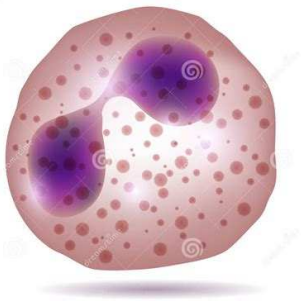
50 NUANCES D'ASTHME

Samedi 08 Octobre 2022 • Maison de la RATP

SPIF

La société de Pneumologie d'Île-de-France



Asthme hyperéosinophilique: quand faut-il s'inquiéter ?

Matthieu Groh

CRMR des Syndromes Hyperéosinophiliques

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Journée annuelle SPIF – 08 octobre 2022

CEREO

Centre de Référence des Syndromes hyperéosinophiliques

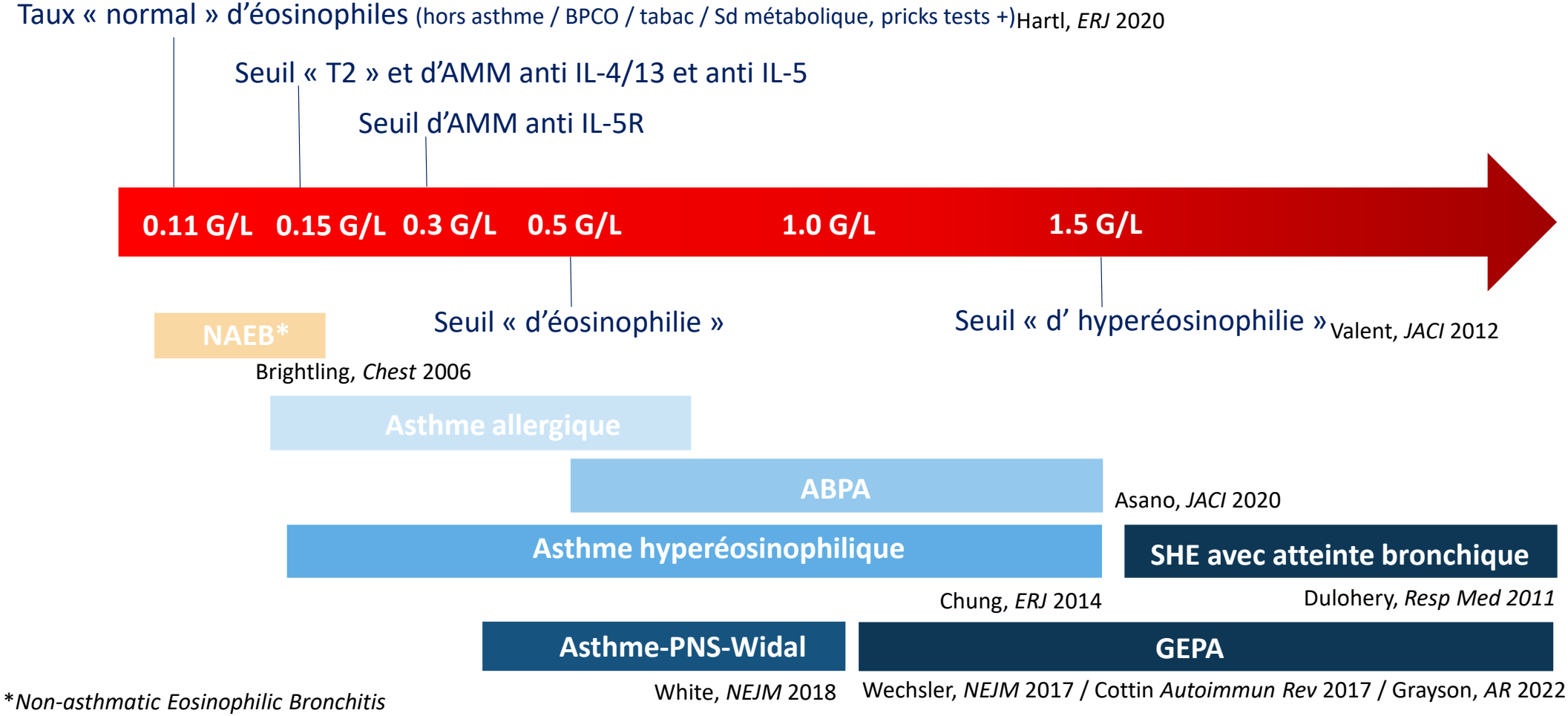
MaRIH

Filière de santé Maladies Rares Immuno-Hématologiques

Liens d’intérêt

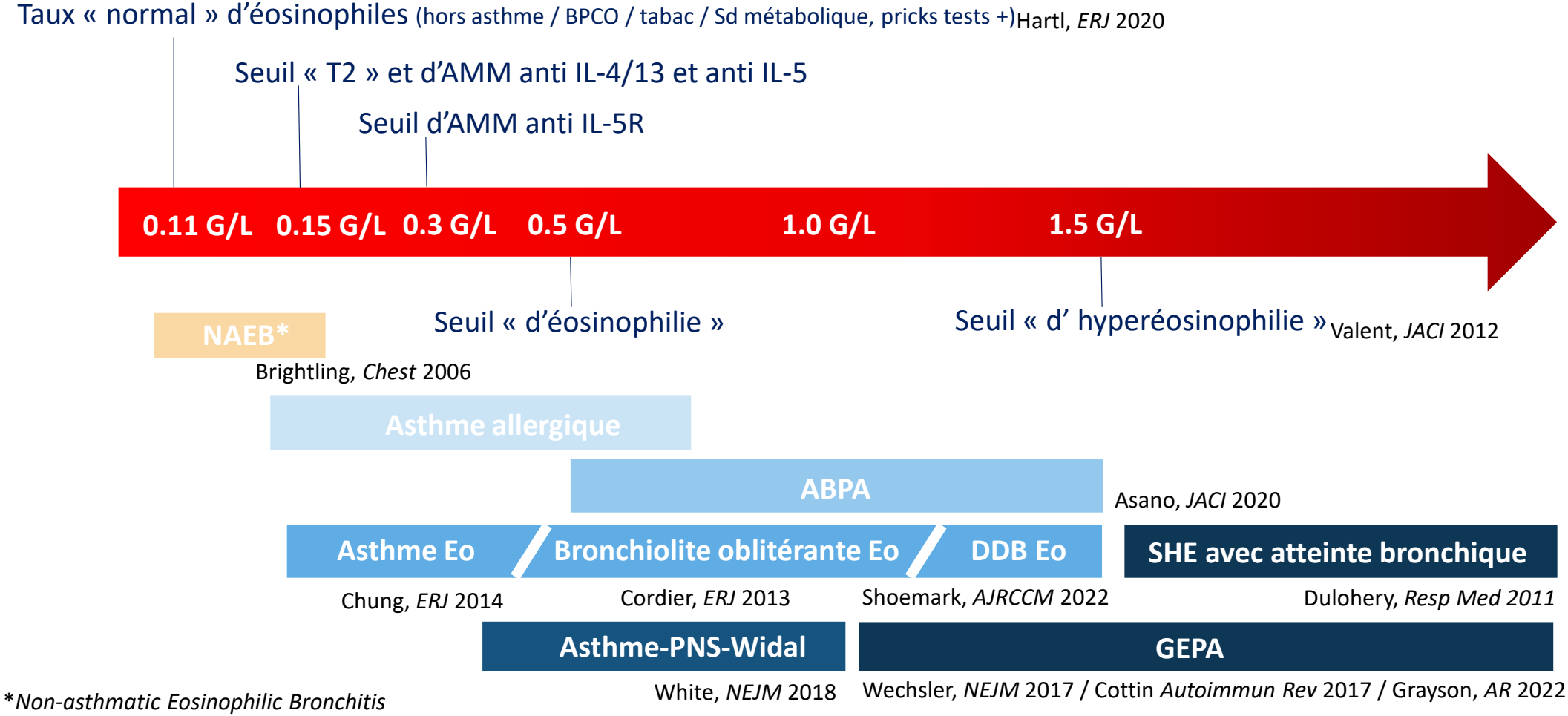
- **Expertises – Ad Board**: GSK, AstraZeneca, Sanofi.
- **Investigateur essais industriels**: GSK, AstraZeneca.

Asthme hyperéosinophilique



**Non-asthmatic Eosinophilic Bronchitis*

Asthme hyperéosinophilique



**Non-asthmatic Eosinophilic Bronchitis*

Asthme hyperéosinophilique

Taux « normal » d'éosinophiles (hors asthme / BPCO / tabac / Sd métabolique, pricks tests +) Hartl, *ERJ* 2020

Seuil « T2 » et d'AMM anti IL-4/13 et anti IL-5

Seuil d'AMM anti IL-5R

0.11 G/L **0.15 G/L** **0.3 G/L** **0.5 G/L** **1.0 G/L** **1.5 G/L**

Seuil « d'éosinophilie »

Seuil « d' hyperéosinophilie » Valent, *JACI* 2012

Vrai changement de maladie … ou « simple » continuum ?

Quand s'inquiéter ?

Comment raisonner ?

Asthme Eo Chung, *ERJ* 2014

Bronchiolite oblitérante Eo Cordier, *ERJ* 2013

DDB Eo Shoemark, *AJRCCM* 2022

SHE avec atteinte bronchique Dulohery, *Resp Med 2011*

Asthme-PNS-Widal White, *NEJM* 2018

GEPA Wechsler, *NEJM* 2017 / Cottin *Autoimmun Rev* 2017 / Grayson, *AR* 2022

#1: Et si c’était un parasite ?

F, 68 ans

- ATCD
  - HTA (ARA2)
  - Tabac 4 PA (sevré depuis 6 ans)
  - Aucun voyage à l'étranger

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  - Aucun voyage à l'étranger
- HDM:
  - Dyspnée progressive, toux, rhinorrhée
  - Hospitalisation
    - Dyspnée d'effort, toux sèche +++, **sibilants**, ronchi
    - **Bio: 7000 Eo** (normaux 6 mois avant)
    - ETT, ECG, tropo RAS

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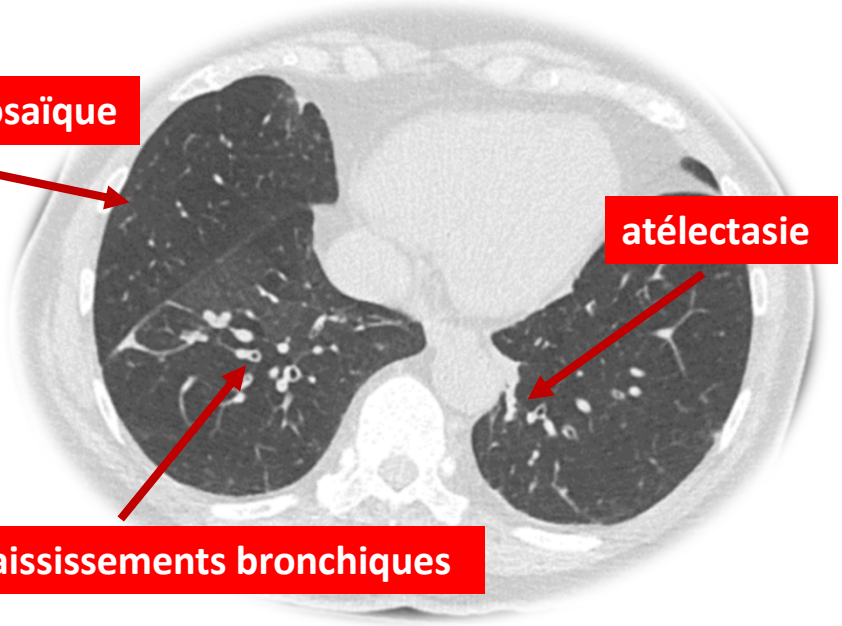

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    - **Bio: 7000 Eo** (normaux 6 mois avant)
    - ETT, ECG, tropo RAS
    - TDM: **épaississements des parois bronchiques, impactions mucoïdes**
    - EFR: diminution des débits distaux
    - CRP 20 mg/l, IgE totales 750 kUI/L, tryptase, B12, ANCA RAS

		Pré	Théo	%Théo	Z-Score	Post BD	%Théo	%Post/Pr
Substance						....		
Dose						.4...		
Capacité Vitale Lente	L	1.93	2.54	76		2.21	87	114
VRE	L	0.38	0.67	56		0.78	116	206
VT								93
CRFpl								110
VR								96
CPT								104
VR % CPT								92
CVF								104
VEMS								108
VEMS % CVF								104
DEP								104
DEM 75								121
DEM 50	L/s	0.81	3.38	24		0.93	27	114
DEM 25	L/s	0.27	1.09	25		0.29	27	108
DEMM 25/75	L/s	0.66	2.61	25		0.77	30	116
Zone expir. D/V	L*L/s	2.42				2.90		120

Toxocarose (sérologie + WB):

→albendazole 2 semaines

→rémisson clinique / bio …

Intérêt du traitement antiparasitaire d'épreuve

Eo < 500-1500 en métropole	Eo > 1500 en métropole	Eo > 1500 en zone endémique
Oxyure Taenia Gale Kyste hydatique Echinococcose	**Toxocarose** Distomatose Trichinose Anisakiase Ascaridiose	**Anguillulose** **Bilharziose** Filariose Ankylostomiose Ascaridiose

➢ **Flubendazole:**
- 100 mg/j pdt 3j
- + monoprise à J15

ou **Albendazole:**
- 400 mg X2/j pdt 3j
- + monoprise à J15

➢ **Albendazole:**
- 400 mg X2/j pdt 5-15j

➢ **Ivermectine:**
- 200 µg/j à jeun

+ **Praziquantel**
- 40 mg/kg dose unique

+ **Albendazole**
- 400 mg X2 pdt 5-15j

PNDS HE et SHE, 2022

Il faut parfois être patient…

#2: Et si c’était une GEPA ?

#2: Quel type de GEPA ?

GEPA: corrélation ANCA vs. phénotype

	GEPA ANCA-positive (10 – 30%)	GEPA ANCA-négative (70 – 90%)
ANCA	Positifs (quasi exclusivement anti-MPO)	absents
Asthme	présent	présent
Atteinte cardiaque	rare	fréquente
Atteinte SNC	AVC hémorragiques	AVC ischémiques jonctionnels « derniers prés »
GN extra-capillaire	possible	absente
HIA	possible	absente
Atteinte SNP	mononeuropathie unique / multiple	polyneuropathie
Sclérite	possible	absente
Vascularite	présente	présente
CRP	augmentée	variable

Sinico, *Arthritis Rheum* 2005 / Comarmond, *Arthritis Rheum* 2013 / Chang, *JACI In Pract* 2020 / Leurs *JACI In Pract* 2018 / Nishi, *Neurology* 2020

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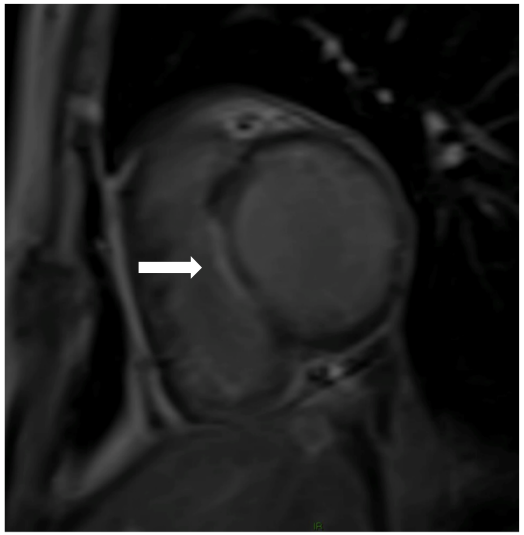
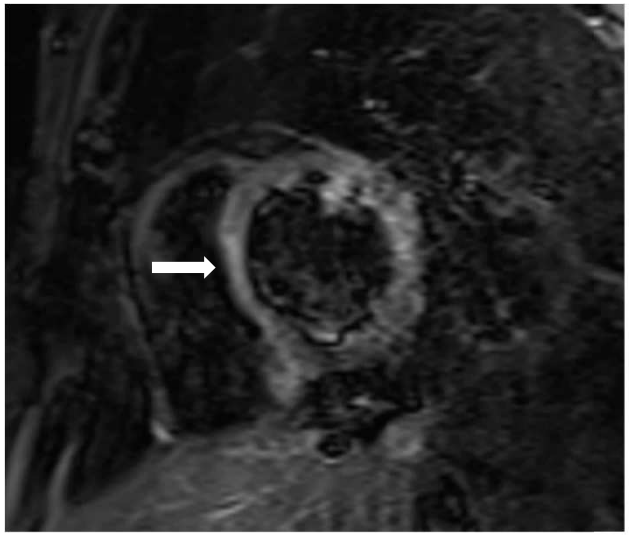
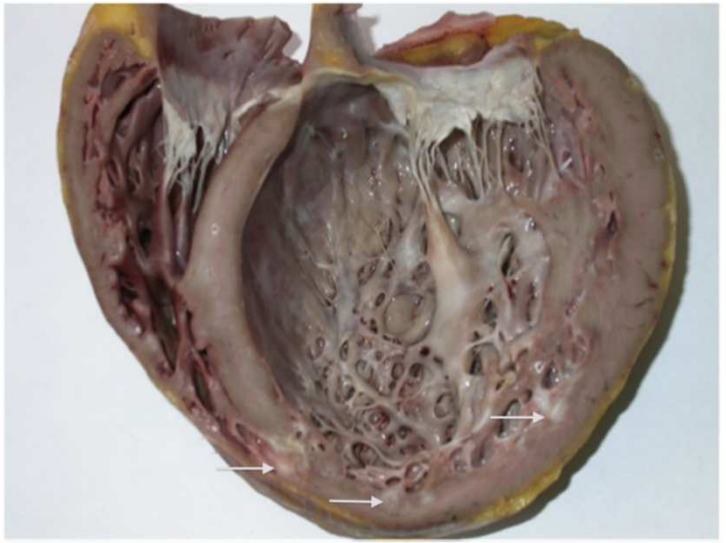
GEPA: focus sur l'atteinte cardiaque



Prise de contraste septale du ventricule gauche (petit axe, T1 Gado)



Hypersignal septal (petit axe, T2)



Fibrose endomyocardique

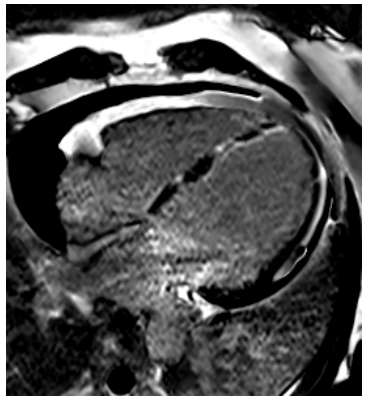
- N = 9 patients transplantés
- **Tous ANCA-négatifs**

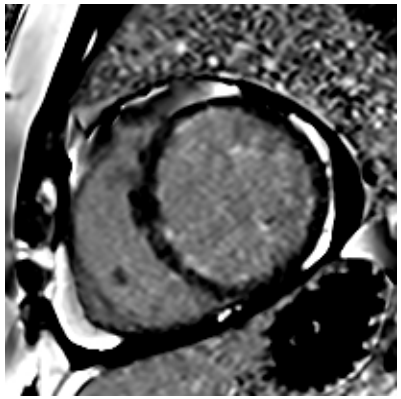
Groh et al, *J Heart Lung Transplant* 2014

Cardiopathie à éosinophiles

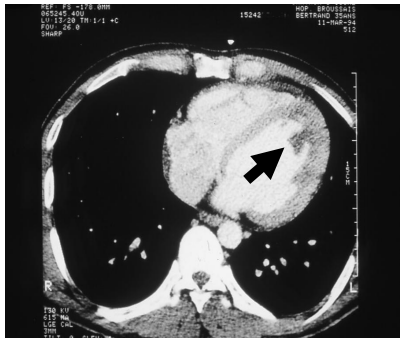
3 phases successives :

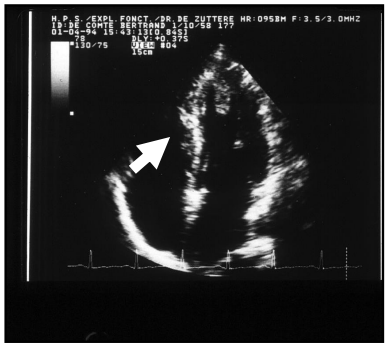
1. **Myocardite à éosinophiles**
   - BAV, ICardiaque aiguë
   - IRM: PDC sous-endocardique non systématisée à un territoire coronarien
   - Atteinte microvasculaire ?



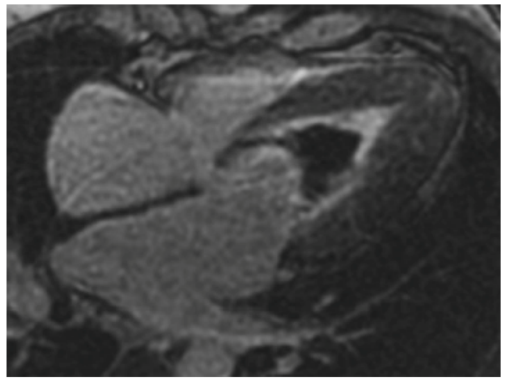


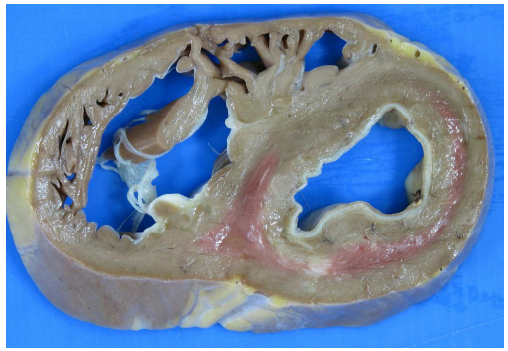
2. **Thrombi au contact**
   - emboles





3. **Fibrose endomyocardique**

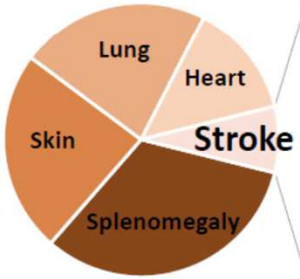




Ogbogu et al, *Immunol Allergy Clin N Am* 2007 / Fassnacht et al, *Transplantation* 2015

AVC « derniers prés » et SHE FIP1L1-PDGFRA+

FIP1L1-PDGRFA (F/P) fusion transcript → Clonal Hypereosinophilic syndrome : *F/P* Myeloproliferative Neoplasm with Eo → Highly sensitive to low-dose Imatinib



Clinical Features of 151 patients with F/P MN-Eo

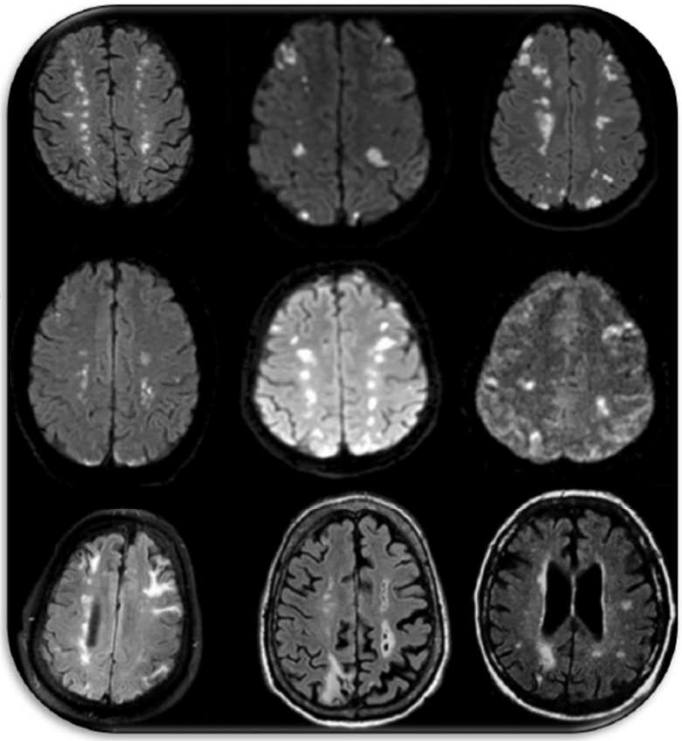
No cardiac involvement

Eosinophilic Cardiomyopathy without features of cardio embolism

Probable Cardioembolic Stroke

16 patients (10%) with Stroke :

- Median age: 51 years old
- Median Eosinophil Count: 12.8 G/L
- Median NIHSS: 4



69% with bilateral watershed distribution

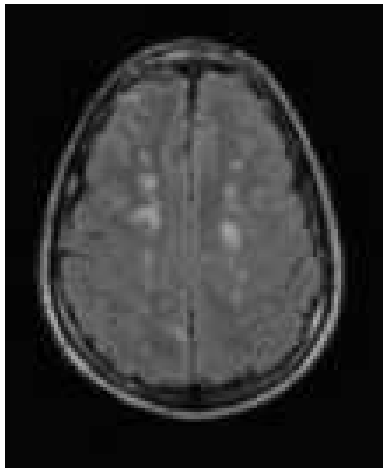
→ **Treatable cause of ischemic stroke**

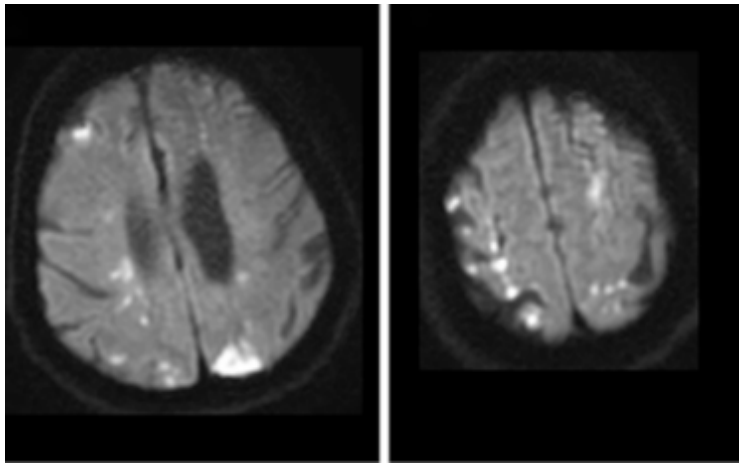
→ **Possibly multifactorial process: cardioembolism and/or eosinophil-related endothelial toxicity ?**

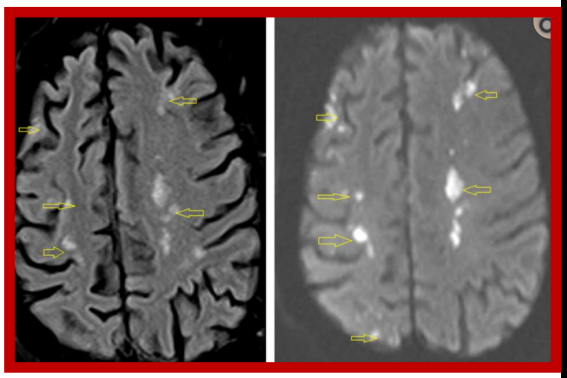
Tennenbaum, Groh et al, *Stroke* 2021

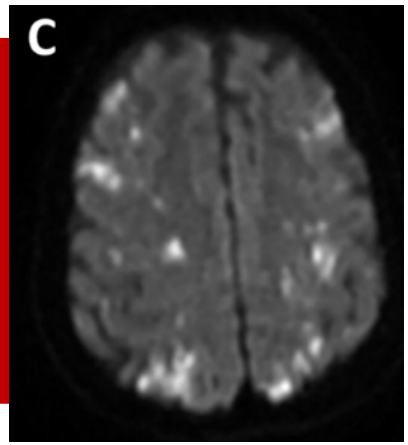
AVC « derniers prés » et maladies à éosinophiles

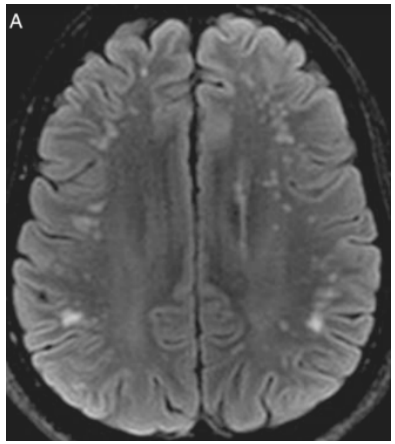
- Bilharziose aigue
  - 19 ans, IRM cardiaque normale, 12 G/L
- Prise de Famotidine
  - 60 ans, ETT normale, 8 G/L
- **GEPA (Churg-Strauss)**
- SHE lymphoïde CD3-CD4+
- Cancer
  - SCA concomitant
  - 18G/L











Gandière Perez, *Clin Infect Dis* 2013 / Wu, *J Neurol* 2012 / André *Autoimmun Rev* 2017 / Lefevre, *Medicine* 2014 / Minupuri *Cureus* 2020

Alors finalement… SHE ou GEPA ?

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Comarmond, *Arthritis Rheum* 2013 / André, *Autoimmun Rev 2016 /* Chang, *JACI In Pract* 2020 / Leurs *JACI In Pract* 2018 / Nishi, *Neurology* 2020

Analogies entre GEPA ANCA-négative et SHE

	GEPA ANCA-négative (70 – 90%)	SHE
ANCA	absents	absents
Asthme	présent	possible
Atteinte cardiaque	fréquente	possible
Atteinte SNC	AVC ischémiques jonctionnels « derniers prés »	AVC ischémiques jonctionnels « derniers prés »
GN extra-capillaire	absente	absente
HIA	absente	absente
Atteinte SNP	polyneuropathie	polyneuropathie
Sclérite	absente	absente
Vascularite	présente	possible
CRP	variable	**basse** (sauf thrombose ou myocardite)

Comarmond, *Arthritis Rheum* 2013 / André, *Autoimmun Rev 2016 /* Chang, *JACI In Pract* 2020 / Leurs *JACI In Pract* 2018 / Nishi, *Neurology* 2020

Alors finalement… SHE ou GEPA ?

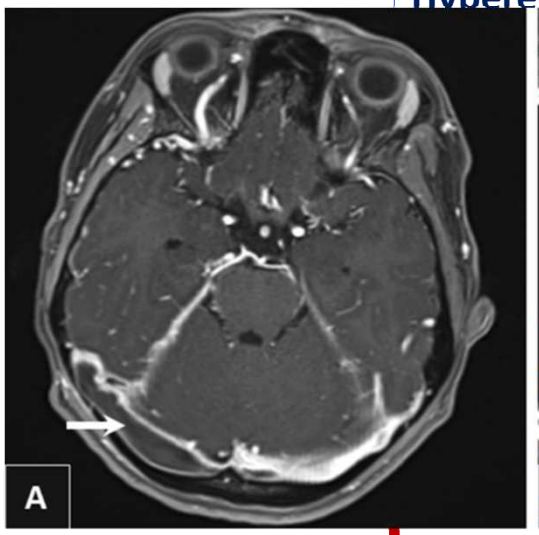
- Peu importe ?!
- **Ce qui compte c'est de dépister les complications et de traiter les complications liées à l'éosinophilie**
- Le mépolizumab prochainement disponible avec ls deux libellés d'AMM

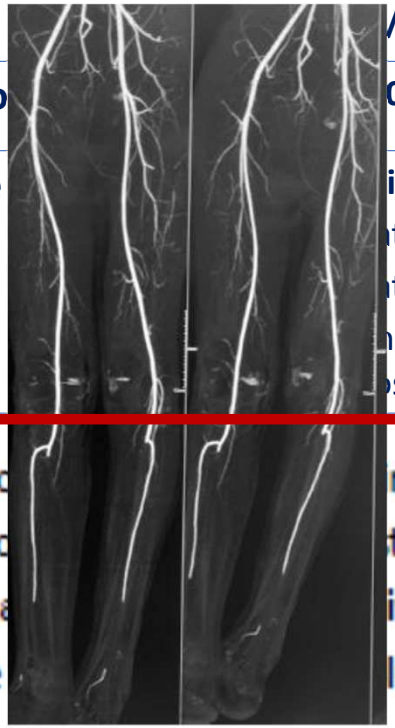
#3: Et si c'était un SHE ? (au fait c'est quoi un SHE ?)

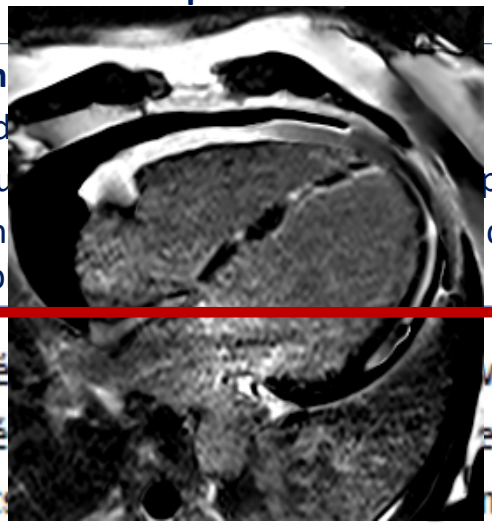
Éosinophilie sanguine	**PNE> 500/mm³**
Hyperéosinophilie (HE)	**PNE> 1500 /mm³ à deux reprises à un mois d'intervalle**
HE tissulaire	**Hyperéosinophilie tissulaire** définie par: - Infiltrat médullaire par des PNE >20% - Infiltrat tissulaire à PNE jugé extensif par le pathologiste - Présence en IHC de dépôts extra-cellulaires de protéines cationiques de l'éosinophile
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 sanguine ± tissulaire** ET **Atteinte ou dysfonction d'organe attribuable aux éosinophiles** ET **Exclusion des autres causes pouvant mener à l'atteinte d'organe**

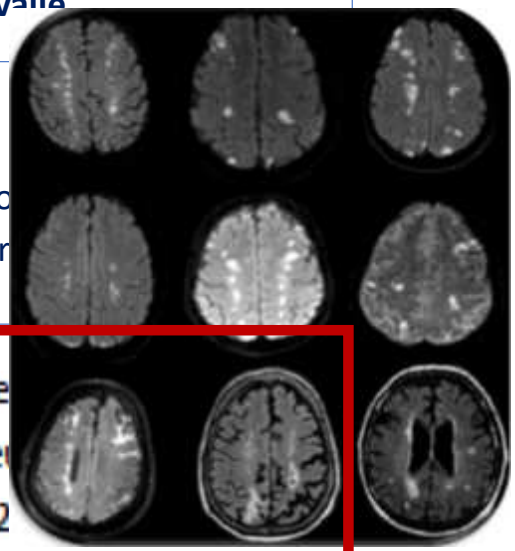
Valent, *J Allergy Clin Immunol* 2012

#3: Et si c'était un SHE ?









Éosinophilie	**/mm³**
Hyperéosino	**0 /mm³ à deux reprises à un mois d'interva**
ulaire	**inoph**
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nce en	de pr
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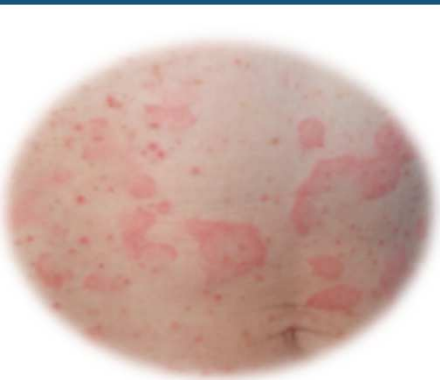
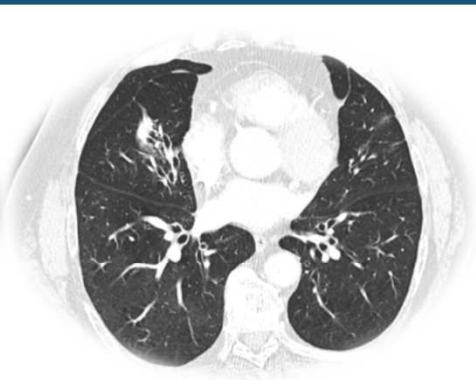
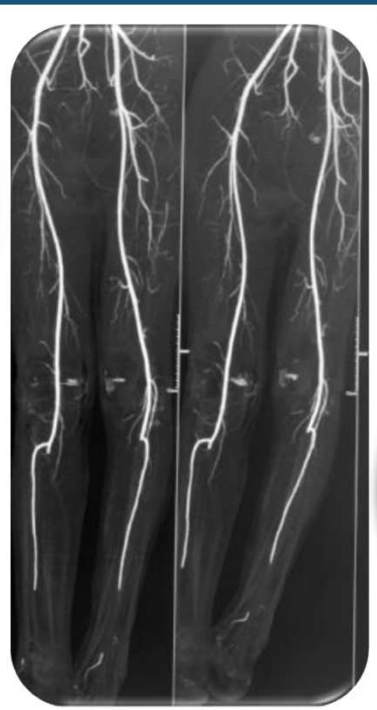
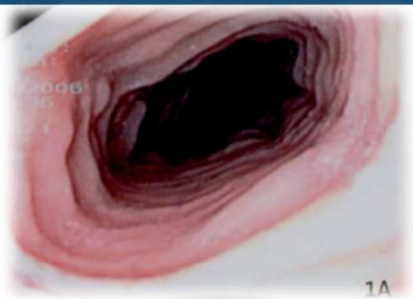
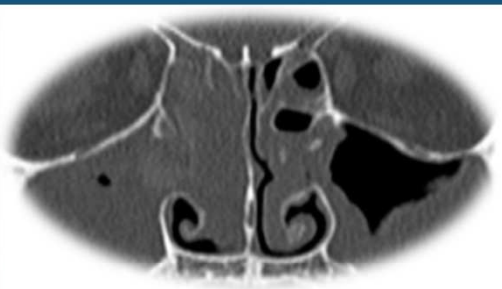
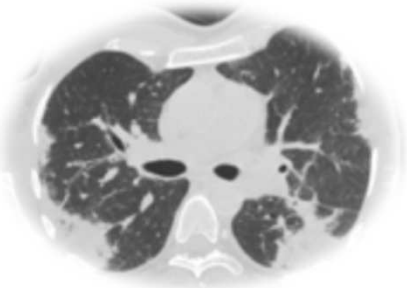
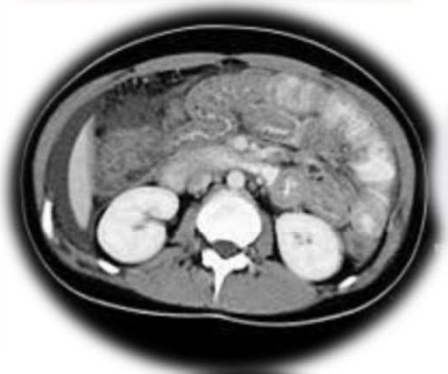
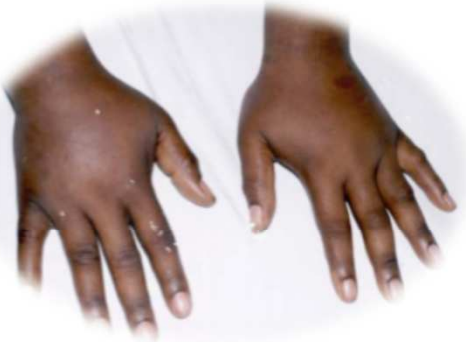
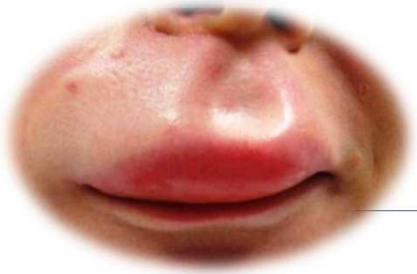
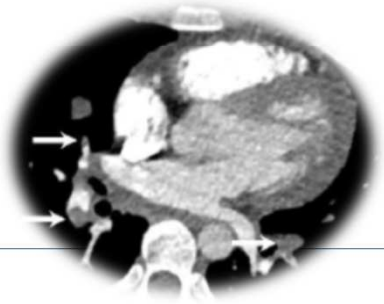
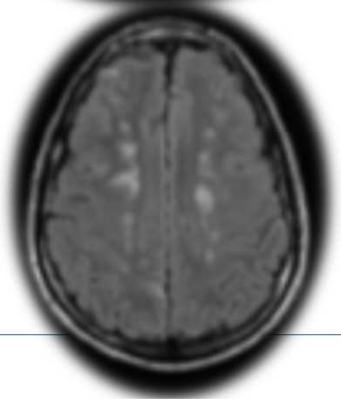
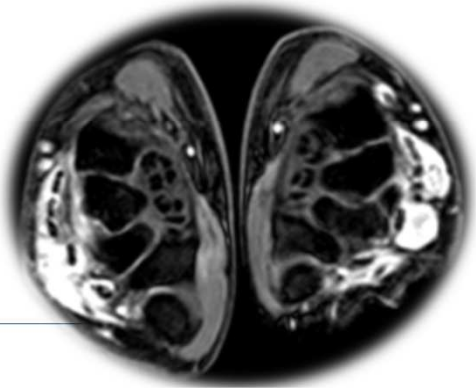
compatible	lution entre l'atteinte d'organe et l'HE sanguine.
Syndrome hyperéosinophilique (SHE)	**Hyperéosinophilie sanguine ± tissulaire** ET **Atteinte ou dysfonction d'organe attribuable aux éosinophiles** ET **Exclusion des autres causes pouvant mener à l'atteinte d'organe**

Valent, *J Allergy Clin Immunol* 2012

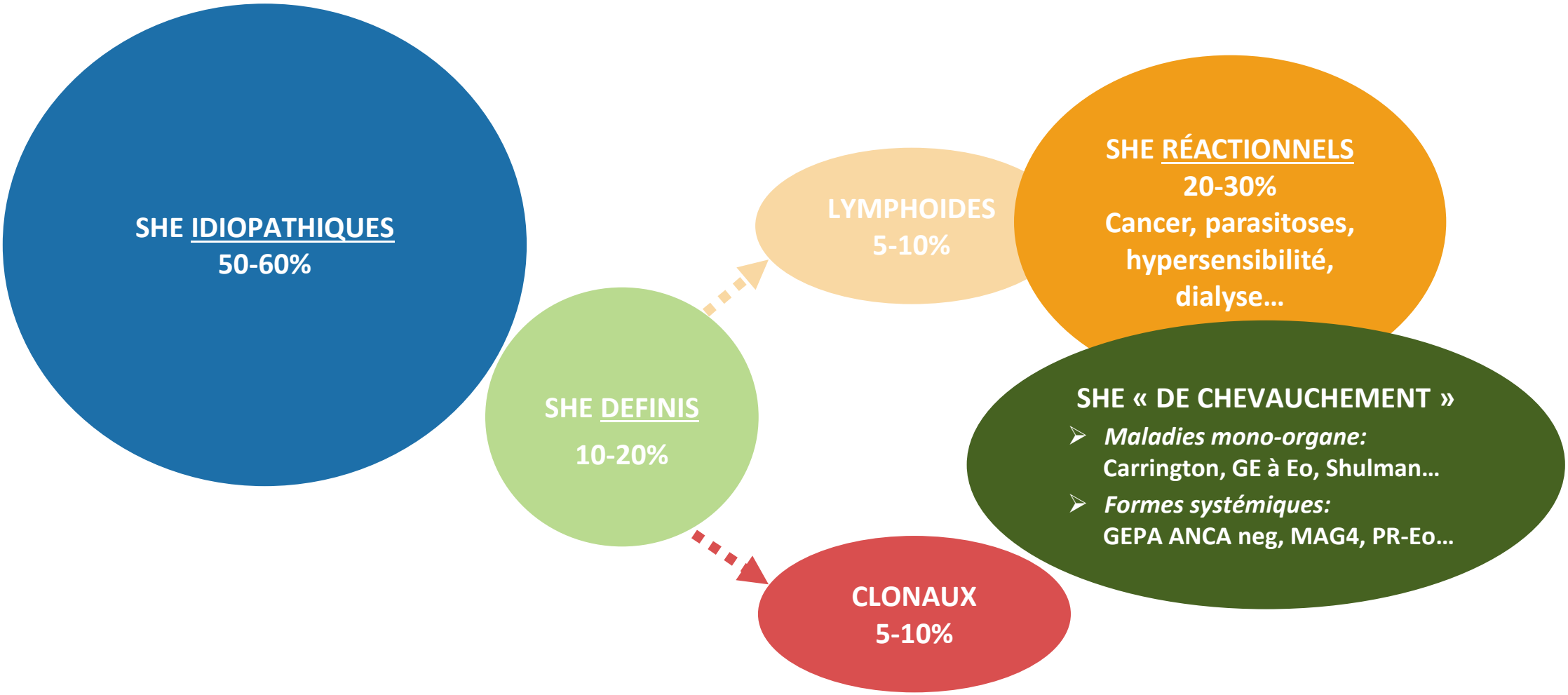
Diversité des manifestations cliniques de SHE

Classification des SHE



Variant myéloïde (leucémie FIP1L1-PDGFRA+)

Received: 19 July 2020 | Accepted: 23 July 2020
DOI: 10.1002/ajh.25945

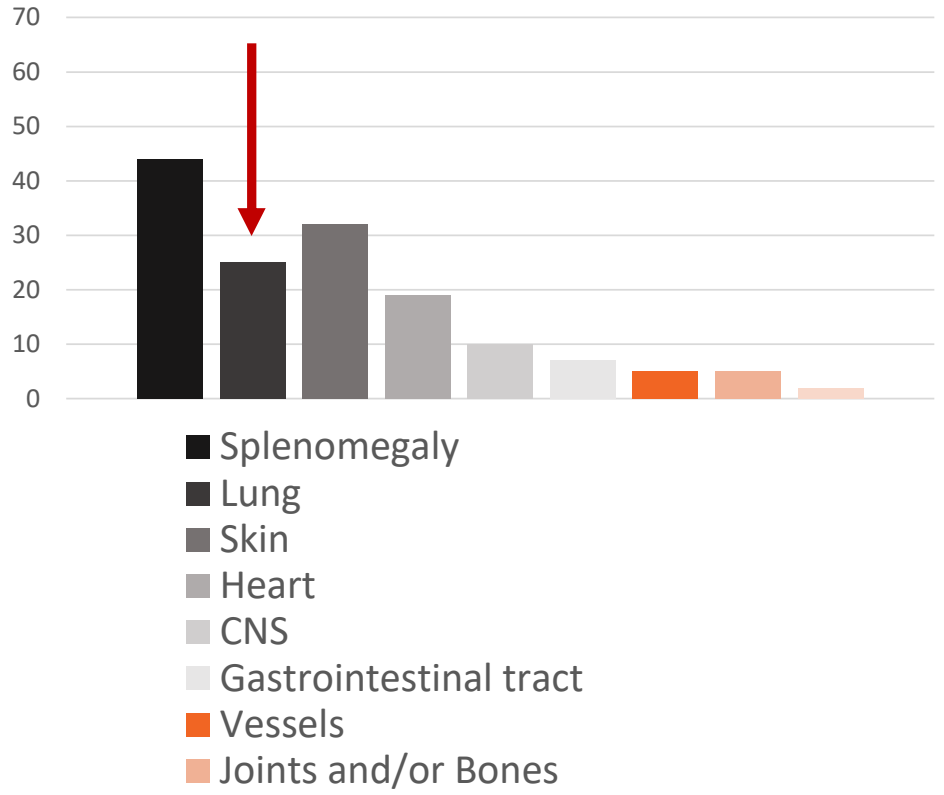
RESEARCH ARTICLE

Epidemiology, clinical picture and long-term outcomes of FIP1L1-PDGFRA-positive myeloid neoplasm with eosinophilia: Data from 151 patients

Julien Rohmer[1,2] | Amélie Couteau-Chardon[1,3] | Julie Trichereau[1,4] | Kewin Panel[1,4] | Cyrielle Gesquiere[1] | Raouf Ben Abdelali[5] | Audrey Bidet[6] | Jean-Sébastien Bladé[7] | Jean-Michel Cayuela[8] | Pascale Cony-Makhoul[1,9] | Vincent Cottin[10,11] | Eric Delabesse[12] | Mikaël Ebbo[1,13] | Olivier Fain[14] | Pascale Flandrin[15] | Lionel Galicier[16] | Catherine Godon[17] | Nathalie Grardel[18] | Aurélien Guffroy[1,19] | Mohamed Hamidou[1,20] | Mathilde Hunault[21] | Etienne Lengline[22] | Faustine Lhomme[23] | Ludovic Lhermitte[24] | Irène Machelart[1,25] | Laurent Mauvieux[26] | Catherine Mohr[27] | Marie-Joelle Mozicconacci[28] | Dina Naguib[29] | Franck E. Nicolini[30] | Jerome Rey[31] | Philippe Rousselot[32] | Suzanne Tavitian[33] | Louis Terriou[1,34] | Guillaume Lefèvre[1,34] | Claude Preudhomme[18] | Jean-Emmanuel Kahn[1,35] | Matthieu Groh[1,2] | CEREO and GBMHM collaborators

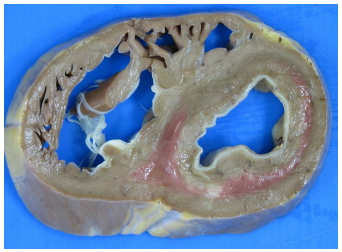
Rohmer, *Am J Hematol* 2020

- Moyenne = 0,18 cas/an/million
- 143 hommes et 8 femmes

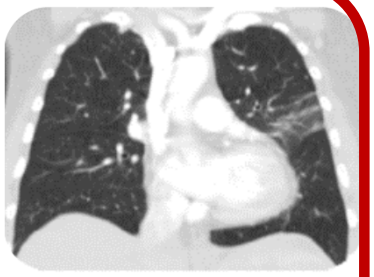


Variant myéloïde (leucémie FIP1L1-PDGFRA+)

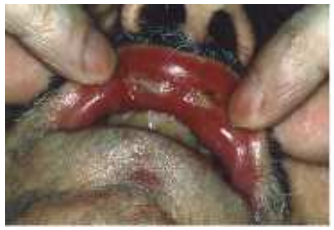
- **Fibrose endomyocardique (n=17)**
  - 3 patients avec ETT normale et IRM anormale
- **Myocardite** (n=6)
- 25 % ETT anormales
- 2 Transplantations cardiaques



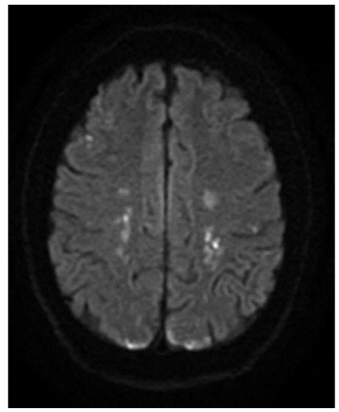
- **Toux (n=43, 28%)**
- Peu d'EFR
- Asthme (n=7)
  - **GEPA (n = 3)**
- Embolie pulmonaire (n=1)



- **Eczema (n=9), prurit (n=9)**
- Ulcerations buccales
- Hémmoragies sous-unguéales
- **Papulose lymphomatoïde (n=11)**



- **AVC ischémiques (n=14)**
- **Multi-systématisés (n=14)**
- Emboliques (n=4)
- Gadolinium enhancement
- Microthrombi et/ou vascularite?



Rohmer et al, *Am J Hematol* 2020

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RESEARCH ARTICLE

AJH WILEY

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Rohmer, *Am J Hematol* 2020

- Atteinte respiratoire fréquente …
  mais d'une **maladie EXCEPTIONNELLE !**
- **Pas de recherche de FIP1L1-PDGFRA en 1ère intention**
  (à fortiori si femme, corticosensible…)
- Explorations hématologiques « raisonnées »

Proportion de patients avec 0,1,2, 3 ou 4 paramètres:

< 10%	Vitamine B12 > 700 pg/ml
10-30%	Tryptase > 15 ng/ml
>30%	Sexe masculin
	Splénomégalie

	n	n=44
0	0	0%
1	1	2%
2	5	11%
3	22	50%
4	16	36%

… 100% de corticorésistance !

H, 30 ans

Cogan, *NEJM* 1994

BRIEF REPORT: CLONAL 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.

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- IgM = 79 g/l (poly) – IgE = 2000 UI/L

GEPA ?

SHE lymphoïde 3-4+: le cas princeps

The NEW ENGLAND JOURNAL of MEDICINE

Cogan, *NEJM* 1994

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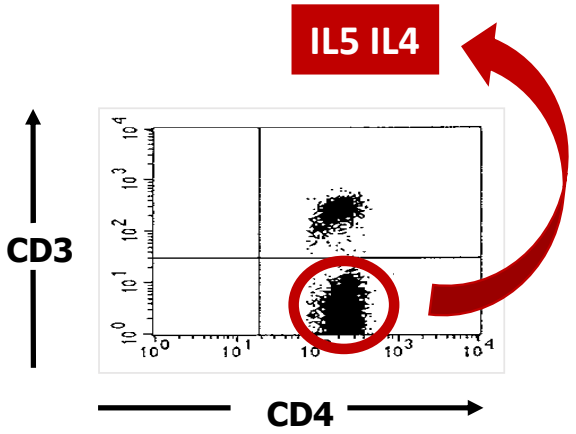

SHE lymphoïde

The Lymphoid Variant of Hyp

Study of 21 Patients With CD3-CD4

Guillaume Lefevre, MD, Marie-Christine Copin, MD
Martine Avenel-Audran, MD, Hélène Aubert, MD, Ala
Hervé Maisonneuve, MD, Kamel Ghomari, MD, Félix A
André Baruchel, MD, PhD, David Launay, MD, PhD,
Chahera Khouatra, MD, Chafika Morati-Hafsa
Raphäel Borie, MD, François Cotton, MD
Franck Morschhauser, MD, PhD, Jacques Tra
Monique Capron, PharmD, PhD, Pierre-Yves Ha
Jean-Emmanuel Kahn, MD, PhD, and

Eosinophilia Associa CD3⁻CD4⁺ T Cells: and Outcome of a Si Cohort of 26 Patient

Caroline Carpentier[1†], Sylvain Verbanck[1†], Liliane Anne-Laure Trépant[4], Elie Cogan[1] and Florence

CENTRE DE REFERENCE SYNDROMES HYPEREOSINOPHILIQUES
Institut d'Immunologie – CHRU Lille - Docteur Guillaume LEFEVRE
Secrétariat: Mme Sylvie FIEVET-KEIRLE ou Mme Cyrielle GESQUIERE-LASSELIN
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EXPLORATION D'UNE HYPEREOSINOPHILIE CHRONIQUE

Date de Prélèvement : ..... / ..... / ..... Heure de prélèvement : ..... : .....
NOM de naissance : .....
PRENOM Complet du Patient : .....
SEXE : F ☐ M ☐ DATE de NAISSANCE : ..... / ..... / .....
NOM (Marital) Complet du Patient : .....

Etiquette patient

Centre demandeur : ..... Service : .....
Médecin prescripteur : ..... Téléphone : .....
Mail du prescripteur : .....

1. **REMPLIR IMPERATIVEMENT LA FICHE DE RENSEIGNEMENTS CLINIQUES (PAGE 2)**

2. **EXAMENS DEMANDES FACTURES : A COCHER SUR CETTE PAGE**

CADRE RECEPTION
- Enregistrement des pages 1 et 2 et analyses cochées:
  OPEN : COMEOS
  MOLIS : COMEOS
- Scanner Pages 1 et 2 pour tous les dossiers

- **Phénotypage lymphocytaire (SHE lymphoïde)** (Enregistrement Open : EOHP , Molis: EOHP)
  ☐ Bilan initial (dépistage) *Sang, EDTA 5 ml, transport à temp. ambiante (B80+BHN400)*
  ☐ Surveillance d'une population anormale (précisez, CD3-CD4+, CD3+CD4+CD7-, CD3+CD4-CD8-TCRab+) :
  ☐ Autre : _____
- **Dosage de Tryptase** (Enregistrement Open : TRYPT, Molis : TRYPT) *Sang, EDTA 5 ml, transport à temp. ambiante (B80)*

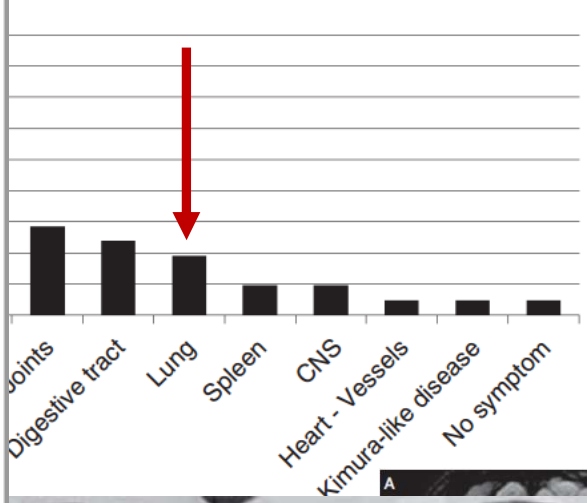
- **Caryotype médullaire conventionnel**
- **Recherche de réarrangements PDGFRA, PDGFRB, FGFR1 par hybridation *in situ* (FISH)** *Moelle, ou sang uniquement pour Eo > 1.5 G/L ou tri cellulaire envisageable sur appel préalable Tube héparine 5 ml, transport à temp. ambiante (B1000)*

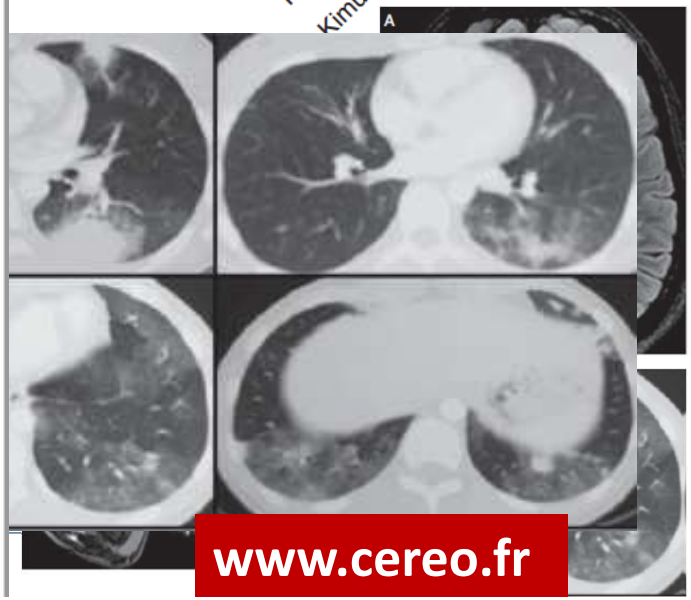
=> **COMPLETER IMPERATIVEMENT LA PAGE 3 PRE-REMPLIE POUR LE LABORATOIRE DE CYTOGENETIQUE**

- **Clonalité T (Réarrangements TCR gamma/delta)** *Sang ou Moelle, EDTA 5 ml, transport à 4°C (BHN 770)*
- **Recherche du transcrit FIP1L1-PDGFRA par RT-PCR** *Sang ou Moelle, EDTA 5 ml, transport à 4°C (BHN 420)*
- **Mutations géniques par NGS (panel SMP/SMD, 36 gènes) : *analyses réalisées uniquement en cas de suspicion d'hyperéosinophilie clonale persistante FIP1L1-PDGFRA nég, JAK2 nég sans anomalie au caryotype médullaire (voir détails des gènes étudiés sur notre site internet)*** *Sang ou Moelle, EDTA 5 ml, transport à 4°C (BHN 8170)*
- **Autres analyses (JAK2, BCR-ABL, panel NGS..) : selon contexte, voir page 4**

=> **COMPLETER IMPERATIVEMENT LA PAGE 4 PRE-REMPLIE POURLE LABORATOIRE D'HEMATOLOGIE**

PRELEVEMENTS A ENVOYER **DANS LES 24 HEURES (OU CONGELE BM)** PAR LE TRANSPORTEUR DE VOTRE CENTRE HOSPITALIER *(Transport à votre charge)* ACCOMPAGNES DE CETTE FICHE A :
Réception Biologie de Recours, CHRU de Lille, Centre de Biologie Pathologie
Rue Paul Nayrac - 59037 LILLE Cedex - **Tél. : 03.20.44.54.31**
MERCI DE PRIVILEGIER L'ENVOI DES TUBES AVANT JEUDI FIN DE MATINEE



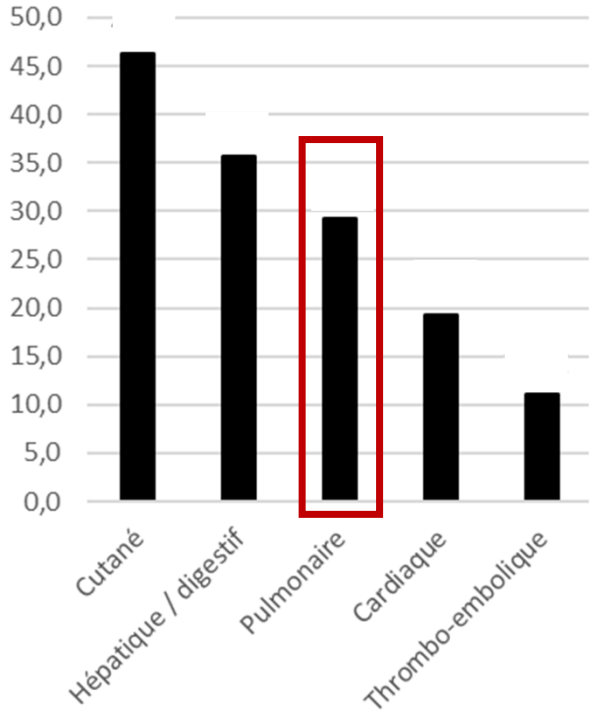


www.cereo.fr

Manifestations respiratoires des SHE

Cohorte nationale COHESion (août 2021)

N= 321 patients (S)HE



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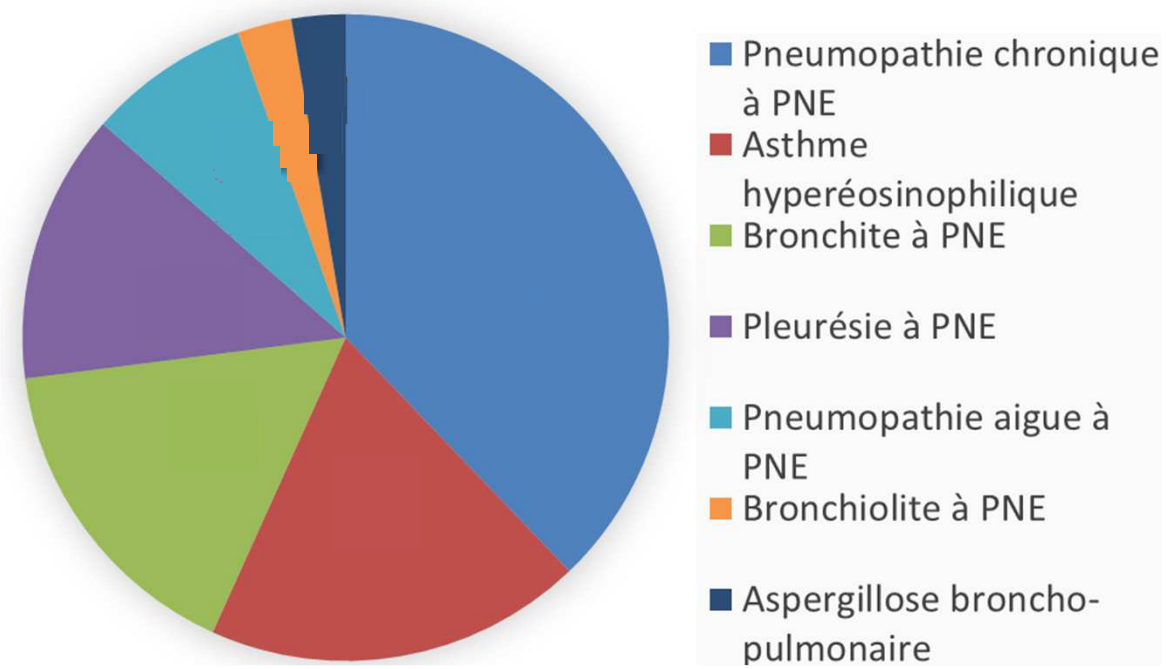
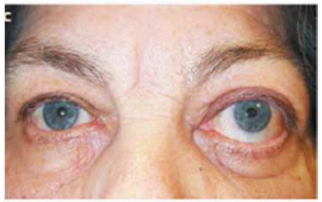
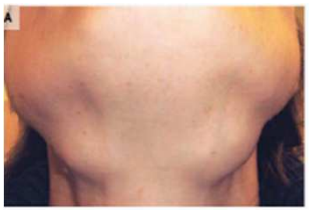


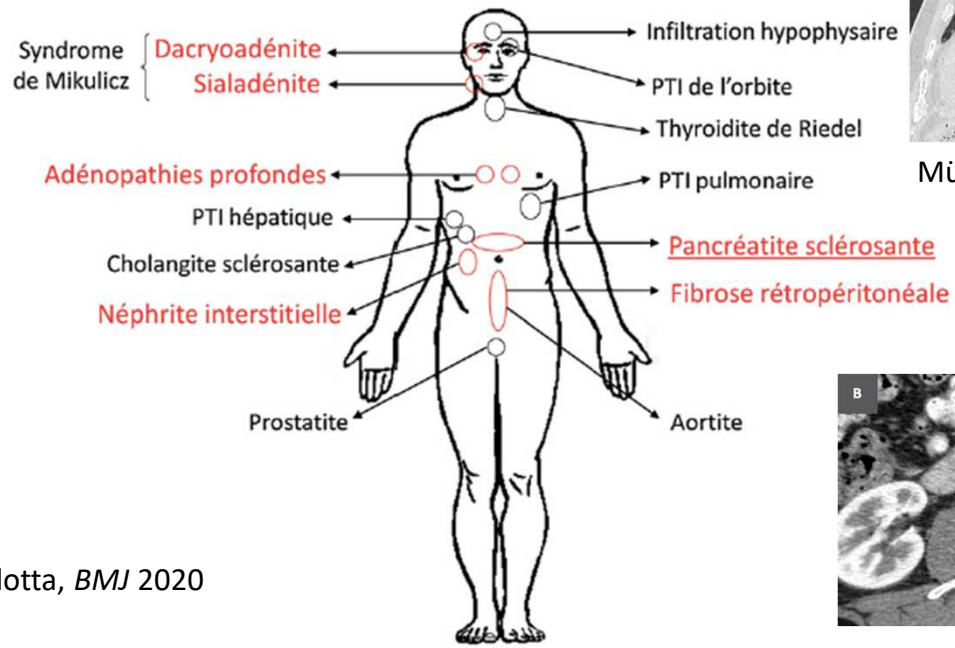
G Lefèvre, données non publiées

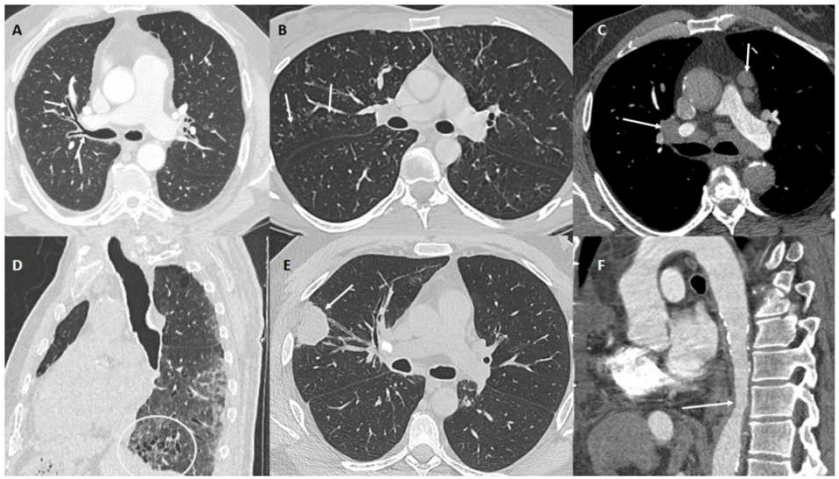
#4: Et si c'était une maladie associée aux IgG4 ?

- Maladie fibro-inflammatoire systémique d'origine inconnue
- Spectre très large
- **Asthme**
  - ➢ **jusqu'à 1/3 des patients**
  - ➢ associé à épaississements péribronchovasculaires et PID

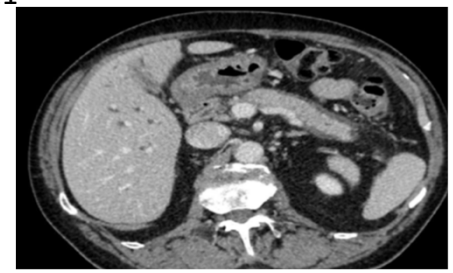


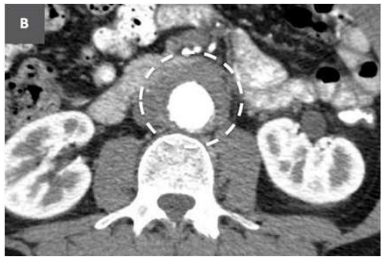






Müller, *Eur Resp Rev* 2021

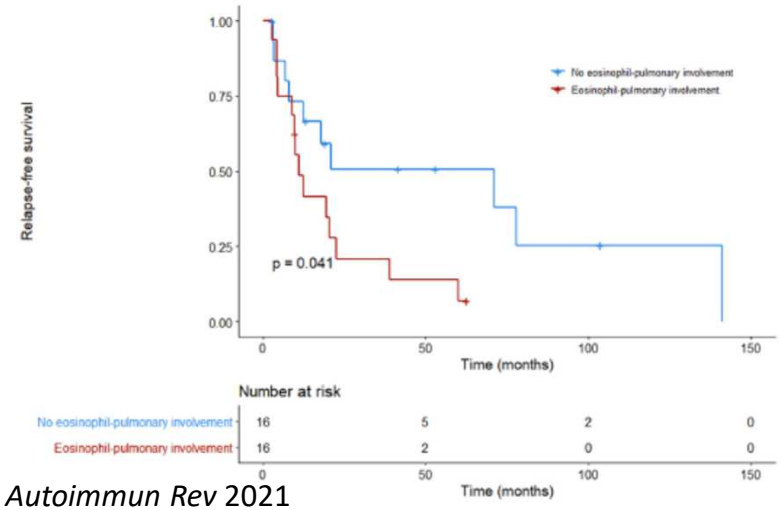




Stone, *NEJM* 2012 / Lanzillotta, *BMJ* 2020

Maladie associée aux IgG4 « hyperéosinophilique »

- Maladie fibro-inflammatoire systémique d'origine inconnue
- Spectre très large
- Asthme fréquent
- **Hyperéosinophilie**
  - 10 à 30% des patients, manifestations liées aux Eos possibles
  - **> 3000/mm³ : critère d'exclusion selon classification**
  - **mais en pratique ne doit pas faire écarter le diagnostic !**



Moussiegt et al, *Autoimmun Rev* 2021

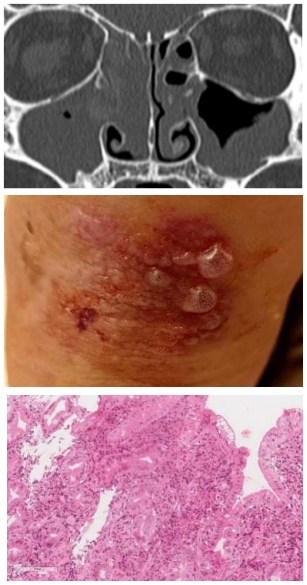


Table 1
Demographic, clinical, and biological features of 44 patients with IgG4-RD and eosinophilia.

	Total ($N = 44$)
Demographic data	
Male	36 (82)
History of atopy	16 (36)
Age at first symptom	57 [42–65]
CDC for IgG4-RD[1]	
Certain	29 (66)
Probable	5 (11)
Possible	10 (23)
Fulfilling ACR/EULAR classification criteria for IgG4-RD[2]	18 (41)
ACR/EULAR criteria score	30 (17–45)
Fulfilling modified ACR/EULAR criteria for IgG4-RD[3]	32 (73)
IgG4-RD organ involvement	
Age at Ig4-RD first symptom	57 [42–64]
Number of affected organs	3 [2–4]
Lymph nodes	28 (64)
Salivary glands	18 (41)
Pancreas	14 (32)
IgG4-related orbital disease	12 (27)
Lungs	13 (30)
Biliary tract	11 (25)
Kidney	11 (25)
[illegible]	5 (11)
Eosinophil-related organ involvements	
Age at first eosinophil-related organ involvement	57 [43–64]
Number of affected organs	1 [0–2]
Lungs	18/29 (62)
Skin	10/29 (34)
GI-tract	7/29 (24)
Heart	5/29 (17)
Peripheral arterial disease	4/29 (14)
Peripheral nervous system	3/29 (10)
Venous thrombosis	3/29 (10)
Main biological features	
Polyclonal hypergammaglobulinemia	38/40 (95)
High IgG4 levels	39/43 (91)
[illegible]	[illegible]
Peak absolute eosinophil count ($X10^3/mm^3$)	2.6 [1.6–7.2]
High total IgE level	28/34 (82)
High tryptase level	0/20 (0)
High vitamin B12 level	3/26 (12)
FIP1L1-PDGFRA fusion gene	0/12 (0)
Aberrant T-cell population	3/40 (8)
CD3−4+	*1/3 (33)*
CD3 + 4 + 7-	*1/3 (33)*
CD3 + 4-8- TCRab	*1/3 (33)*
Clonal TCR γ-gene rearrangement	6/18 (33)

Conclusion

Taux « normal » d'éosinophiles (hors asthme / BPCO / tabac / Sd métabolique, pricks tests +) Hartl, *ERJ* 2020

Seuil « T2 » et d'AMM anti IL-4/13 et anti IL-5

Seuil d'AMM anti IL-5R

NAEB*

Seuil « d'éosinophilie »

Seuil « d' hyperéosinophilie »

Valent, *JACI* 2012

Asthme allergique

SHE lymphoïde

SHE FIP+

IgG4

Asthme Eo / Bronchite éosinophilique / DDB

Asthme-PNS-Widal

GEPA ANCA neg / SHE

GEPA ANCA pos

**Non-asthmatic Eosinophilic Bronchitis*

#5: Une complication rare chez les patients T2 ?

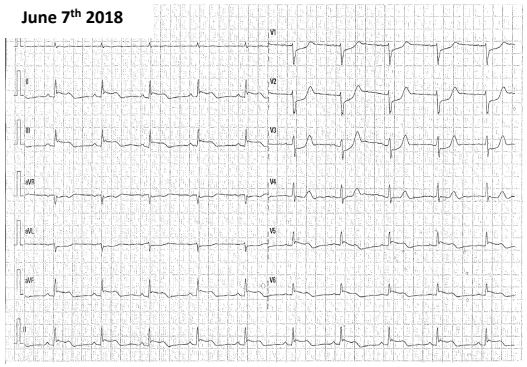
Margaux, 24 ans

- Sd Widal
- Asthme non traité
- PNS: ethmoïdectomie

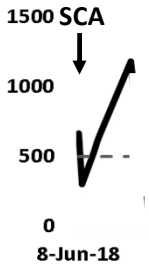
Margaux, 24 ans

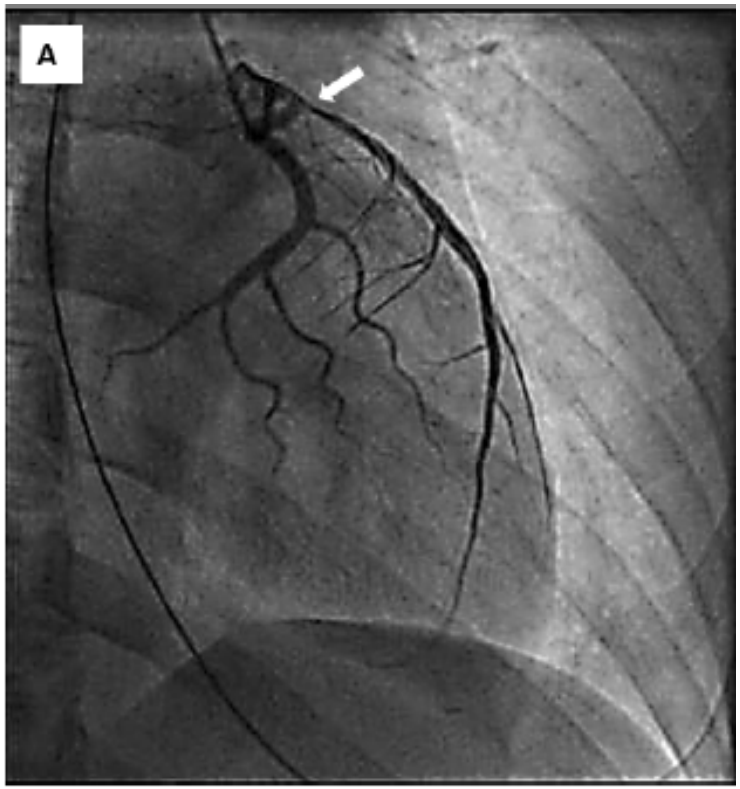
- Sd Widal
- Asthme non traité
- PNS: ethmoïdectomie

ECG



AEC (/mm3)





Margaux, 24 ans

Anti-eosinophil drugs

Prednisone (po) — 90mg qd

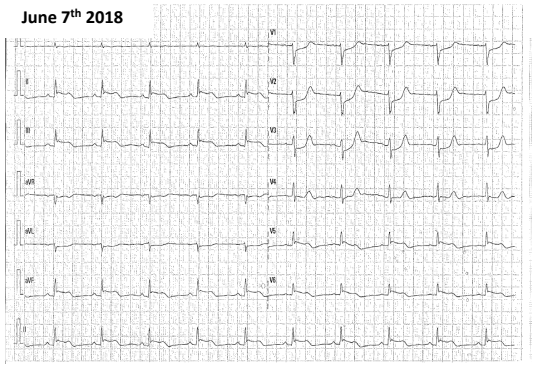
Vasodilators

Isosorbide dinitrate (iv)

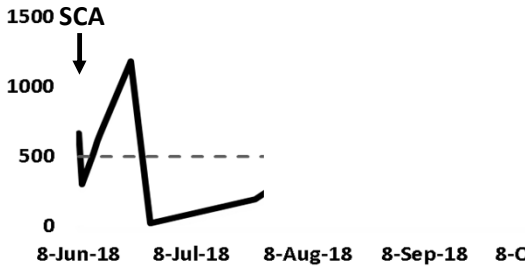
Verapamil (po) — 120mg qd

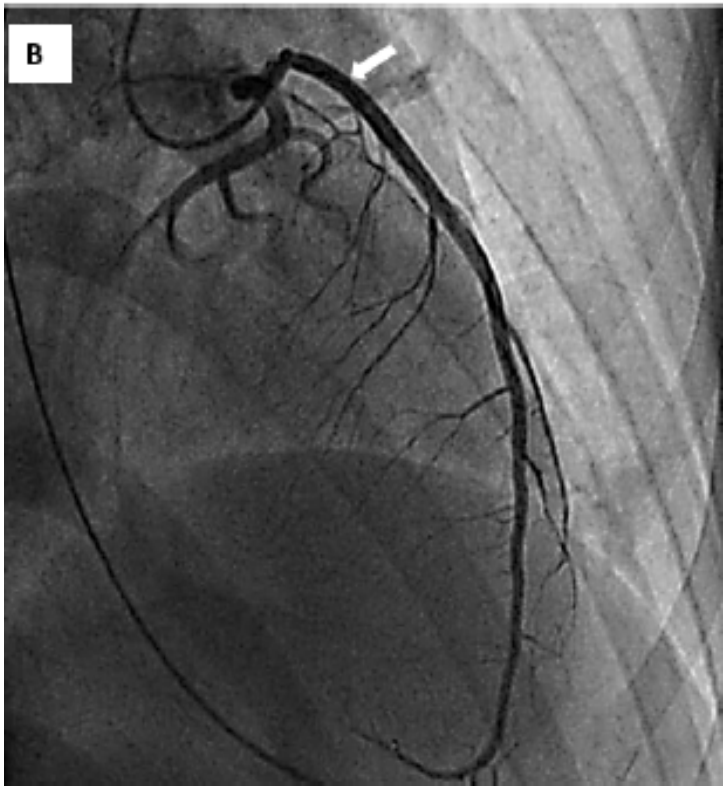
Nifedipine (po) — 30mg sr

ECG

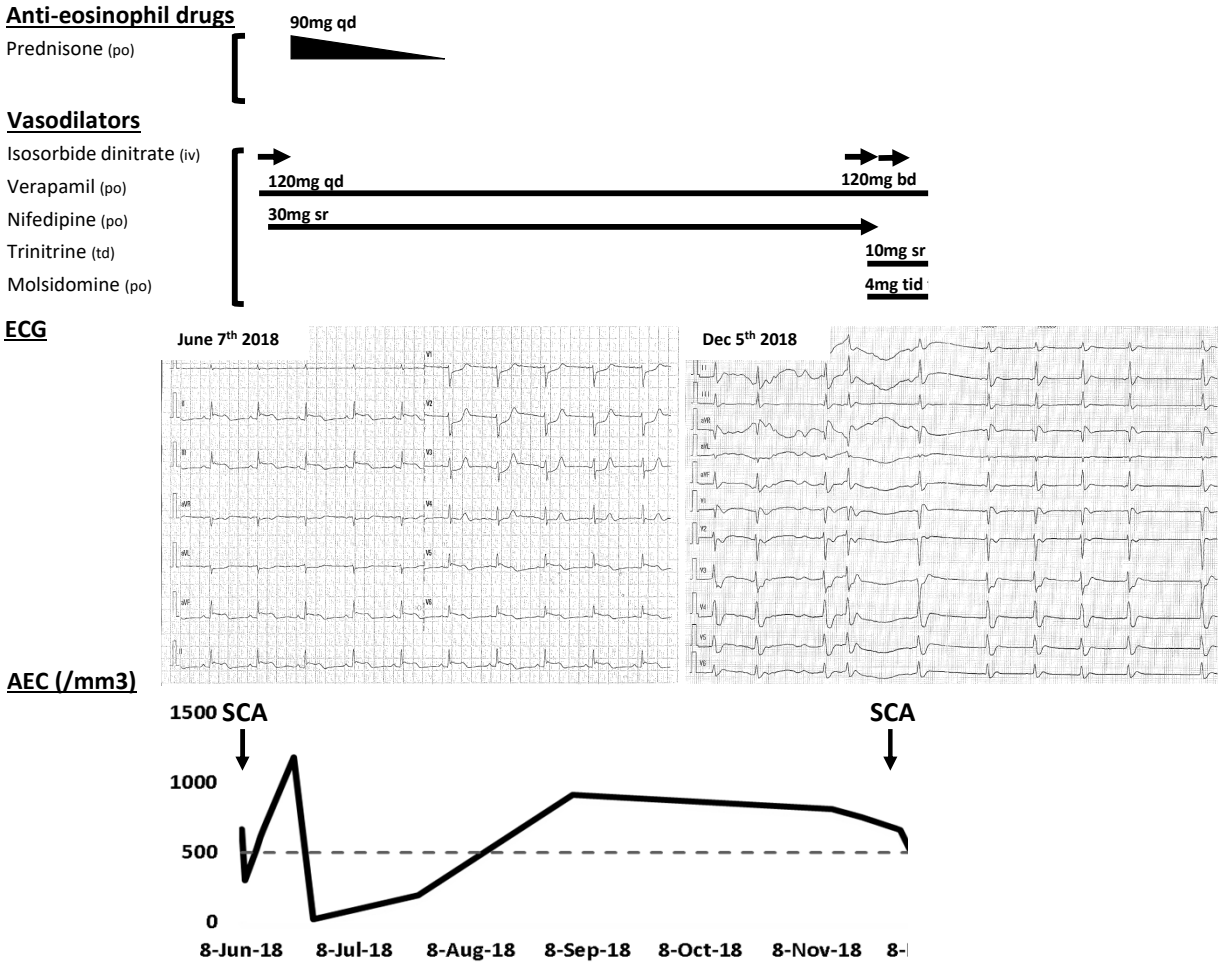


AEC (/mm3)

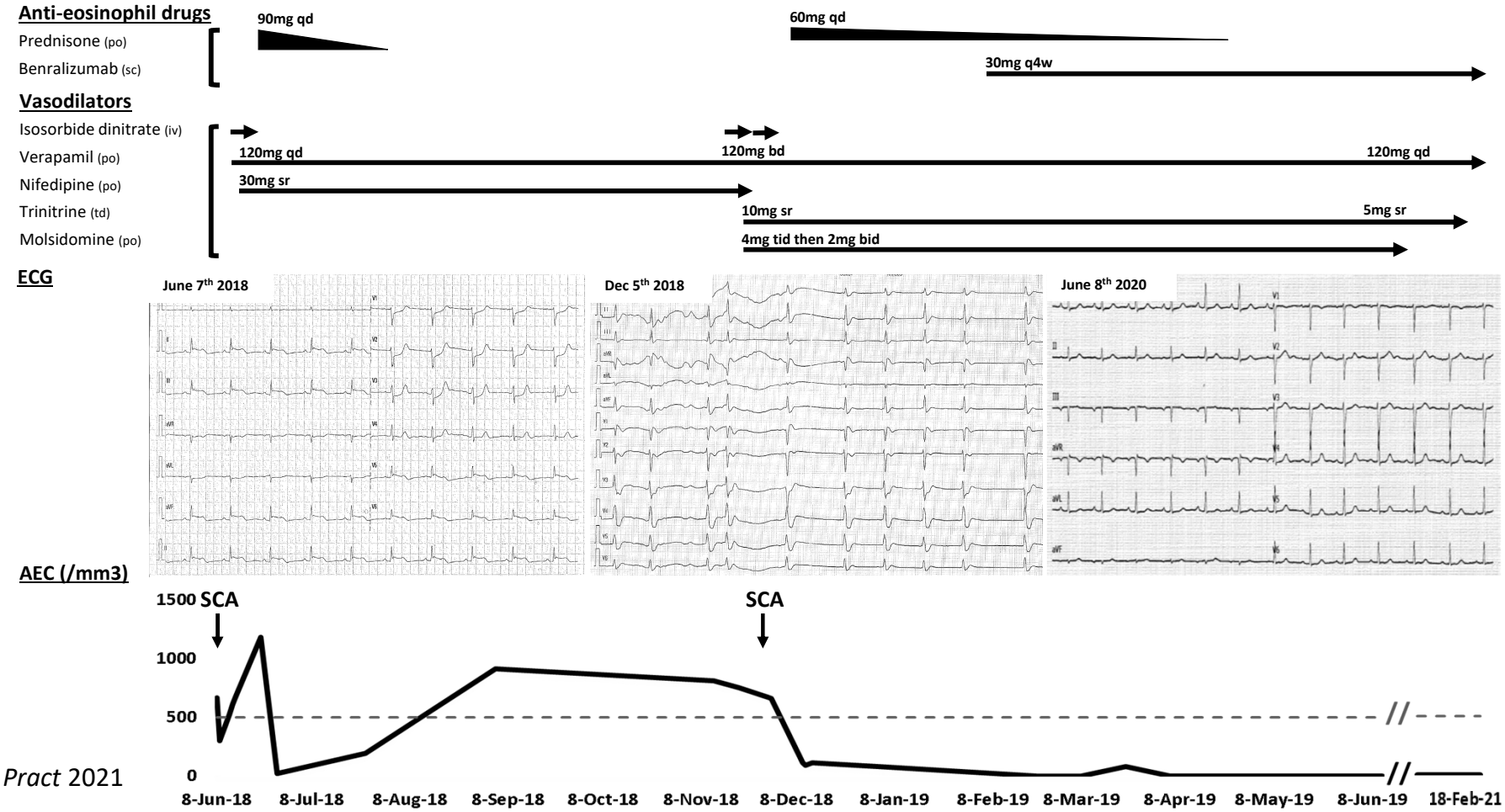




Margaux, 24 ans



Vasospame coronaire à éosinophiles
(Syndrome de Kounis de type 1 – « SCA allergique »)



Groh, *JACI In Pract* 2021

Vasospame coronaire à éosinophiles
(Syndrome de Kounis de type 1 – « SCA allergique »)

Published in final edited form as:
J Allergy Clin Immunol Pract. 2016 ; 4(6): 1215–1219. doi:10.1016/j.jaip.2016.04.028.

Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Disease

Neelam H Shah, MD[a,b,c], Thomas R Schneider, BA[d], Doreen DeFaria Yeh, MD[e,f], Katherine N Cahill, MD[c,f], and Tanya M Laidlaw, MD[a,c,f]

Etude nationale rétrospective « SPASMEO »

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m.groh@hopital-foch.com

- **153 patients avec AERD** suivis au Brigham & Women's hospital
- **N =10 (7%) pts** avec historique de douleurs thoraciques sans coronaropathie, dont 2 vasospasmes documentés

"history of chest pain which did not improve with conventional cardiac ischemia ... but responded to prednisone with subsequent recurrence following discontinuation or tapering of OCS"

- **Désensibilisation à l'aspirine = période à risque**
- **Traitement non codifié**

Shah, *JACI In Pract* 2017

Conclusion

Taux « normal » d'éosinophiles (hors asthme / BPCO / tabac / Sd métabolique, pricks tests +) Hartl, *ERJ* 2020

Seuil « T2 » et d'AMM anti IL-4/13 et anti IL-5

Seuil d'AMM anti IL-5R

NAEB*

Seuil « d'éosinophilie »

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Valent, *JACI* 2012

Asthme allergique

SHE lymphoïde

SHE FIP+

IgG4

Asthme Eo / Bronchiolite oblitérante Eo / DDB

Asthme-PNS-Widal

GEPA ANCA neg / SHE

Kounis

GEPA ANCA pos

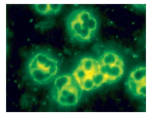
**Non-asthmatic Eosinophilic Bronchitis*

Take home messages

Traitement antiparasitaire: selon le taux d'Eo et l'anamnèse

Examen clinique + TDM TAP: dépister manifestations extra-respiratoires liées à la toxicité des éosinophiles (peau, tube digestif, cœur, thrombose…)

Troponine, BNP (+/- ETT)



ANCA anti-MPO: dépister les manifestations vascularitiques (multinévrite, HIA, GNRP, sclérite …) et les manifestations respiratoires liées à l'anti-MPO (PID, DDB)

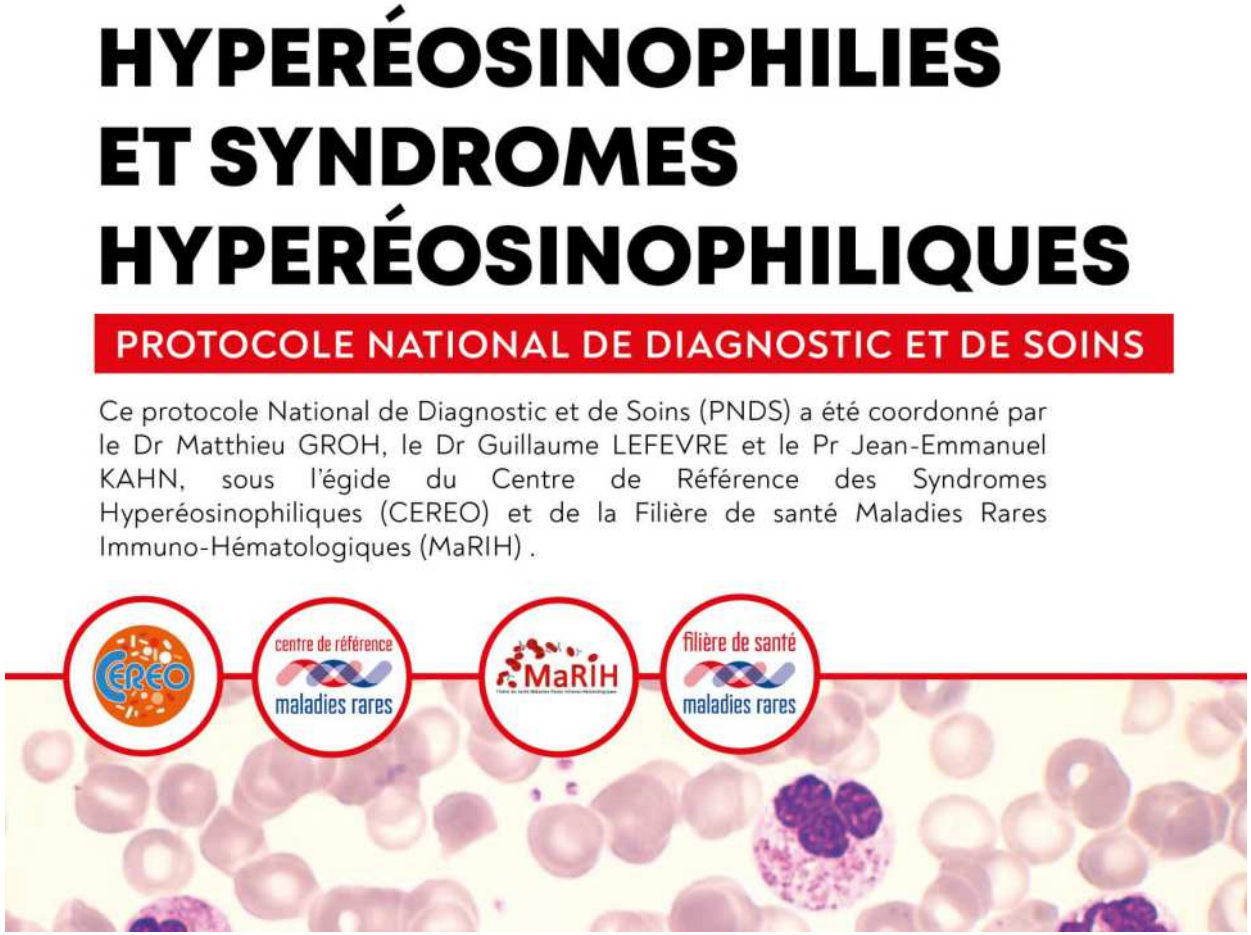
FIP1L1-PDGFRA et investigations médullaires: si tableau clinico-biologique évocateur (SMG, cytopénies, tryptase, B12, corticorésistance)

Phénotypage lymphocytaire T (3-4+): si eczéma / polyarthrite / polyADP

Hypery polyclonale: penser IgG4 (et LAI-T)

CRP élevée: attention thrombose, myocardite, cancer ou vascularite

Si vous voulez aller plus loin



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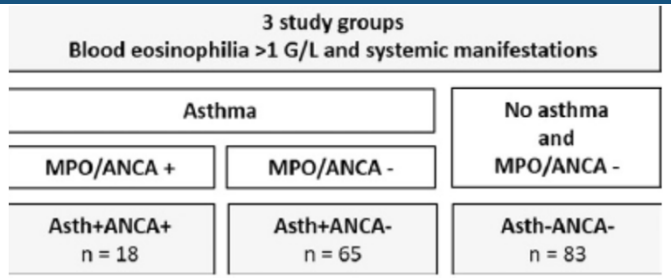
GEPA ou SHE: intérêt de la CRP ?

CHU de Lille (2006 – 2016): N = 166 pts

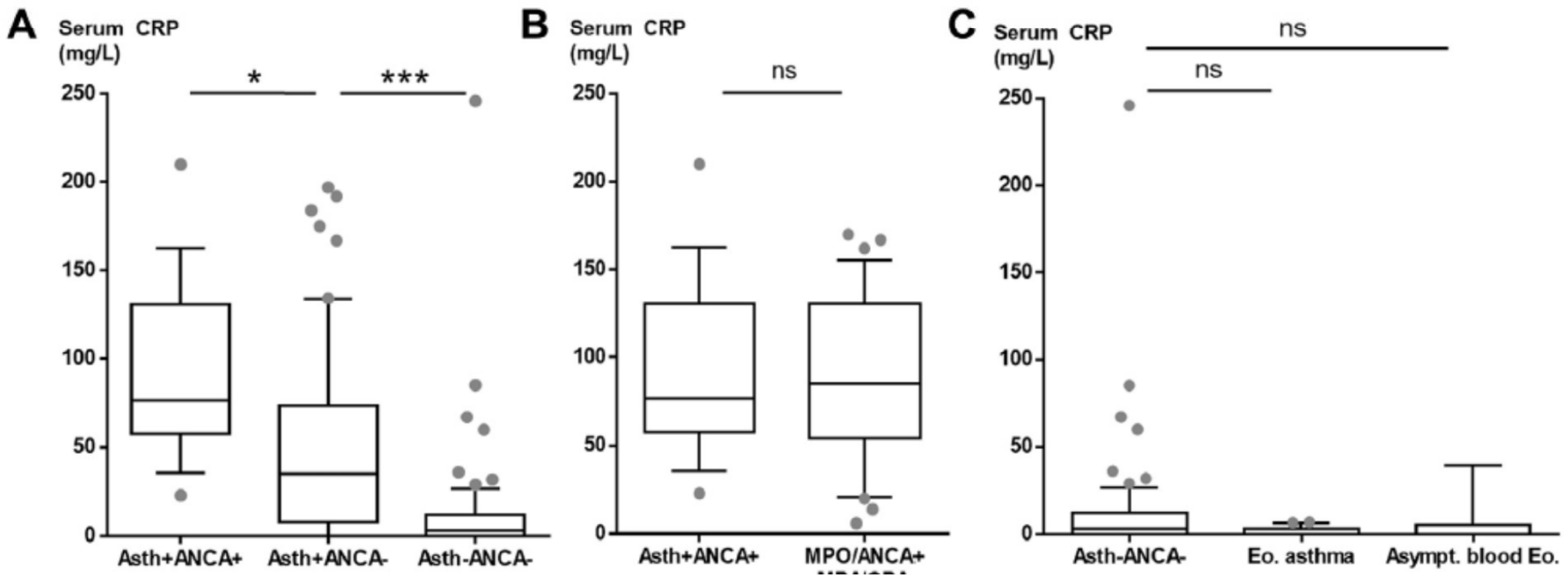


Leurs et al, *JACI In Pract* 2019

GEPA ou SHE: intérêt de la CRP ?

CHU de Lille (2006 – 2016): N = 166 pts

3 study groups Blood eosinophilia >1 G/L and systemic manifestations		
Asthma		No asthma and MPO/ANCA -
MPO/ANCA +	MPO/ANCA -	
Asth+ANCA+ n = 18	Asth+ANCA- n = 65	Asth-ANCA- n = 83



Leurs et al, *JACI In Pract* 2019

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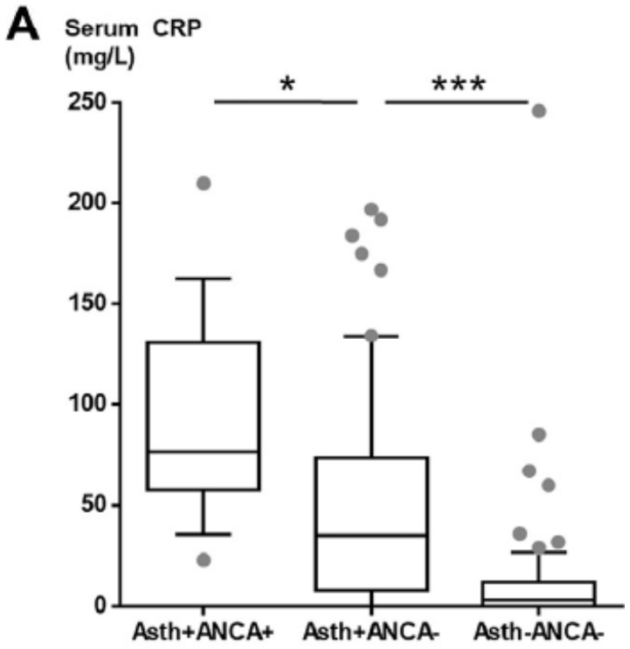
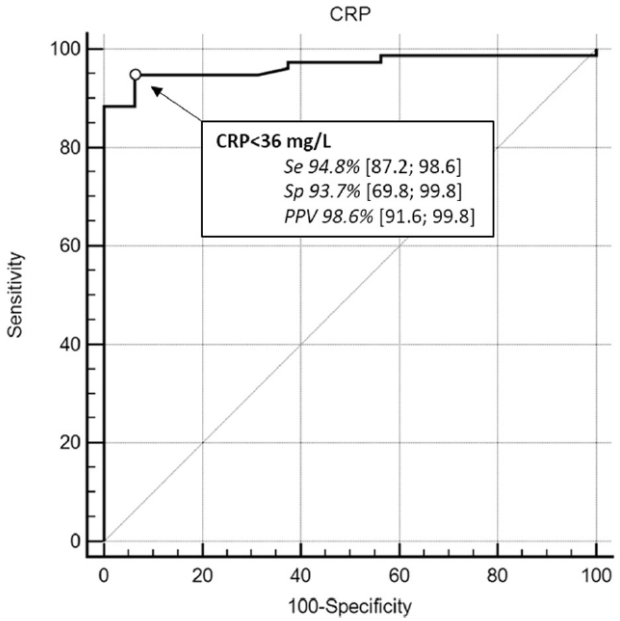




CRP < 36mg/L

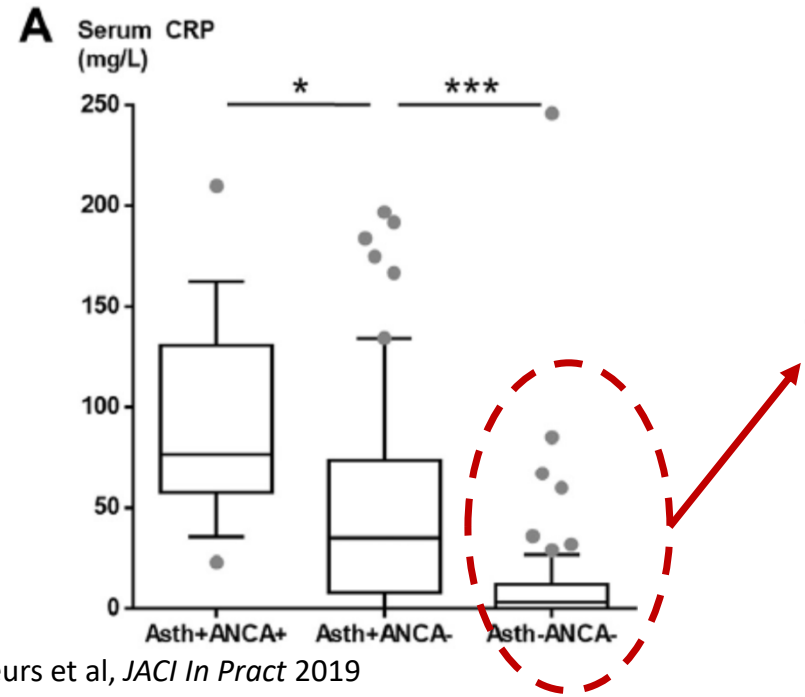
évocateur de SHE plus que de GEPA

(VPP: 98.6%)

Leurs et al, *JACI In Pract* 2019

GEPA ou SHE: intérêt de la CRP ?

<u>CHU de Lille (2006 – 2016):</u> N = 166 pts



Leurs et al, *JACI In Pract* 2019

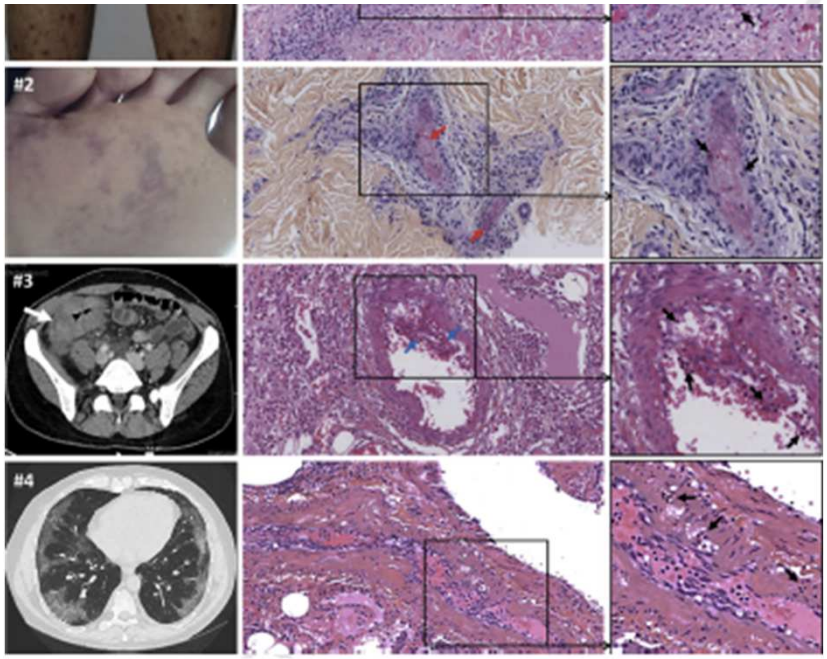
Pas d'asthme, …
Pas d' ANCA, …

… mais des manifestations de vascularite chez n=10/83 (12%) des patients SHE !?

Vascularite Eosinophilique

Original Article

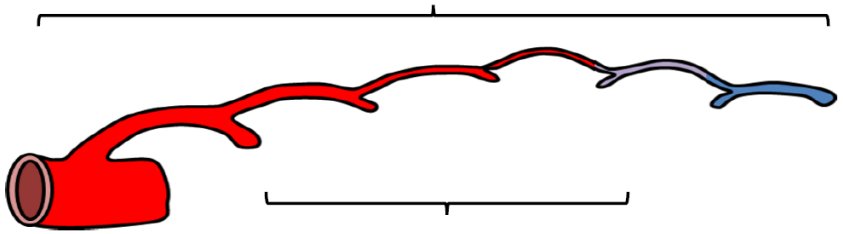
"Idiopathic Eosinophilic Vasculitis": Another Side of Hypereosinophilic Syndrome? A Comprehensive Analysis of 117 Cases in Asthma-Free Patients



Lefèvre, *JACI In Pract* 2020

- **Diagnostic de vascularite** (cutanée, digestive, cérébrale, coronarite, artérite temporale, …)
- **Exclusion des autres causes de VNS** (ANCA neg, pas d'asthme) **et de SHE**
- **Atteinte « mono-organe »** ou **systémique**
- **CRP < 36 mg/l** (84%)
- **Corticothérapie « seule » efficace**

Idiopathic EoV (or idiopathic HES-associated vasculitis) (n=76)
ANCA-negative non-granulomatosis necrotizing vasculitis
Small to large-sized vessel involvement (variable-vessel vasculitis)



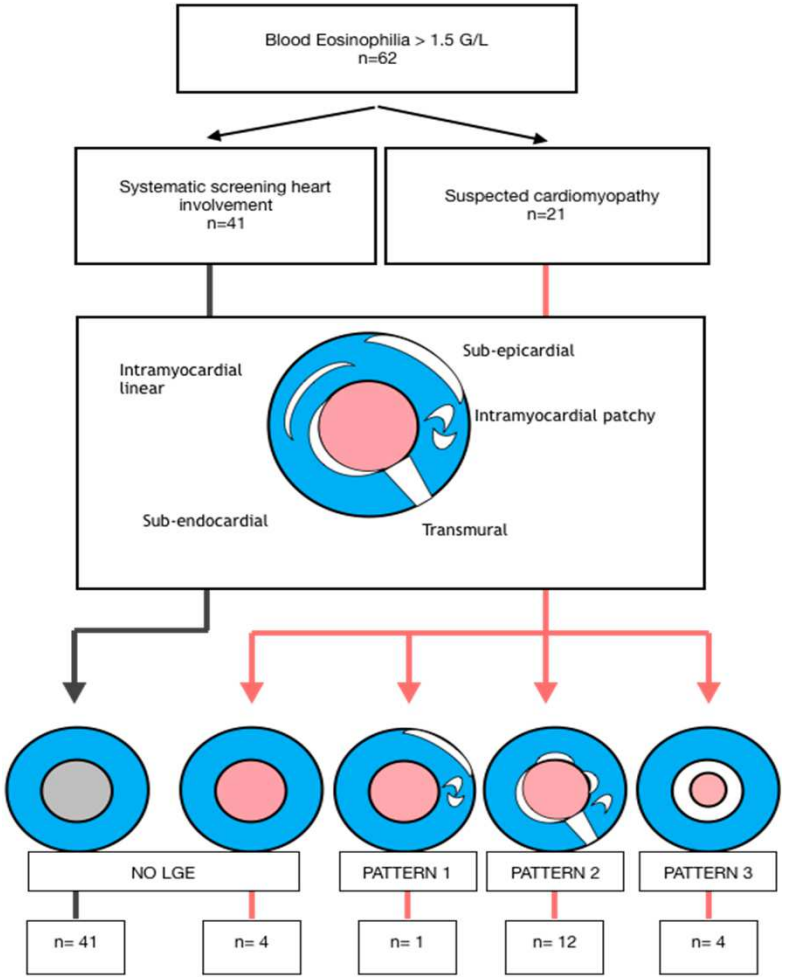
Single-organ EoV (n=41)
Small- to medium-sized vessel involvement
Isolated coronary (n=29), temporal (n=8), cerebral EoV (n=4)

IRM cardiaque au cours des HE/SHE/GEPA

Quelle place pour l'IRM cardiaque ?

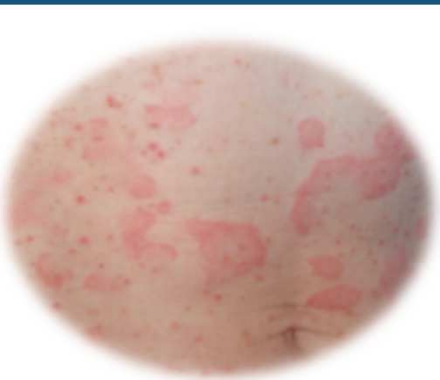
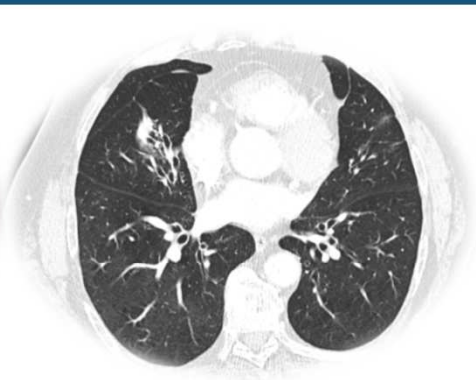
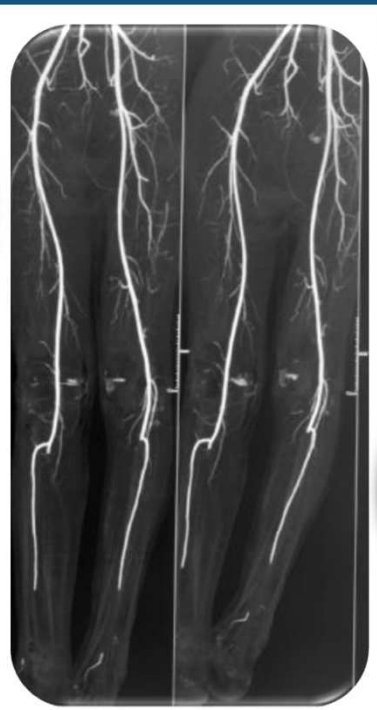
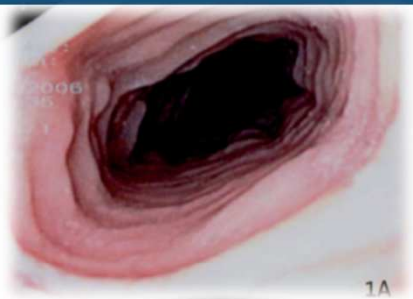
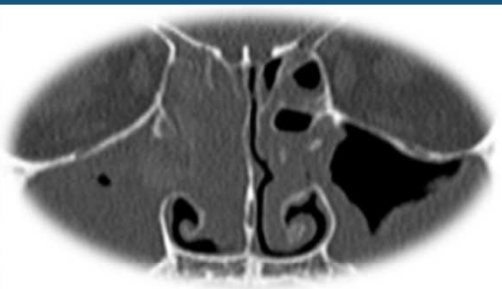
- **Etude monocentrique CHU Lille (F. Pontana; G. Lefèvre)**

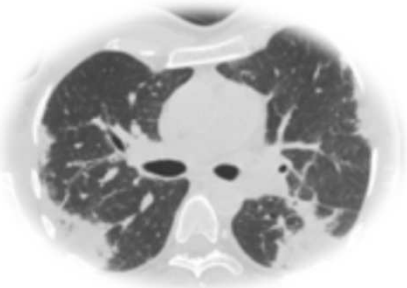
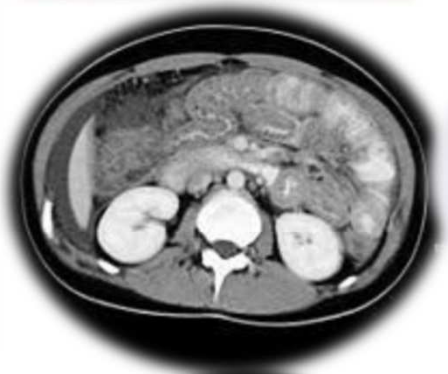
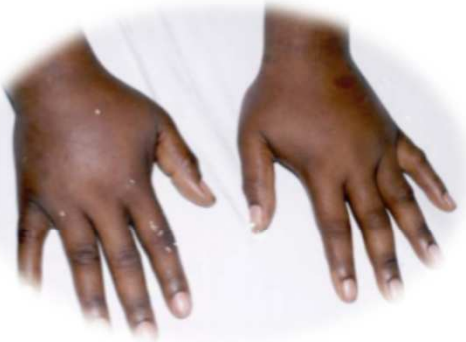
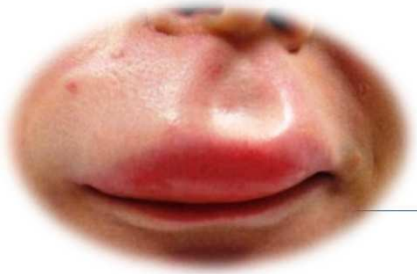
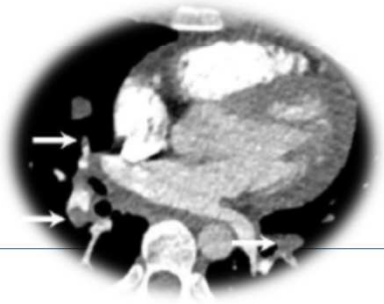
1. **Aucun intérêt de l'IRM systématique** si tropo, ECG, et ETT normaux et patient asymptomatique
2. **IRM peut être normale** malgré myocardite sur critères tropo ECG
3. **IRM ne distingue pas les myocardites de GEPA (n=4/4) vs. SHE (n=6/6) qui ont principalement un pattern IRM #2**

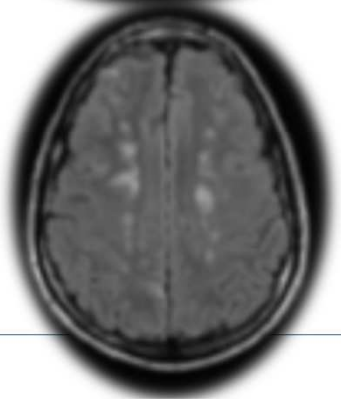
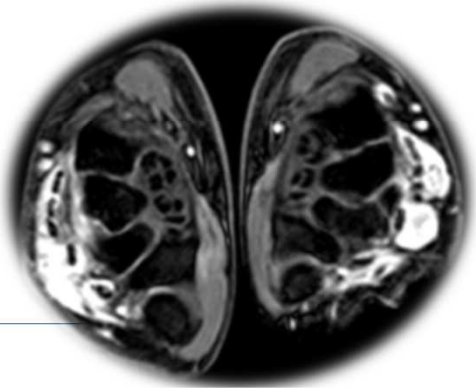


Dubois et al, *soumis*

Diversité des manifestations cliniques de SHE

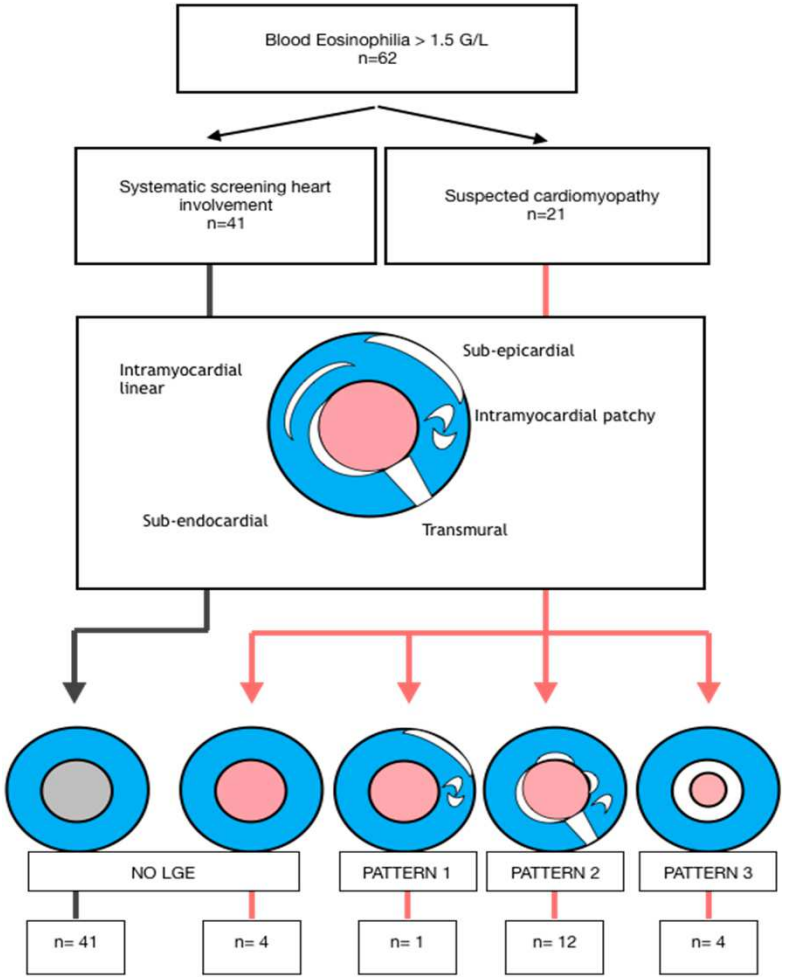



IRM cardiaque au cours des HE/SHE/GEPA

Quelle place pour l'IRM cardiaque ?

- **Etude monocentrique CHU Lille (F. Pontana; G. Lefèvre)**

1. **Aucun intérêt de l'IRM systématique** si tropo, ECG, et ETT normaux et patient asymptomatique
2. **IRM peut être normale** malgré myocardite sur critères tropo ECG
3. **IRM ne distingue pas les myocardites de GEPA (n=4/4) vs. SHE (n=6/6) qui ont principalement un pattern IRM #2**



Dubois et al, *soumis*