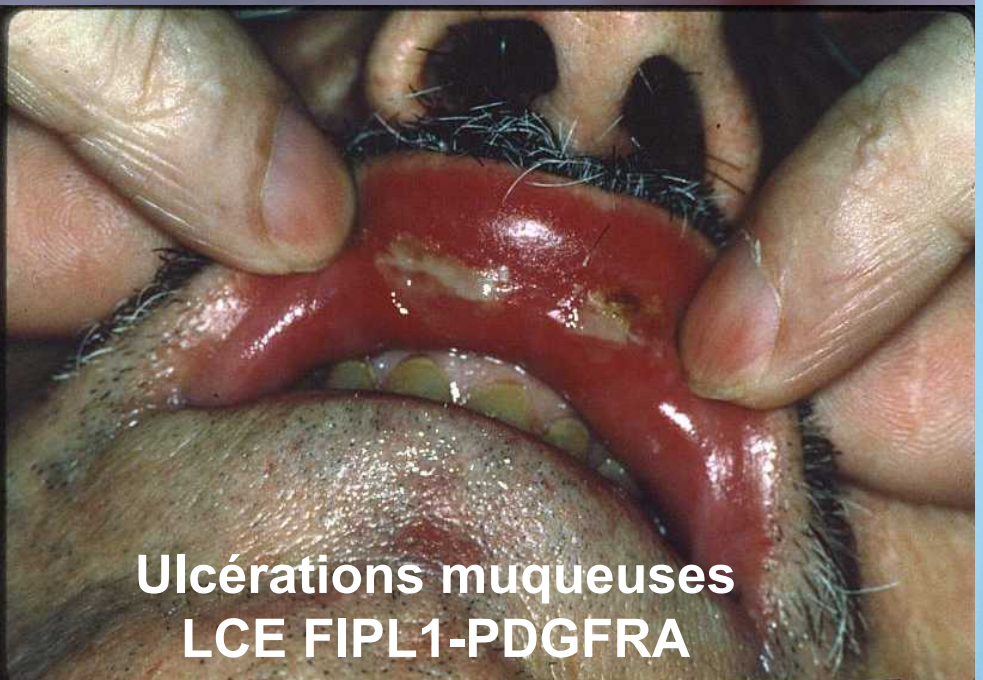
« Urticaire »

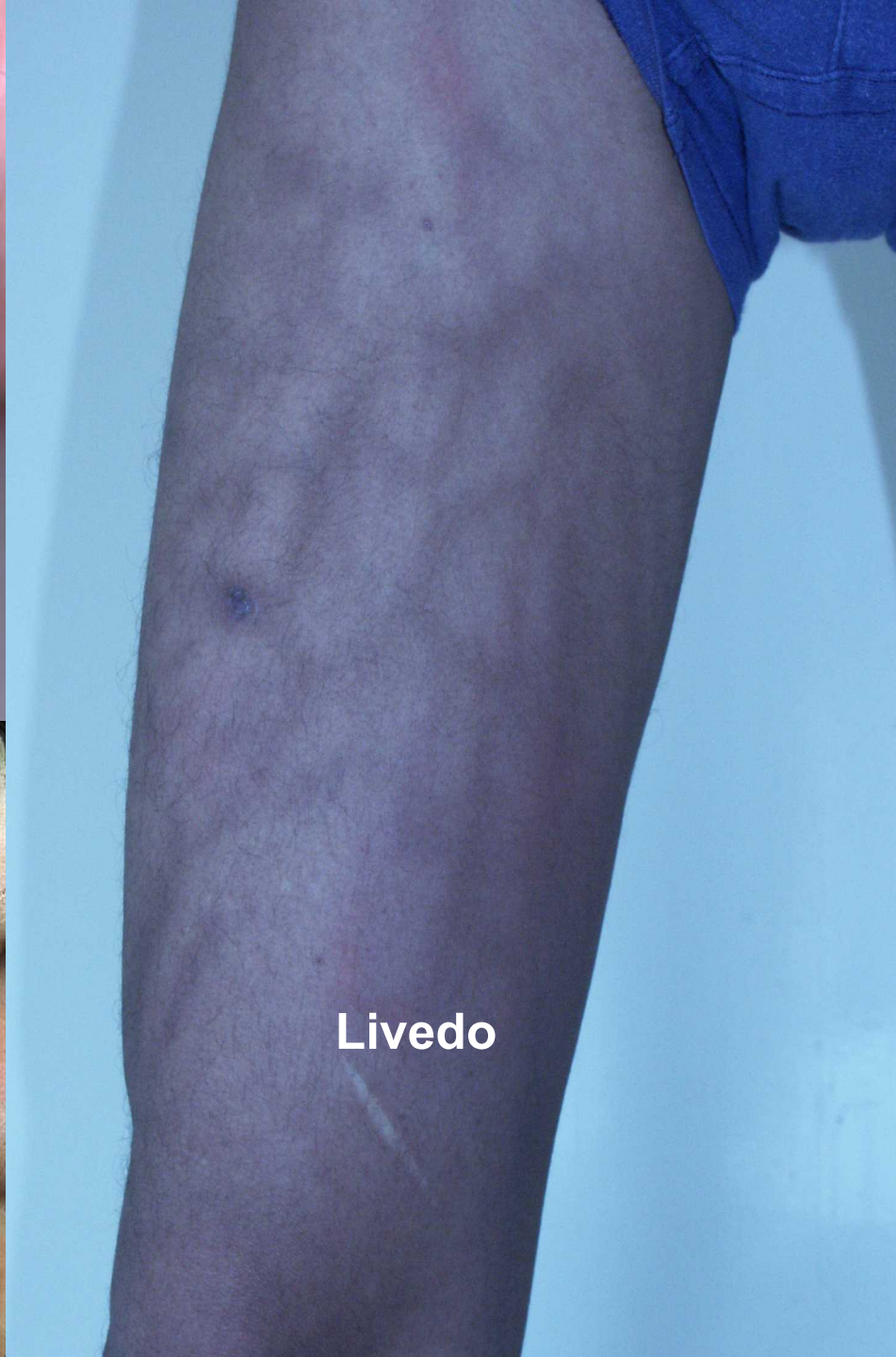
« Eczema » – SHE-L

Eruption vésiculeuse

Angioedeme (Gleich)
SHE-L


Hemorragies sous-unguéales


Ulcérations muqueuses
LCE FIPL1-PDGFRA


Livedo

Quelques pièges…

- ♀ 50 ans
- **Eos= 183 000/mm^3**
- Leucémie à PNE ?
- **Asymptomatique**
- **Eosinophilie induite par le Piroxicam (AINS)**

Pas de corrélation entre le taux de PNE et le degré de dommages tissulaires !

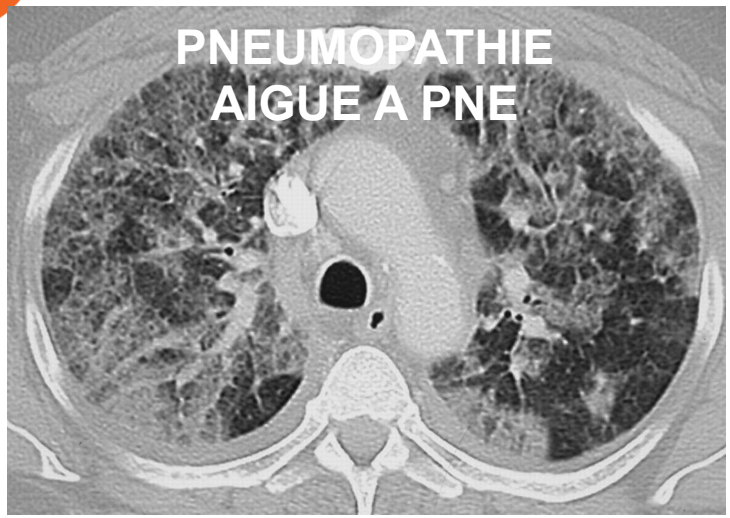
Quelques pièges…

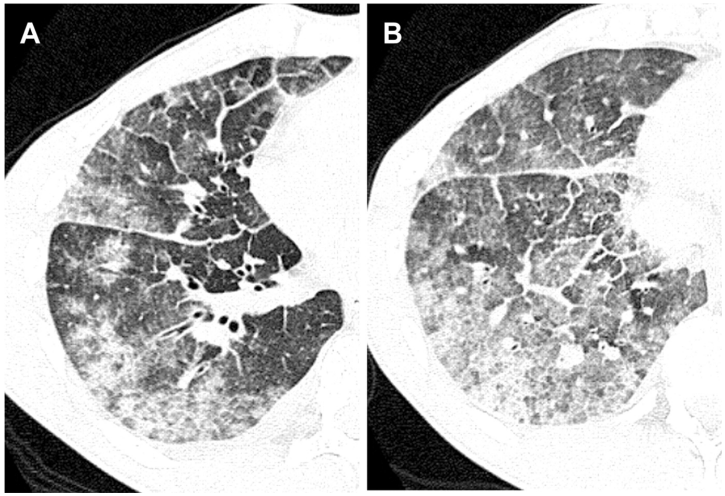
- ♀ 50 ans
- **Eos= 183 000/mm^3**
- Leucémie à PNE ?
- **Asymptomatique**
- **Eosinophilie induite par le Piroxicam (AINS)**

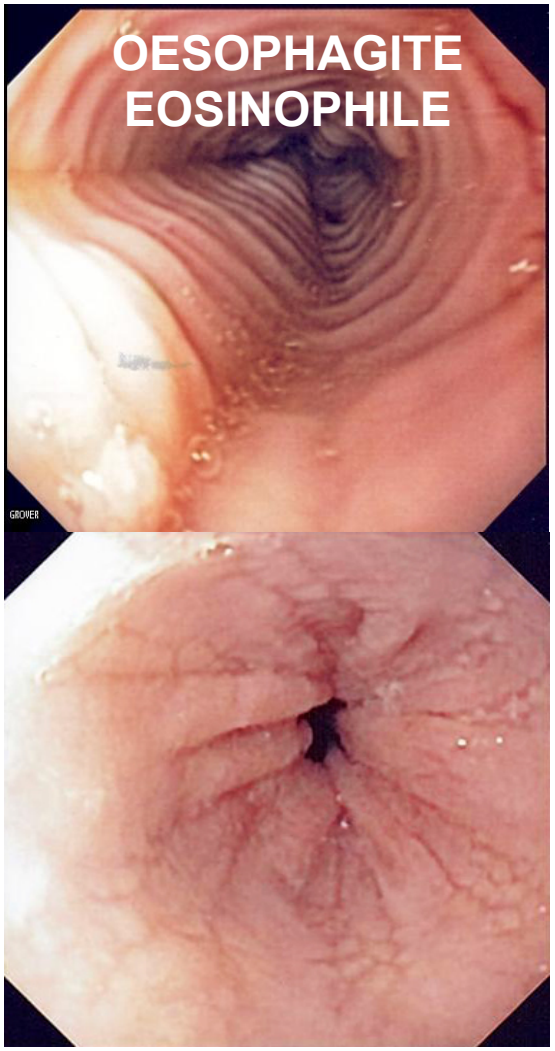
- ♂ 32 ans
- Asthénie
- **Eos = 5 000/mm^3**
- **Fibrose endomyocardique**
- **FIP1L1-PDGFRA+**
- Imatinib en 2008
- **2009: Tx cardiaque**

Pas de corrélation entre le taux de PNE et le degré de dommages tissulaires !

Quelques pièges…







Eosinophilie tissulaire…
sans éosinophilie sanguine !

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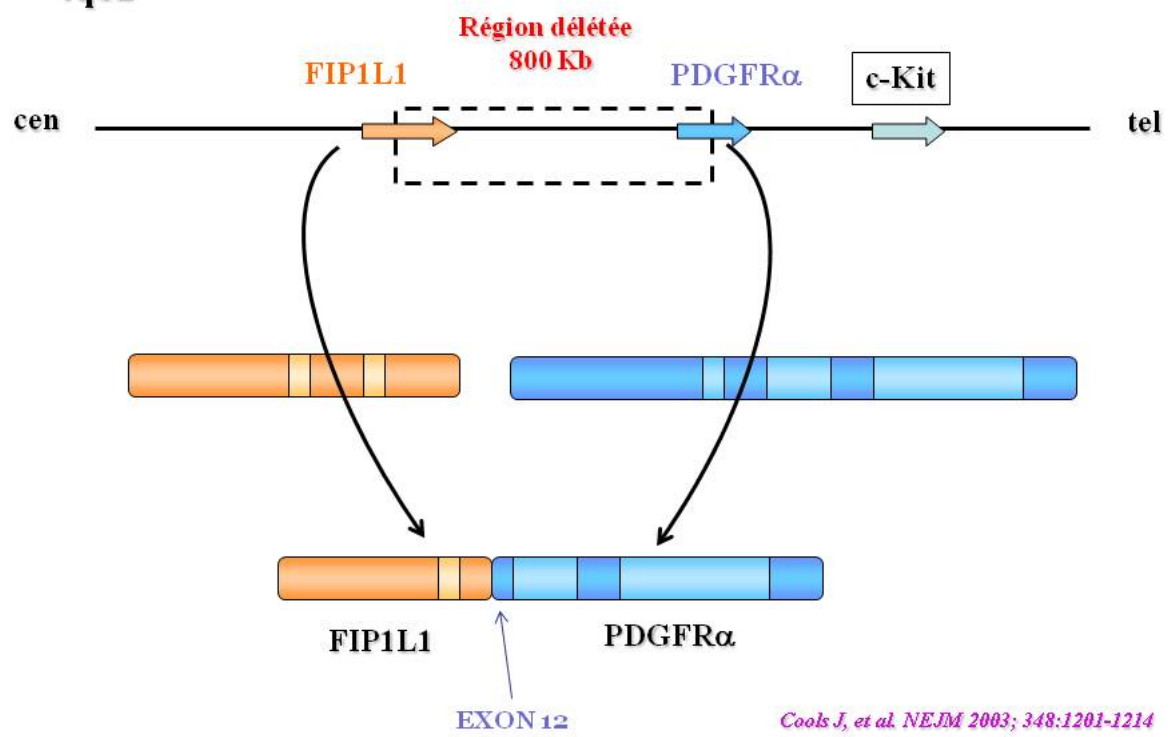
La Leucémie à PNE FIP1L1-PDGFRA (LCE F/P+)

The NEW ENGLAND JOURNAL of MEDICINE

DEMONSTRATION DU CARACTERE CLONAL DE CERTAINS SHE

A Tyrosine Kinase Created by Fusion of the *PDGFRA* and *FIP1L1* Genes as a Therapeutic Target of Imatinib in Idiopathic Hypereosinophilic Syndrome

Jan Cools, Ph.D., Daniel J. DeAngelo, M.D., Ph.D., Jason Gotlib, M.D., Elizabeth H. Stover, M.Phil., Robert D. Legare, M.D., Jorges Cortes, M.D., Jeffrey Kutok, M.D., Ph.D., Jennifer Clark, M.D., Ilene Galinsky, R.N., James D. Griffin, M.D., Nicholas C.P. Cross, Ph.D., Ayalew Tefferi, M.D., James Malone, M.D., Rafeul Alam, M.D., Ph.D., Stanley L. Schrier, M.D., Janet Schmid, M.D., Michal Rose, M.D., Peter Vandenberghe, M.D., Ph.D., Gregor Verhoef, M.D., Ph.D., Marc Boogaerts, M.D., Ph.D., Iwona Wlodarska, Ph.D., Hagop Kantarjian, M.D., Peter Marynen, Ph.D., Steven E. Coutre, M.D., Richard Stone, M.D., and D. Gary Gilliland, M.D., Ph.D.



Cools J, et al. NEJM 2003; 348:1201-1214

Cools, NEJM 2003

Epidémiologie de la LCE F/P+

	Total	Hommes	Femmes
Patients, n	145	137	8
Age, moyenne ± EC	50 ± 16	49 ± 15	53 ± 24
(Min - Max)	(6 - 88)	(15 - 88)	(6 - 81)
Diagnostic, n	LCE (71)	LCE (67)	LCE (4)
	LAM (2)	LAM (2)	LAM (0)

Année	Incidence, n cas par million d'habitants
2003	0,11
2004	0,10
2005	0,29
2006	0,16
2007	0,27
2008	0,11
2009	0,12
2010	0,08
2011	0,11
2012	0,14
2013	0,14
2014	0,17
2015	0,23
2016	0,12

- ✓ Incidence:0,15 cas / millions/an
- ✓ Moins de 10% des SHE
- ✓ Maladie « exclusivement » masculine

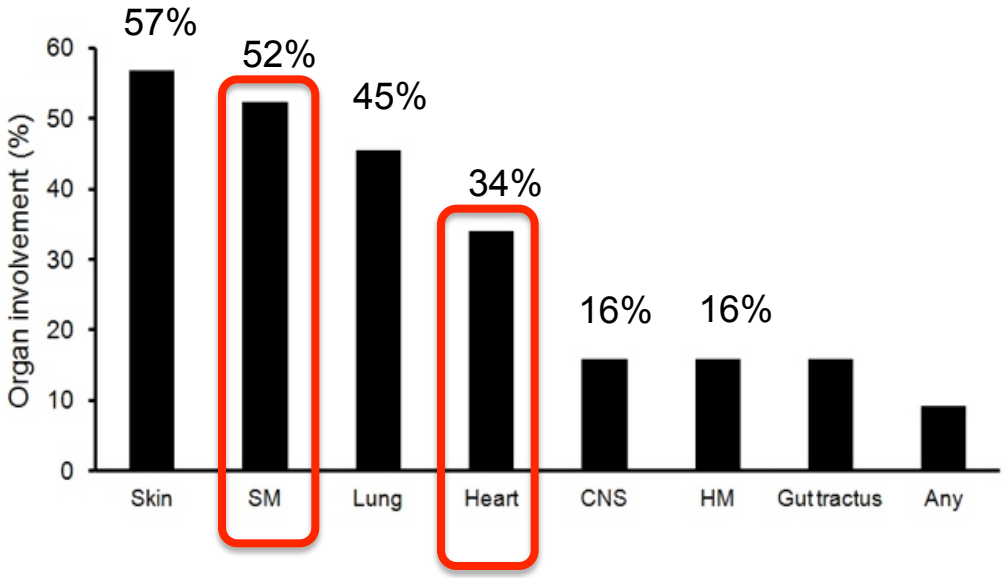
A Couteau-Chardon, SNFMI, 2018

Manifestations cliniques de la LCE F/P+

LCE F/P+

N = 44 patients

Sex-Ratio 43♂ / 1♀

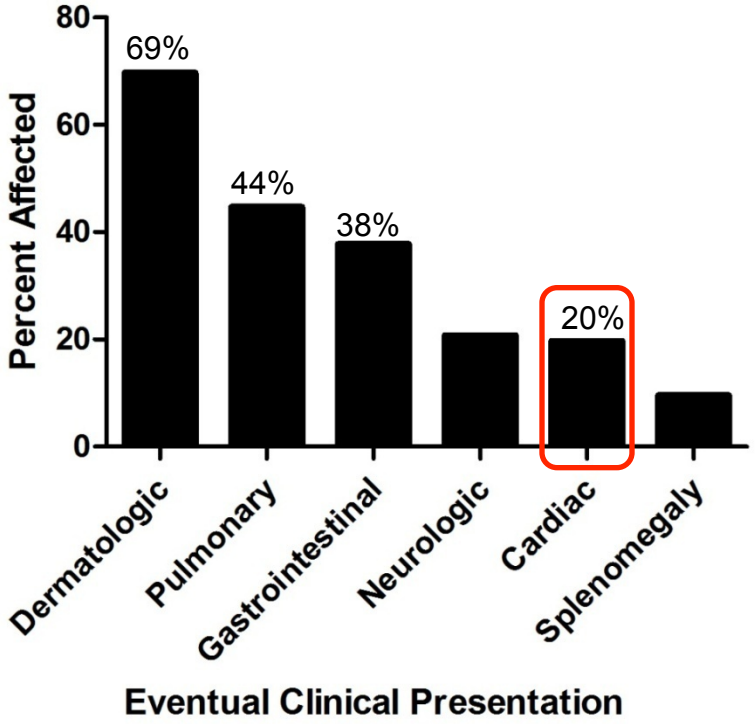


F Legrand, Medicine 2013

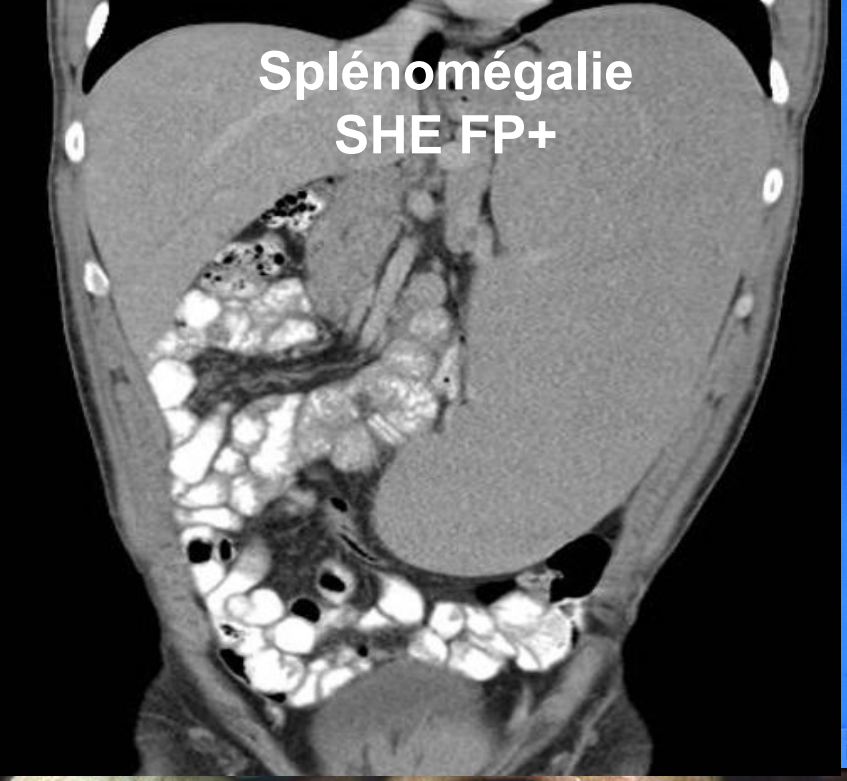
SHE tous types

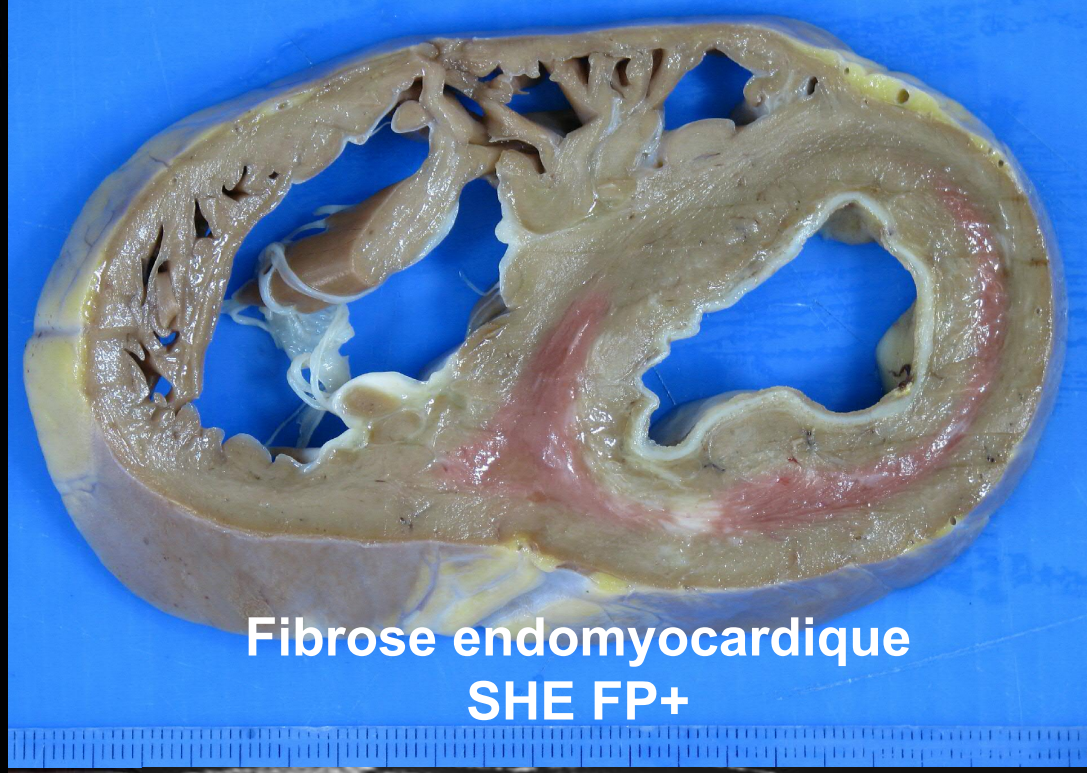
N = 188 patients

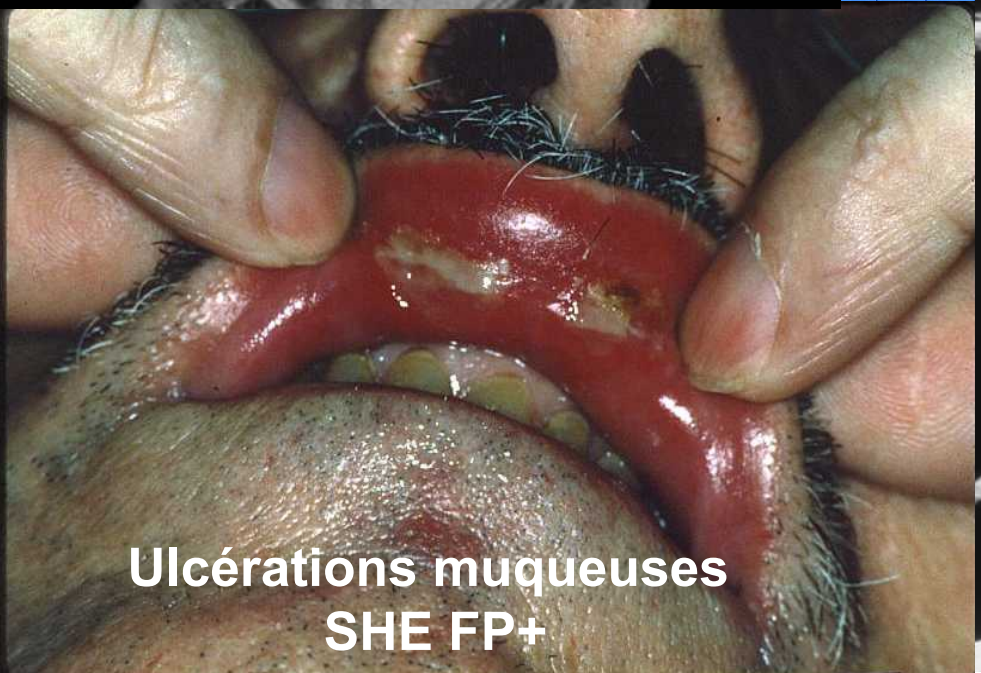
Sex-Ratio 1♀ / 1♂



Ogbogu, J Allergy Clin Immunol 2009


Splénomégalie
SHE FP+


Fibrose endomyocardique
SHE FP+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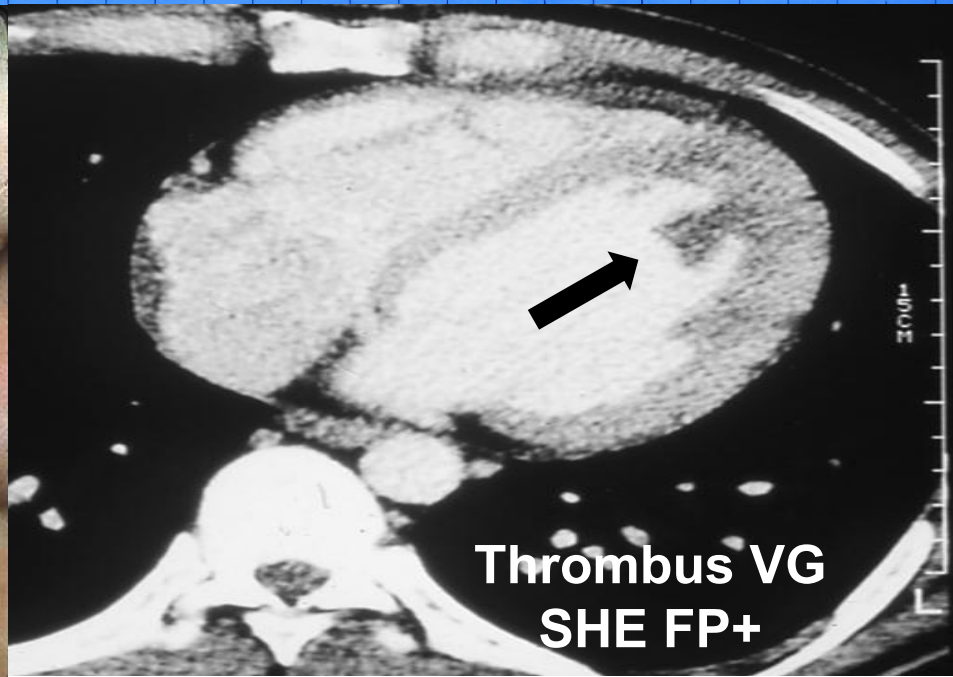
SHE FP+


Thrombus VG
SHE FP+

Manifestations biologiques de la LCE F/P+

Laboratory findings (n=44)	Value
Anemia	16 (37%)
Thrombocytopenia	16 (37%)
γδTCRclonality (n=37)	8 (21%)
T cell abnormal phenotype	2 (5%)
↗ Vitamin B12 (n=34)	28 (82%)
↗Tryptase (n= 27)	21 (78%)
↗ IgE (n=31)	5 (16%)
Eosinophilia $_{max}$ (/mm^3)	
Median	10,100
Range	1910-36,920
Therapeutic	
Corticosteroid use	14 (32%)
CHR on corticosteroid	0 (0%)

Legrand, Medicine 2013

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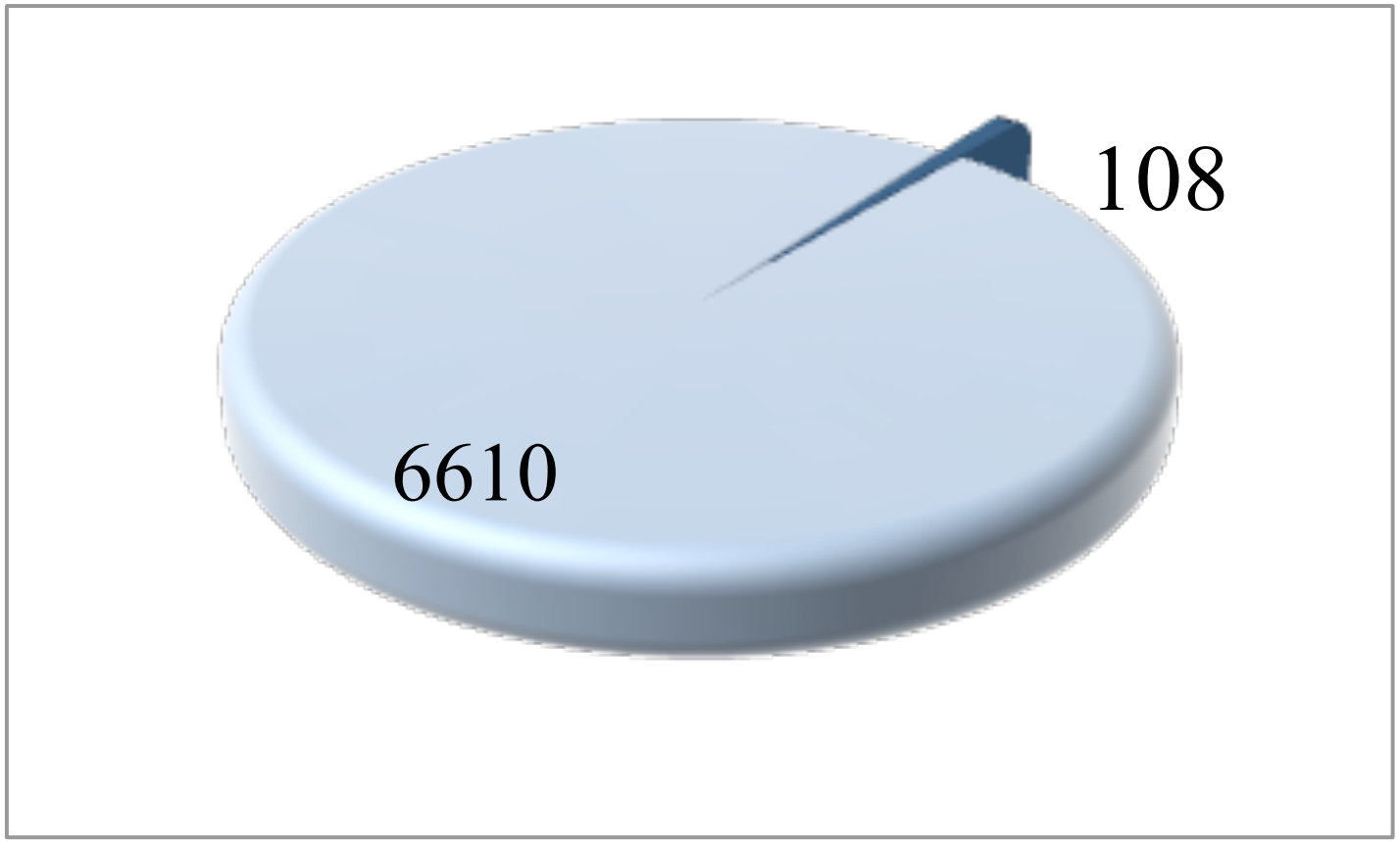
Legrand, Medicine 2013

Surprescription de FIP1L1-PGDFRA



3 laboratoires de CHU, taux de positivité: 1,6% !

A Couteau-Chardon, SNFMI 2018

Autres SHE clonaux

Néoplasie myéloïde avec HE constante et anomalie génétique récurrente	• **Délétion FIP1L1-PDGFRRA et translocations impliquant PDGFRA** • Translocations impliquant PDGFRA • Translocations impliquant FGFR1 (leucémie-lymphome) • Translocation PCM1-JAK2 (t 8-9) • Translocations impliquant FLT3 (leucémie aigue myéloïde)
Néoplasie myéloïde définie (OMS) avec HE inconstante	• Leucémie myéloïde chronique BCR-ABL • Mutation JAK2 V617F • Mastocytose systémique KIT avec hyperéosinophilie • Leucémie aigue à éosinophiles CBFß-MYH11 : LAM4-Eo, LAM inv(16) • Syndromes myélodysplasiques avec HE • Autres néoplasies myéloïdes définies avec HE
Néoplasie myéloïde avec HE et anomalie génétique non récurrente	• Critères d'exclusion : néoplasies myéloïdes définies ci dessus, leucémies aigues, autres syndromes hyperéosinophiliques ▪ Blastes <2% dans le sang et <20% dans la moelle ▪ Présence d'autre(s) anomalie(s) cytogénétiques non spécifiques (telles trisomie 8, isochromosome 17), anomalies en séquençage haut début (NGS)

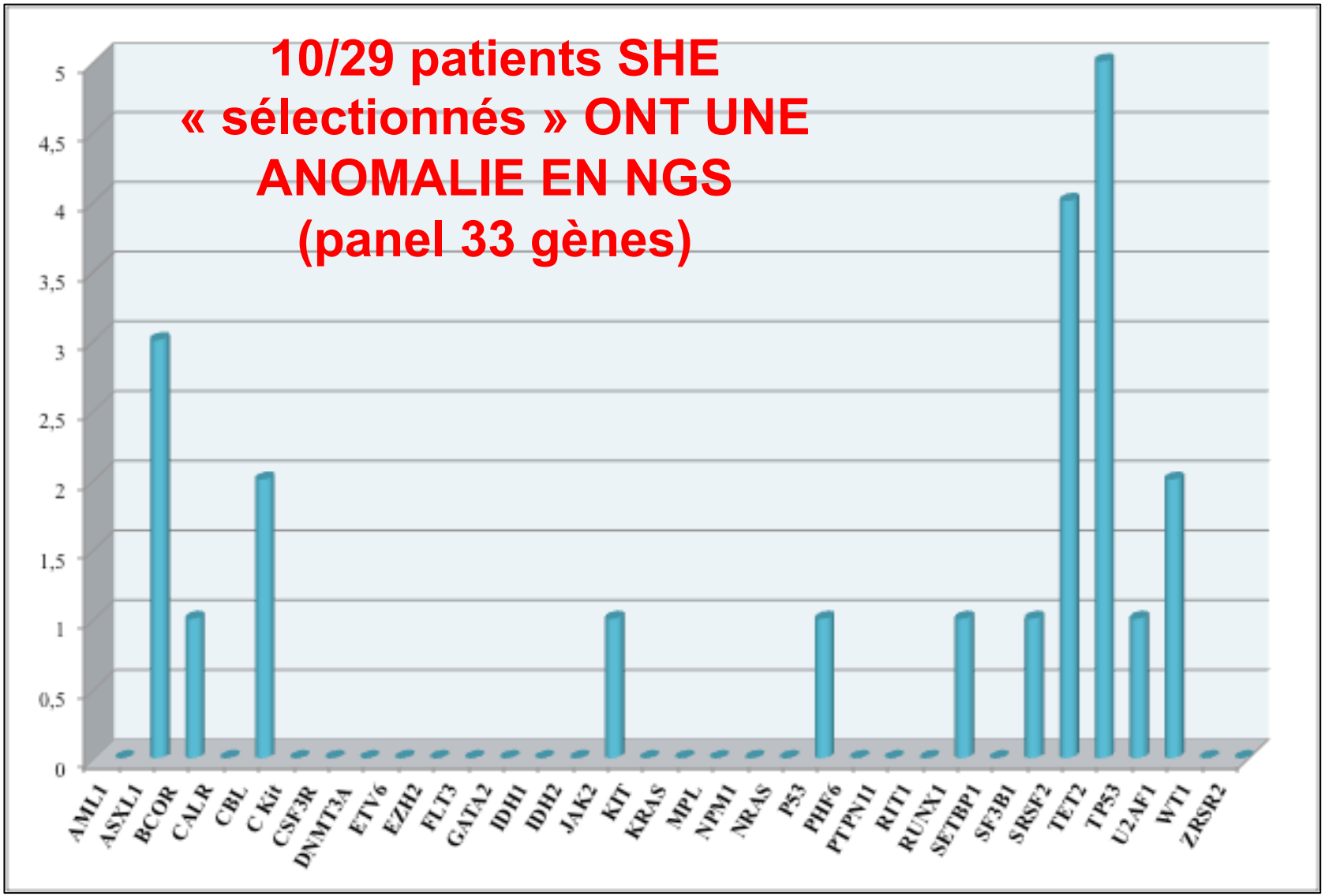
Reiter, Blood 2017

Stratégie devant HE/SHE d'allure clonale

1. **Transcrit F/P par PCR selon profil clinico-biologique**
2. **Si négatif:**
   - **F/P en FISH,**
   - **caryotype médullaire**
   - **JAK 2, BCR-ABL, C-KIT** (selon présentation et tryptase)
3. **Si négatif: Place de la BOM ?**

   Bilan mutationnel NGS exhaustif ?

Quelle place pour le NGS myéloïde ?



A Couteau, SFH 2018

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SHE lymphoïde: le cas princeps

)NAL PROLIFERATION OF TYPE 2 HELPER T CELLS IN A MAN WITH THE HYPEREOSINOPHILIC SYNDROME

ELIE COGAN, M.D., LILIANE SCHANDENÉ, M.SC., ALAIN CRUSIAUX, B.S., PASCALE COCHAUX, PH.D., THIERRY VELU, M.D., AND MICHEL GOLDMAN, M.D.

THE hypereosinophilic syndrome is characterized by persistent eosinophilia of unknown origin often associated with the dysfunction of multiple organs as a result of tissue infiltration by eosinophils and the toxic effects of their products.[1] Previous studies have suggested that T lymphocytes may be involved in the induction of the syndrome through the secretion of an eosinophil differentiation factor.[2,3]

Helper T lymphocytes (CD4+ T cells) play a central part in normal and pathologic immune responses through the secretion of cytokines. Interleukin-2, interferon gamma, and tumor necrosis factor are involved in cell-mediated immunity, whereas interleukin-4 stimulates the production of IgE antibodies and interleukin-5 promotes the differentiation and activation of eosinophils.[4,5] Functional analysis of murine and human T-cell clones generated in vitro led to the identification of several subpopulations of CD4+ cells with two strongly polarized subgroups: the type 1 helper T cells, which produce interleukin-2 and interferon gamma but not interleukin-4 or interleukin-5, and type 2 helper T cells, which produce interleukin-4 and interleukin-5 but not interleukin-2 or interferon gamma.[6,7] These two subgroups may have a role in several immunopathologic processes. Indeed, cells resembling type 1 helper T cells have been found in infectious granulomatous diseases, whereas cells resembling type 2 helper T cells have been identified in lepromatous leprosy, visceral leishmaniasis, and atopic disorders.[8-13] However, studies of monoclonal T-cell disorders are required to determine whether clones of human type 2 helper T cells arise in vivo. We investigated this possibility in a man with the hypereosinophilic syndrome characterized by excessive production of serum IgE and clonal expansion of CD4+CD3− T cells. We found that this T-cell clone produced high levels of interleukin-4 and interleukin-5 but had a markedly reduced ability to secrete interleukin-2 and interferon gamma. This observation indicates that clones of type 2 helper T cells differentiate in vivo and suggests that clonal expansion of type 2 helper T cells can cause the hypereosinophilic syndrome.

From the Department of Internal Medicine, Hôpital Universitaire Brugmann (E.C.), the Department of Immunology, Hôpital Universitaire Erasme (L.S., A.C., M.G.), and the Department of Medical Genetics, Institute of Interdisciplinary Research, Université Libre de Bruxelles (P.C., T.V.) — all in Brussels, Belgium. Address reprint requests to Dr. Cogan at the Department of Internal Medicine, Hôpital Universitaire Brugmann, 4, place Van Gehuchten, B 1020 Brussels, Belgium.

Supported by grants from the Fonds de la Recherche Scientifique Médicale (Belgium) and the Université Libre de Bruxelles.

CASE REPORT

A 30-year-old man presented with a four-month history of generalized pruritus, a cough productive of yellowish sputum, intermittent fever, and exertional dyspnea. Physical examination disclosed a few papular skin lesions and some bronchial rales. Major laboratory findings included marked eosinophilia (absolute eosinophil count, 6117 per cubic millimeter) and a polyclonal increase in serum levels of IgM (7200 mg per deciliter; normal, <250) and IgE (2000 IU per milliliter [4800 μg per liter]; normal, <100 IU per milliliter [240 μg per liter]). Immunophenotyping of peripheral-blood mononuclear cells (PBMC) by flow cytometry revealed the following proportions of cells: 42 percent CD3+, 75 percent CD4+, 16 percent CD8+, and 90 percent CD2+ T cells. Double- and triple-staining studies indicated that 66 percent of the CD4+ cells did not express CD3 on their surface. These CD4+CD3− cells did not stain with monoclonal antibodies against α/β or γ/δ T-cell receptors but expressed the CD2 marker. Antibodies were not detected against the human immunodeficiency virus types 1 and 2 or human T-cell lymphotropic virus type I. The patient's karyotype was normal. Computed tomography of the thorax revealed slight pleural effusions. Abdominal computed tomography and echocardiography revealed no abnormalities. A skin biopsy demonstrated a dermal perivascular infiltration with monocytes and numerous eosinophils. Oral administration of methylprednisolone was begun at a dose of 32 mg per day and resulted in rapid clinical improvement and a drop in the eosinophil count (Fig. 1) and in serum IgM and IgE levels (data not shown). When the dose of methylprednisolone was tapered, the initial symptoms and biologic abnormalities recurred. In addition, pain and blanching of the first two fingers of the right hand developed. Thrombotic vasculitis was confirmed by a biopsy. An iliac-bone biopsy and histologic examination of a left cervical lymph node revealed no abnormalities except for the presence of numerous eosinophils. An increase in the dose of methylprednisolone to 48 mg per day controlled this flare, but the symptoms recurred when the dose was tapered (Fig. 1). Since interferon alfa therapy has been successful in the hypereosinophilic syndrome,[14-16] a therapeutic trial of subcutaneous interferon alfa-2b (Schering-Plough, Innishannon, Ireland) was started at a dose of 5 million IU per day. The addition of this drug resulted in a rapid decrease in eosinophilia (Fig. 1). Serum levels of IgE remained unchanged, whereas serum levels of IgM progressively decreased from 7950 mg per deciliter at the beginning of treatment to 2530 mg per deciliter after two months of interferon alfa-2b. During treatment, the percentage of CD4+CD3− cells decreased from 60 to 31 percent while the percentage of CD3+CD4+ cells increased from 17 to 41 percent.

METHODS

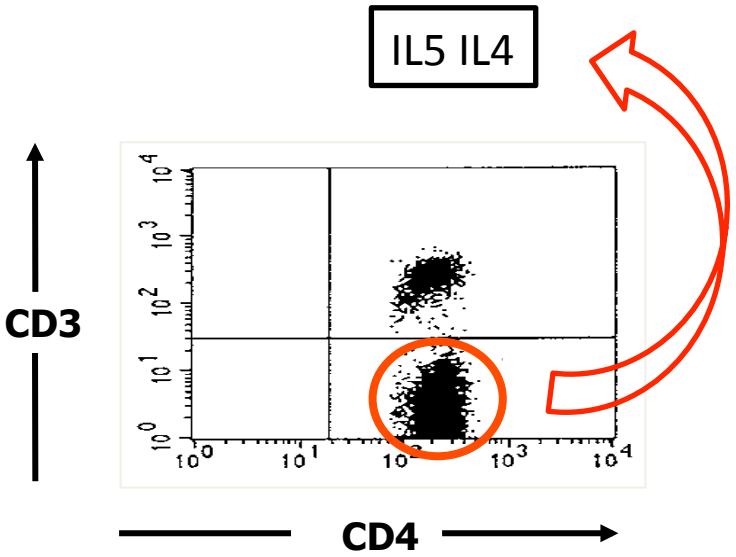
Isolation of PBMC

PBMC from the patient and five healthy volunteers were isolated from freshly drawn heparin-treated blood by density gradient centrifugation on Lymphoprep (Nycomed, Oslo, Norway). CD4+ cells were selected through the use of immunomagnetic beads coated with an anti-CD4 monoclonal antibody (Dynabeads M450 CD4 and Detachabead, Dynal, Oslo, Norway). Non-T cells were obtained by the successive depletion of CD4+ cells and CD8+ cells with the use of immunomagnetic beads coated with corresponding monoclonal antibodies (Immunotech, Marseilles, France). The patient's CD4+CD3− cells were prepared from CD4+ cells by the selective depletion of CD3+ cells through incubation with an anti-CD3 monoclonal antibody (Ortho Biotech, Raritan, N.J.) and immunomagnetic particles coated with goat antimouse IgG (Immunotech). The purity of the resulting cell preparations was more than 95 percent, as determined by flow cytometry.

Southern Blot Analysis of Gene Coding for the β Chain of the T-Cell Receptor

Southern blot analysis of the gene coding for the β chain of the T-cell receptor was performed according to standard procedures.[17,18] The probe (JUR-β2) used was a complementary DNA clone of the second constant region of the gene.[19]

- Homme 30 ans
- Rash - Infiltrat PNE dermique
- Toux – dyspnée – Ep pleural
- Ischémie digitale - vascularite
- Adénopathie non lymphomateuse
- PNE = 6,1 G/L
- IgM = 79 g/l (poly) – IgE = 2000 UI/L



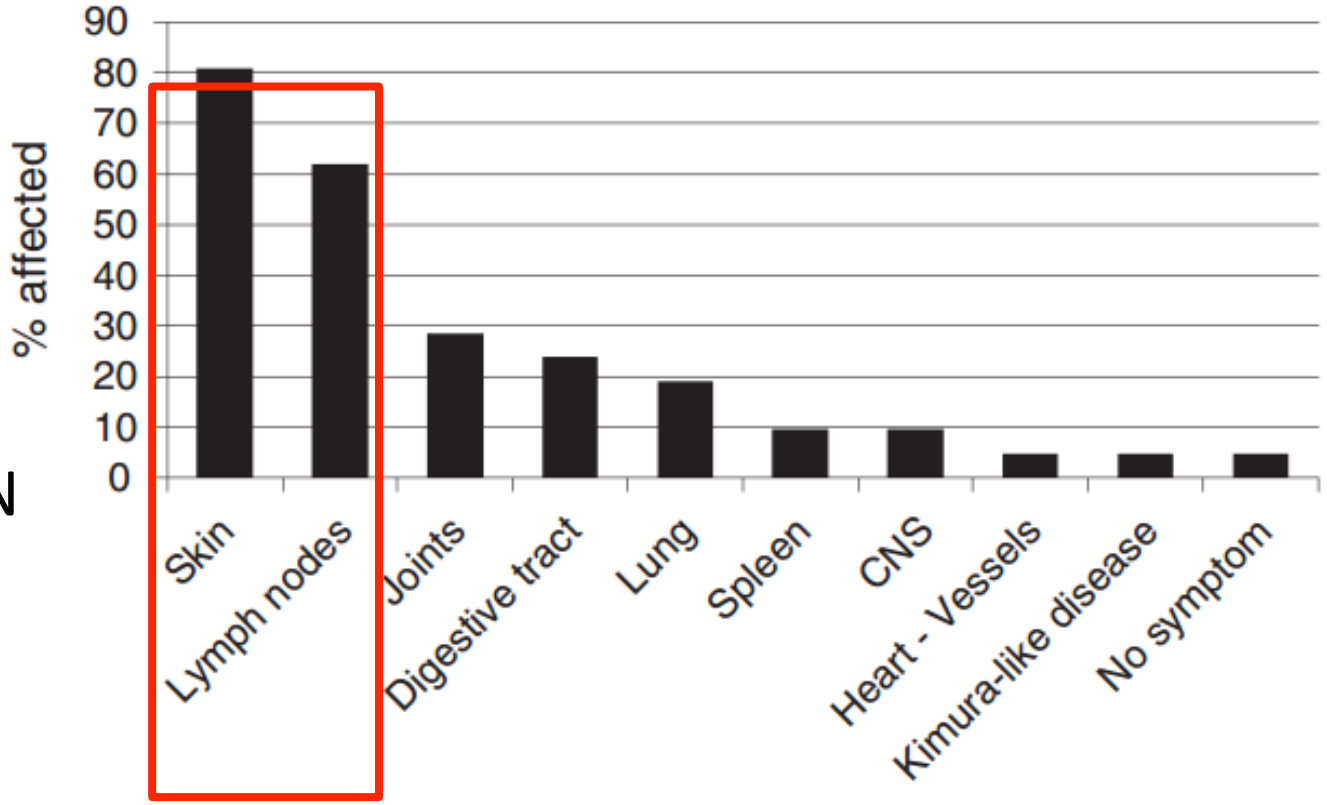
Cogan, NEJM 1994

SHE lymphoïde… 25 ans plus tard

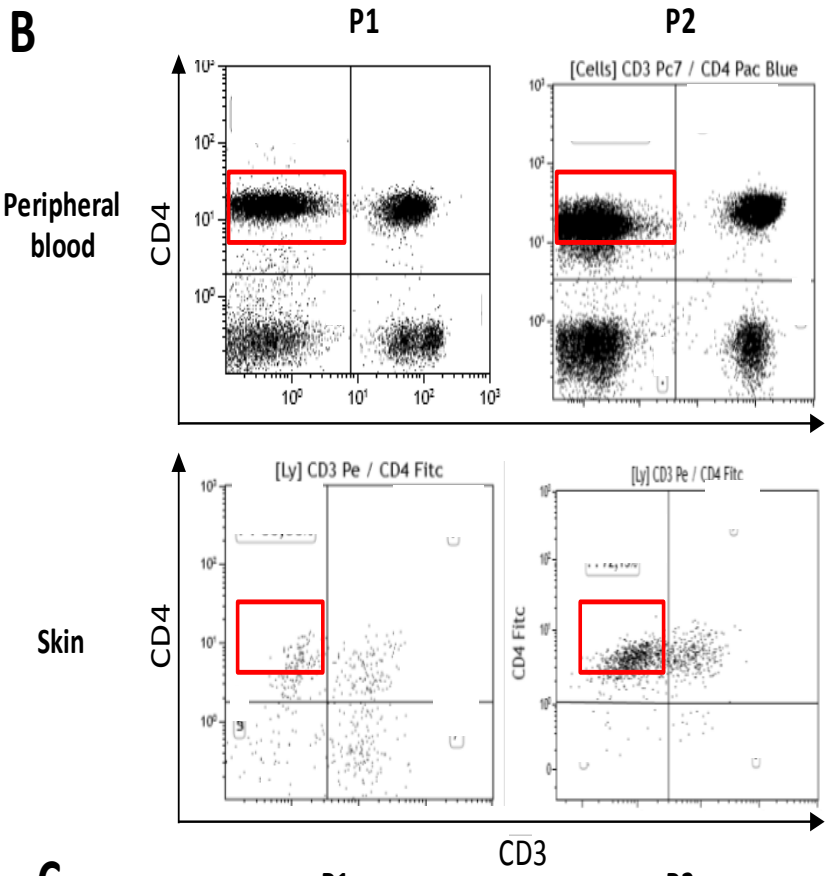
The Lymphoid Variant of Hypereosinophilic Syndrome

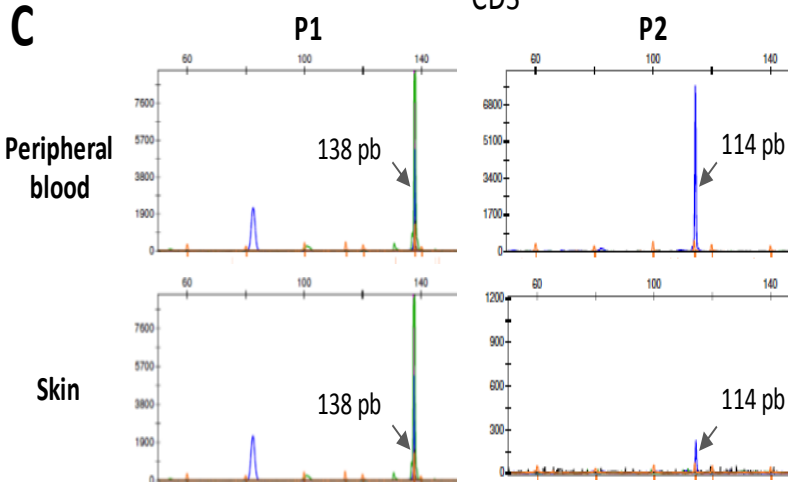
Study of 21 Patients With CD3-CD4+ Aberrant T-Cell Phenotype

- 13 F / 8 H
- 42 ans [5-75]
- Atopiques: 48%
- IgE augmentés
- B12 et tryptase: N



Lefèvre, Medicine, 2014





- ✓ **Infiltrats tissulaires T clonaux CD3-CD4+ dans tous les organes atteints par les PNE,**
- ✓ **Depuis parfois 20 ans**
- ✓ **En IHC: CD3+CD4+**
- ✓ **Pas d'expression CD10 ni marqueurs T FH (PD1, CXCL13…)**

Lefevre Haematologica 2015

Quelques marqueurs utiles

TABLE E2. Comparison of baseline characteristics between F/P+ LCE and CD3-CD4+ L-HES cohorts of the French Eosinophil Network

	F/P+ CEL patients (n=44)	CD3-CD4+ L-HES patients (n=21)	p value
Age at eosinophilia onset (years)			
Median	41	42	
Range	6-67	5-69	
Sex ratio M/F (% M)	43/1 (98%)	8/13 (38%)	
Other laboratory findings			
Anemia	16 (37%)	0	0.001
Thrombocytopenia	16 (37%)	0	0.001
gd TCR clonality	8/37 (21%)	16 (76%)	7.7 10-5
Increased vitamin B12	28/34 (82%)	2/17 (12%)	1.6 10-6
Increased tryptase	21/27 (78%)	2/17 (12%)	1.6 10-6
Increased IgE	5/31 (16%)	18 (86%)	2.8 10-6

B12, Tryptase, IgE totales permettent d'orienter le diagnostic

Beaucoup de caryotypes et biologie mol. inutiles +++

Lefèvre, Medicine, 2014

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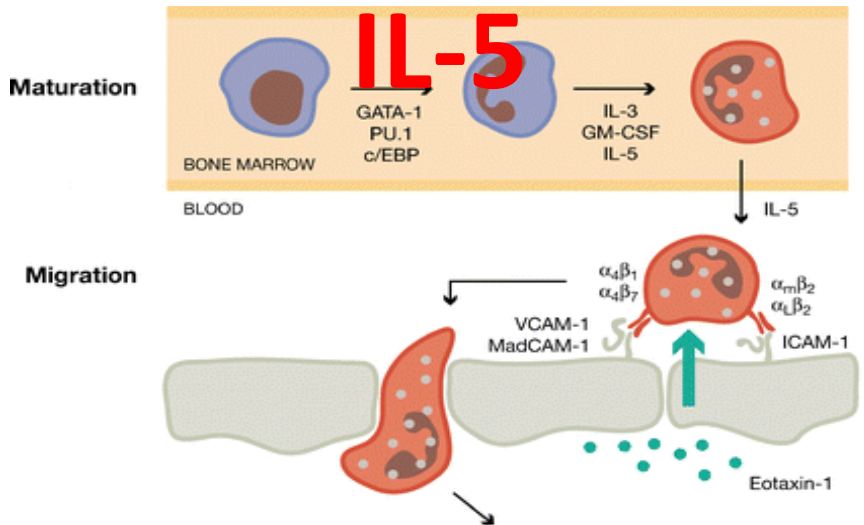
Concept de SHE réactionnel

Proposed terminology	Proposed abbreviation
Hereditary (familial) HE	HE_{FA}
HE of undetermined significance	HE_{US}
Primary (clonal/neoplastic) HE†	HE_{N}
Secondary (reactive) HE†	HE_{R}



Hyperéosinophilies réactionnelles

Causes fréquentes :

- ✓ Réactions médicamenteuses
- ✓ Helminthiases
- ✓ Atopie *(PNE < 1,5G/L)*

Causes rares :

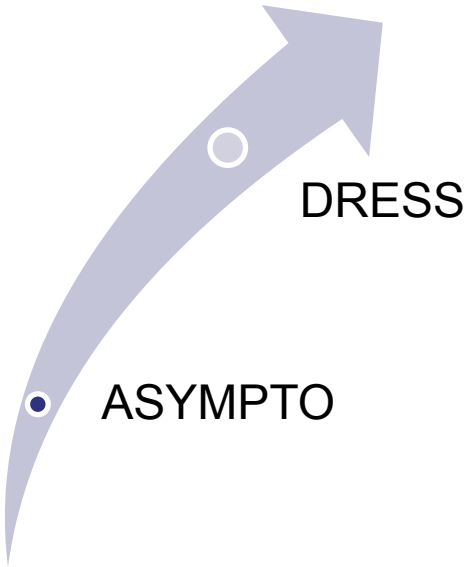
- ✓ ABPA
- ✓ Virales (VIH1, HTLV1)
- ✓ Maladies auto-immunes (PB, PR, GEPA, MICI)
- ✓ Cancers solides
- ✓ SHE lymphoïde (3-4+; 3+4+7-; 3+4-8-TCRab)
- ✓ Lymphomes (Hodgkin, lymphomes T)
- ✓ Mastocytose

1. *Valent, J Allergy Clin Immunol 2012*
2. *Kahn, Front Med 2017*

PNE et hypersensibilité médicamenteuse

TABLE I. Drugs associated with DRESS

Drug group	Drug examples
Aromatic anticonvulsants	Carbamazepine
	Phenobarbital
	Phenytoin
	Primidone
Nonaromatic anticonvulsants	Lamotrigine
	Valproic acid
	Gabapentin
	Benzodiazepines
Anticancer drugs	Allopurinol
Antimicrobial agents	Minocycline
	Terbinafine
	Nitrofurantoin
	Isoniazid
	Abacavir
Sulfa drugs	Sulfonamides
	Dapsone
	Sulfasalazine
Nonsteroidal anti-inflammatory drugs	Oxicam
	Thalidomide
Antihypertensive drugs	Captopril
	Diltiazem
Antidiabetics	Sorbinil



MAIS AUSSI, en cours d'hospitalisation

- **Antibiotiques**
- **HBPM**
- **AVK**
- **PDC iodés**

💣**DUREE 10j à 6 MOIS ++++**

Se donner du temps si arrêt d'un TTT

DRESS : intérêt du score RegiSCAR

Item	présent	absent
Fièvre	0	-1
Adénopathies	1	0
Eosinophilie	1 ou 2	0
Eruption > 50%	1	0
Eruption suggestive	1	0
Atteinte viscérale	1 ou 2	0
Durée > 15 jours	0	-1
Bilan excluant d'autres causes	1	0

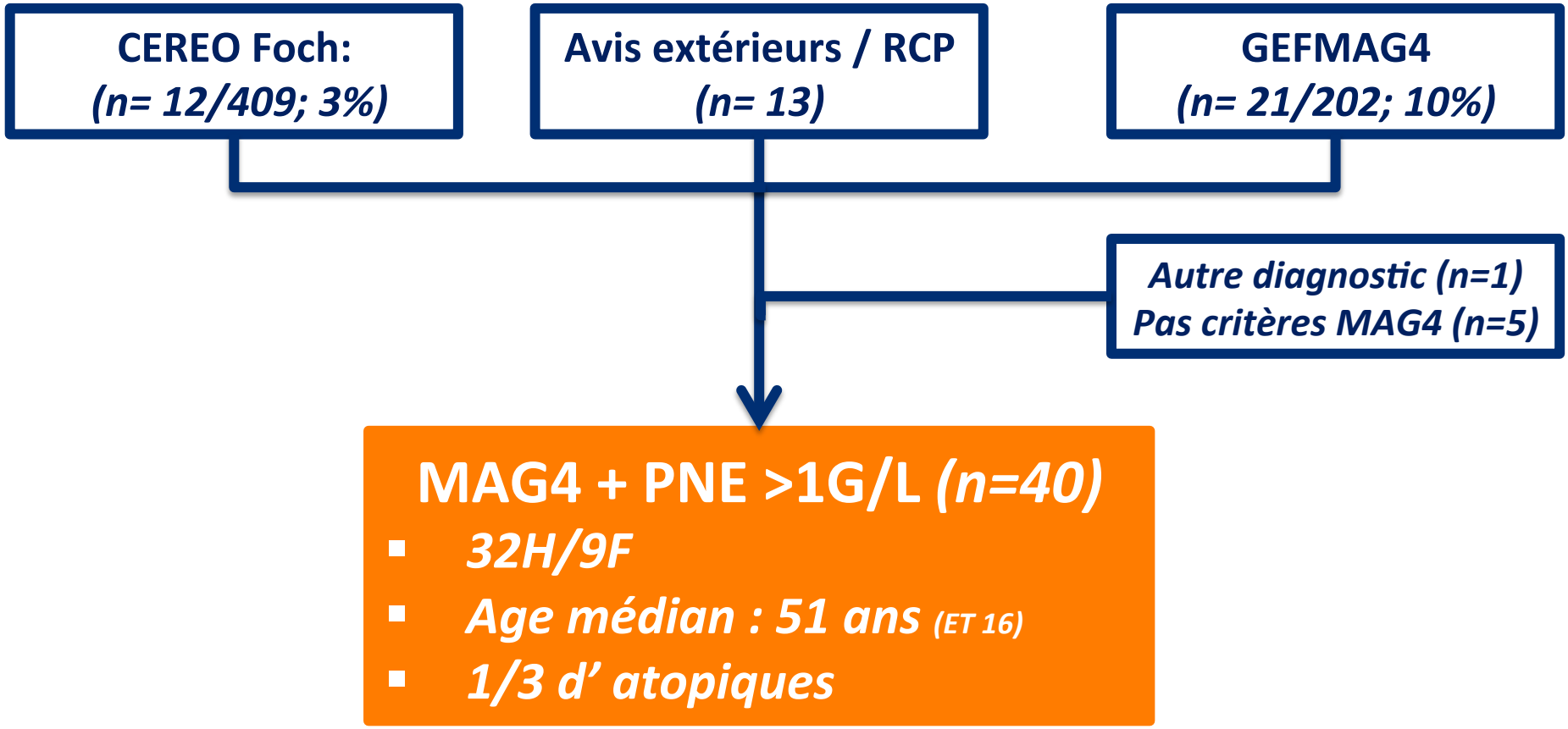
Score total: < 2 Exclu 2-3 Possible 3-4 probable > 4 certain

Réactivation virales (EBV, CMV, HHV6, HHV7)

fréquentes au cours du DRESS

Kardaun, Br J Dermatol, 2007

MAG4 et SHE (1)



R Muller, SNFMI 2019

MAG4 et SHE (2)

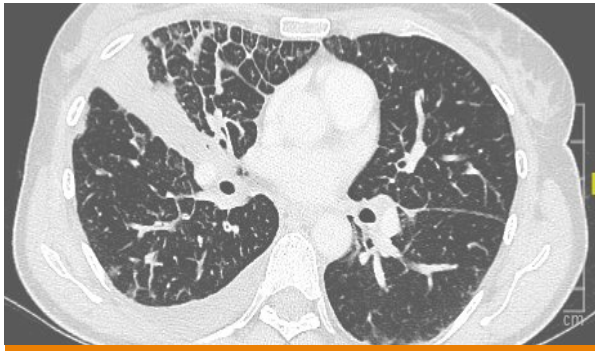
Clinique

27/40 (67%) patients symptomatiques

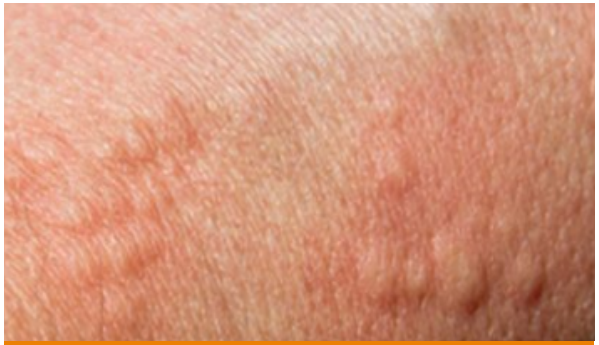
- **Poumon: 16/27 (60%)**
- **Peau: 11/27 (40%)**
- **ORL: 8/27 (30%)**
- **Coeur: 6/27 (22%)**
- **Vascularite: 5/27 (18%)**

Biologie

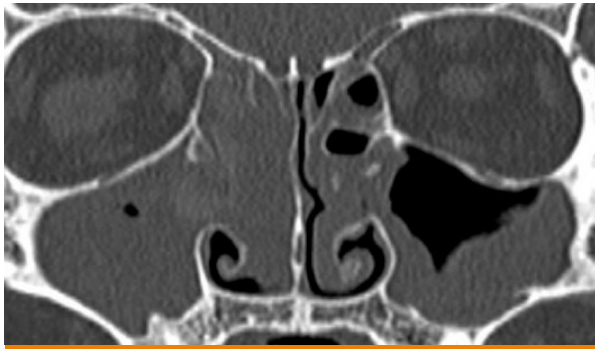
- **PNE moyens: 6 G/L**
  - ***> 1,5G/L: 70%***
  - ***> 3G/L: 50%***
- **IgE totales ↑: 25/30 (85%)**
- **B12 ou tryptase ↑: 1/18 (5%)**
- **Phénotypage Ly anormal (3/36)**
  - ✓ ***3-4+ (n=1)***
  - ✓ ***3+4+7- (n=1)***
  - ✓ ***3+4-8-TCRab (n=1)***



Atteinte pulmonaire



Atteinte cutanée



Atteinte ORL

R Muller, SNFMI 2019

MAG4 et SHE (3)

Corticothérapie

- Prescrite chez 34/38 (89%)
- Efficacité MAG4 32/34 (94%)
- Réponses hématologiques
  - ✓ complète (RHC) 26/33 (79%)
  - ✓ partielle (RHP): 7/33 (21%)
- Rechutes:
  - ✓ 26/32 (81%)
  - ✓ après sevrage chez 8/26 (30%)
  - ✓ à +/- 11 mg/j chez 18/26 (70%)
  - ✓ manifestations cliniques
    - MAG4 24/26 (92%)
    - SHE 7/26 (27%)

Lignes ultérieures

- DMARDs 11/38 (29%)
  - ✓ efficacité MAG4 10/11 (90%)
  - ✓ RHC: 8/11 (72%); RHP: 2/11 (20%)
  - ✓ Rechutes: 9/11 (80%)
- RITUXIMAB n=17 (45%)
  - ✓ efficacité MAG4 17/17 (100%)
  - ✓ RHC: 4/17 (24%); RHP: 12/17 (71%)
  - ✓ Rechutes: 25% (>> *RTX d'entretien)*
- MEPOLIZUMAB n=2 (5%)
  - ✓ efficacité MAG4: (0%)
  - ✓ RHC: 1/2 (50%); RHP: 1/2 (50%)

R Muller, SNFMI 2019

PR et SHE (n=48)

Characteristics of Eosinophilia	
Mean time to Eosinophilia, years	5.4 (-2-29)
Eosinophilia at RA onset (+/- 6 months)	20 (41.67%)
Eosinophilia before RA onset (> 6 months)	2 (4.1%)
Mean peak value, G/L	5.6 (0.6-52)
>1.5G/L	36 (75%)
>3G/L	20 (41.7%)
Mean PGA at peak of HE (range)	3.8 (0-9)
Organ involvement related to HE	28 (58.3%)
Skin involvement	7 (14.6%)
Lung involvement	7 (14.6%)
Angioedema	3 (6.3%)
ENT	2 (4.2%)
Myocarditis	1 (2.1%)
Serositis	4 (8.3%)
Vasculitis	4 (8.3%)
Myositis	2 (4.2%)
Others	4 (8.3%)
HES criteria fulfilled	23 (60.4%)

Enquête étiologique

- Pauvre
- Tardive

IgE: n=23/48 (47.9%)

- Augmentées n=20/23 (87.0%)

Phéno T: n=27 (56.3%)

- SHE L CD3+CD4+CD7-: n=1

Bilan myéloïde:

- toujours normal… quand fait…

Intérêt du Rituximab ?

M Killian, SNFMI 2019

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Maladies localisées à un organe

Maladie gastrointestinales à Eosinophiles (colite, gastro-entérite, oesophagite)
Cholangite à éosinophiles
Pancréatite à éosinophiles
Ascite à éosinophiles
Asthme éosinophilique
Bronchite et bronchiolite à éosinophiles
Pneumopathie aigue et chroniques à éosinophiles
Néphrite interstitielle à éosinophiles
Cystite à éosinophiles
Mastite à éosinophiles
Myocardite à éosinophiles
Myosite à éosinophiles
Endométrite à éosinophiles
Synovites à éosinophiles
Fasciite à éosinophiles

Valent, J Allergy Clin Immunol 2012

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HE-US: on ne traite pas une NFS…

Marked and persistent eosinophilia in the absence of clinical manifestations

Yun-Yun K. Chen, BS,[a] Paneez Khoury, MD,[a] JeanAnne M. Ware, MSN, CRNP,[a] Nicole C. Holland-Thomas, MSN,[b] Jennifer L. Stoddard, BS,[c] Shakuntala Gurprasad, BS,[c] Amy J. Waldner, BA,[a] and Amy D. Klion, MD[a] *Frederick and Bethesda, Md*

- 8 patients **HE-US** (dont 4 HE-L; 3 CD3-CD4+)
- PNE: 1,8 G/L-7,8 G/L
- Suivie médian 11 ans (7-29 ans)
- **AUCUNE MANIFESTATION CLINIQUE SANS TRAITEMENT**

Clinical implications: A subset of patients who present with unexplained marked eosinophilia (AEC > 1500/μL) and no clinical manifestations attributable to eosinophilia appear to have a benign prognosis and can be followed closely without therapy.

Chen, J Allergy Clin Immunol 2015

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Plate-forme de génomique fonctionnelle U837

M Cheok, P Peyrrouze