Eosinophilia and hypereosinophilia:

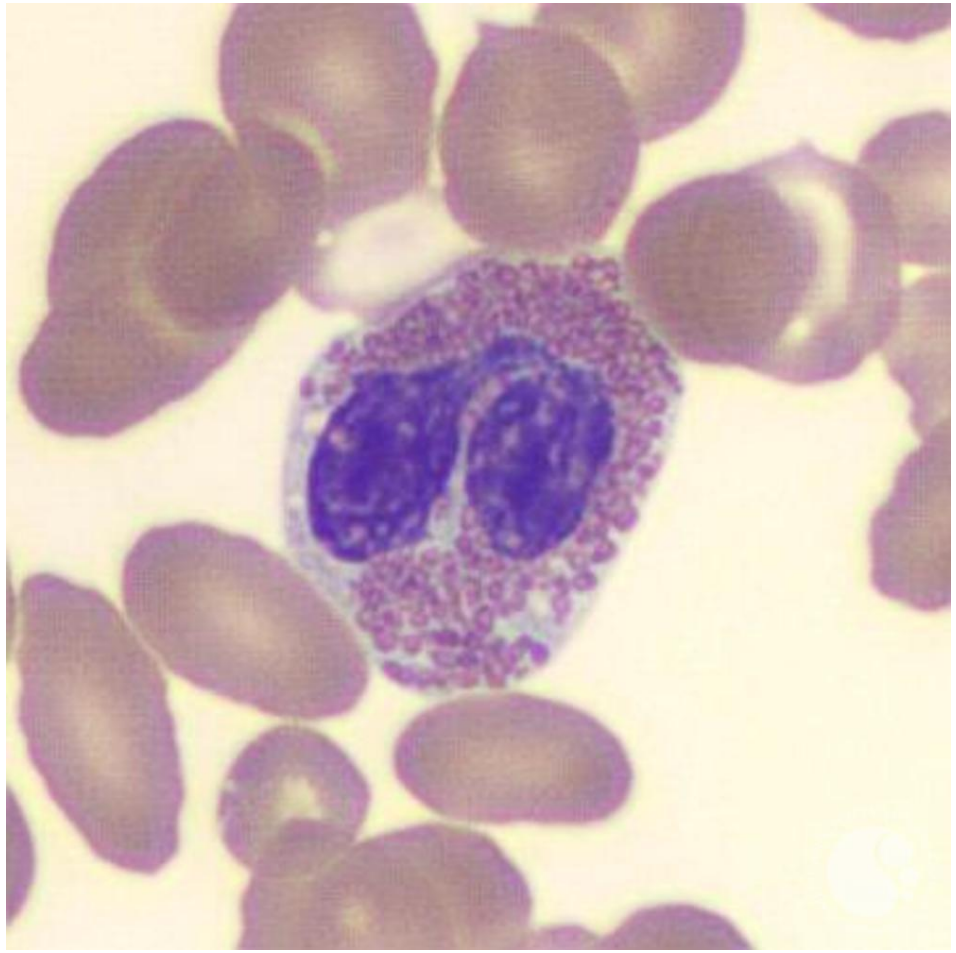
Clinical and therapeutic approach

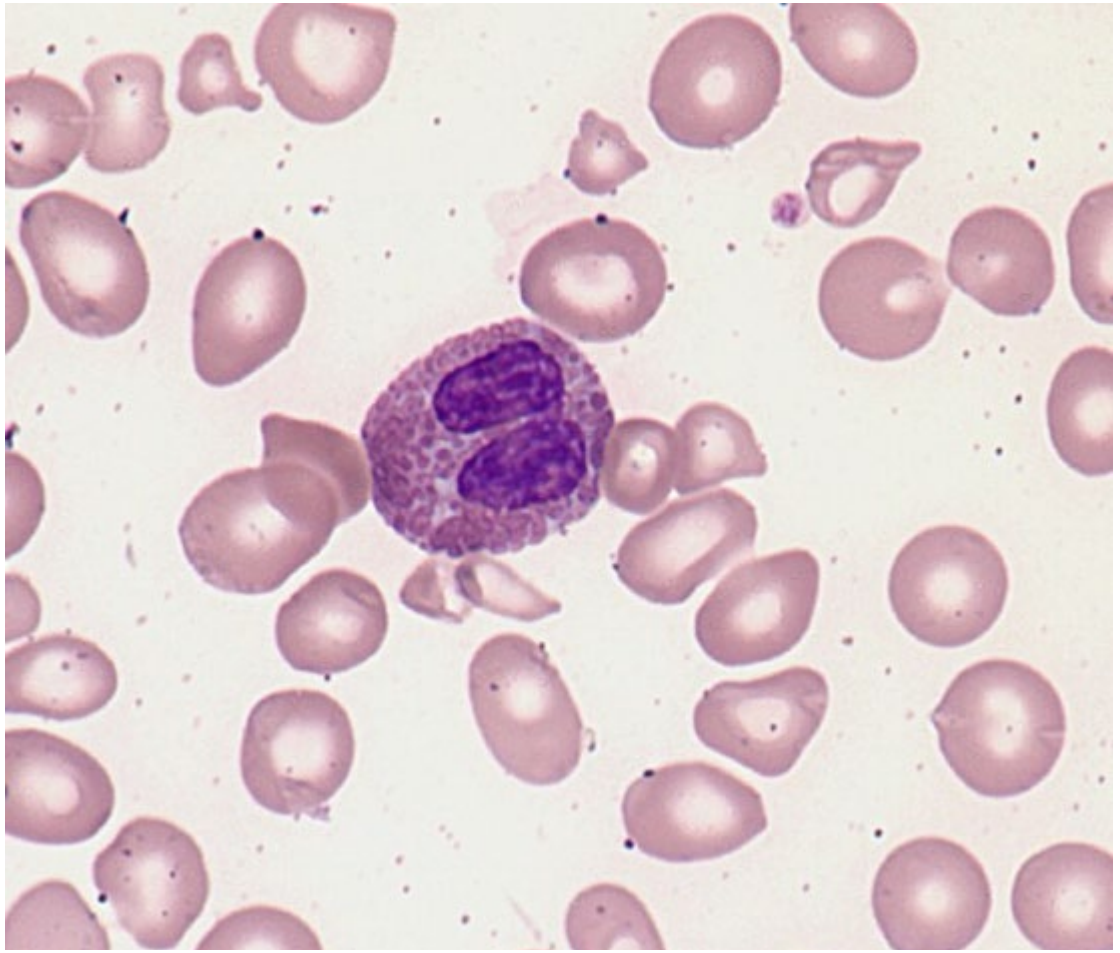
BHS Course, Oct 15, 2022

Peter Vandenberghe, Hematology, University Hospitals Leuven

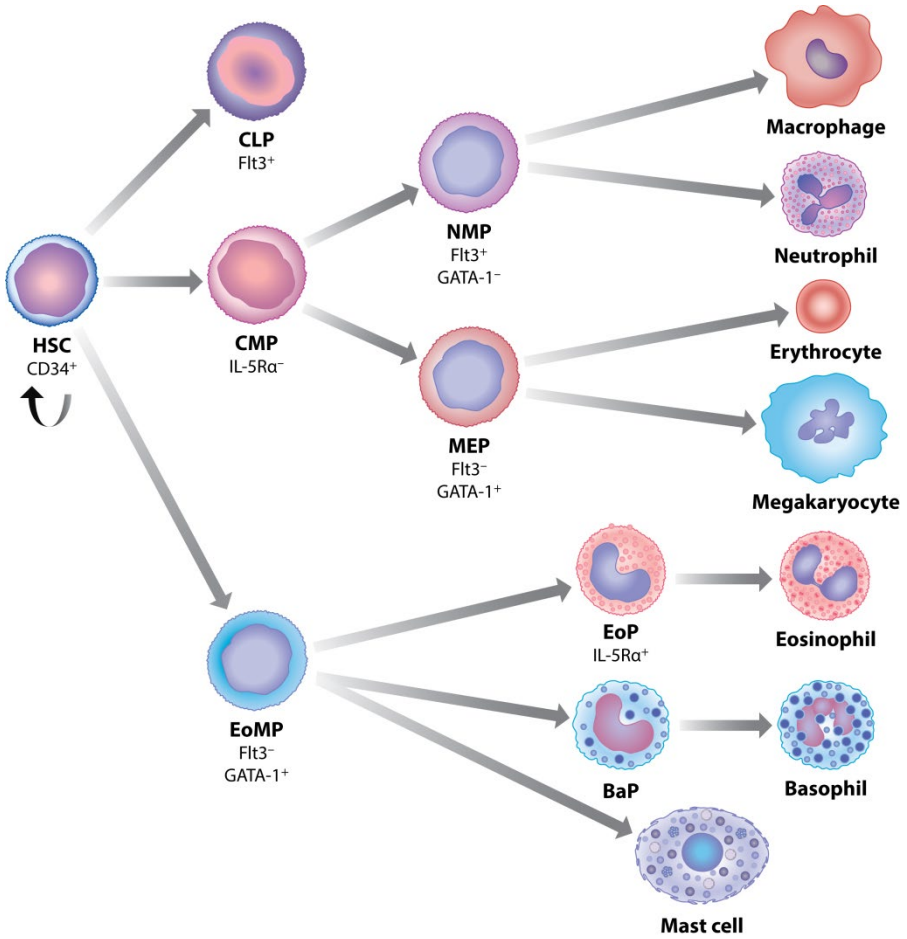
SAMEN GRENZEN VERLEGGEN

The eosinophil (0-0,45 x 10^9/L; 0-7%)





The life cycle of the eosinophil



Klion AD, et al. 2020.
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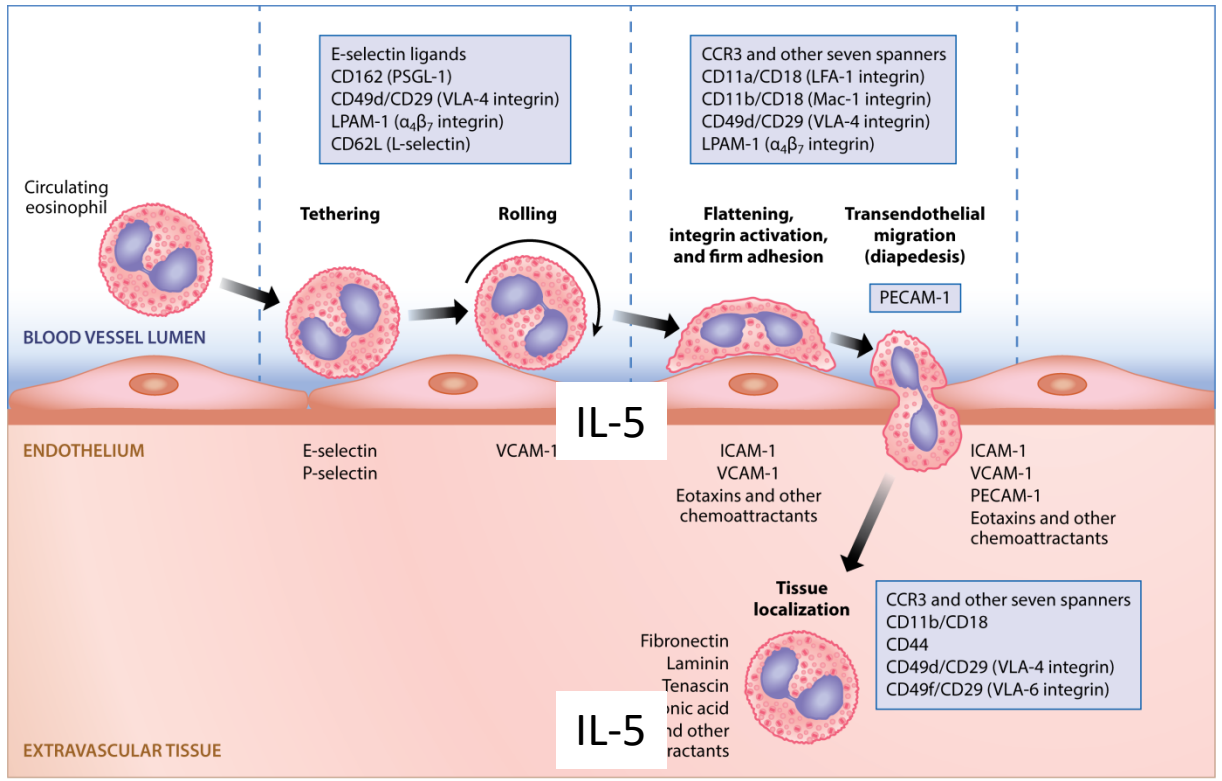

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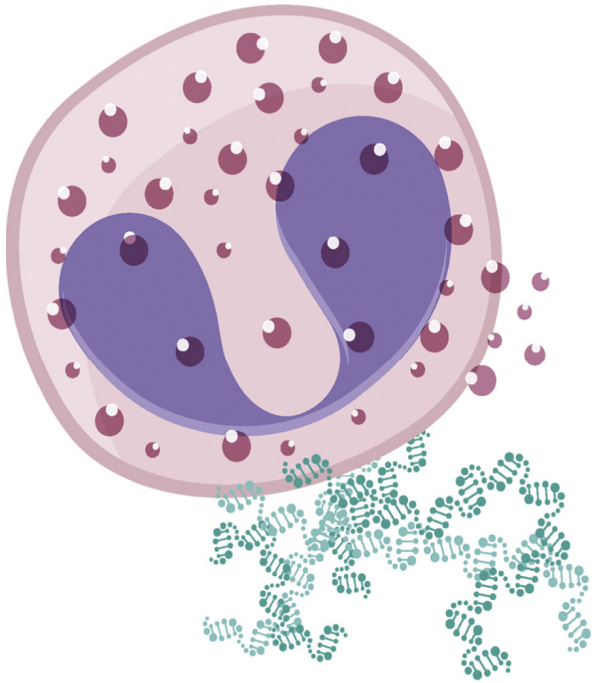
~1d

~a few days

IL-3, IL-5; GM-CSF

Eosinophils in health

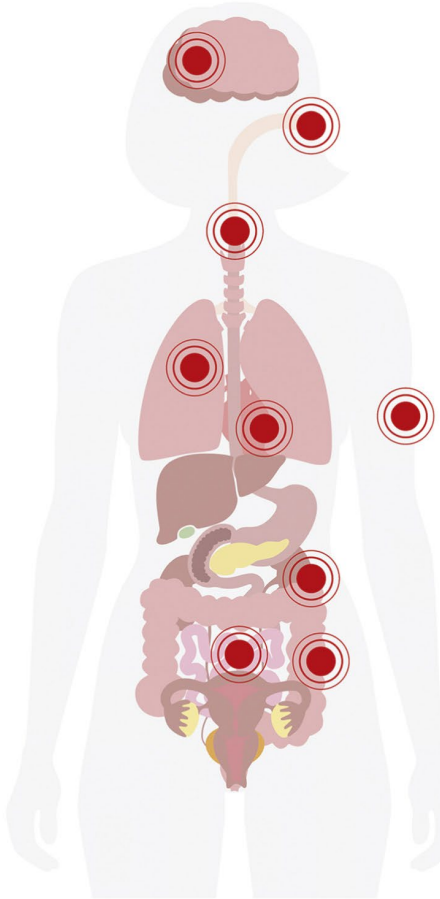


	Helminth toxicity	Antibacterial	Antiviral	Immune system	Epithelial activation and remodeling factor expression
EPX	✓	—	—	—	✓
MBP	✓	✓	—	Neutrophil, mast cell and basophil activation	✓
ECP	✓	✓	✓	—	—
EDN	—	—	✓	Dendritic cell recruitment and activation	—
CLC/gal-10	—	—	—	Th2 activation	—
EET	—	✓	—	—	—

Mayo Clinic Proceedings 2021 962694-2707DOI: (10.1016/j.mayocp.2021.04.025)

Eosinophilia and hypereosinophilia in disease

- Asthma
- Eosinophilic chronic obstructive pulmonary disease
- Eosinophilic pneumonia
- Fungal infections/allergic bronchopulmonary aspergillosis
- Cancer (e.g. leukemia/lymphoma)



- Chronic rhinosinusitis with nasal polyps
- Eosinophilic esophagitis
- Hypereosinophilic syndrome* and eosinophilic granulomatosis with polyangiitis
- Inflammatory bowel disease
- Systemic inflammation/ drug reaction

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Eosinophilia, Peter Weller

Box 22.3.8.1 Diseases and disorders associated with eosinophilia

Infectious diseases

- Helminth parasites
- Coccidioidomycosis
- Other infections—infrequent, but includes HIV-1 and HTLV-1

Allergic and immunological disorders

- Allergic rhinitis, asthma
- Medication-related eosinophilias
- Immunological diseases: hyperIgE syndromes, Ommen's syndrome, and IgG4-related diseases
- Transplant rejections

Myeloproliferative and neoplastic disorders

- Hypereosinophilic syndromes
- Leukaemia, notably M4Eo subtype of acute myeloid leukaemia
- Lymphoma- and tumour-associated, notably with nodular sclerosing Hodgkin lymphoma
- Systemic mastocytosis

Pulmonary syndromes

- Parasite-induced eosinophilic lung diseases:
  - — Transpulmonary passage of developing larvae (Löffler syndrome): patchy migratory infiltrates, especially ascaris
  - — Tropical pulmonary eosinophilia: miliary lesions and fibrosis; heightened immune responses to lymphatic filariae with increased IgE and antifilarial antibodies
  - — Pulmonary parenchymal invasion: paragonimiasis
  - — Heavy haematogenous seeding with helminths: disseminated strongyloidiasis, trichinellosis, schistosomiasis, larva migrans
  - — Allergic bronchopulmonary aspergillosis
- Chronic eosinophilic pneumonia: dense often peripheral infiltrates, fever; blood eosinophilia may be absent; may be antecedent to EGPA
- Acute eosinophilic pneumonia—acute presentation, often without blood eosinophilia; diagnosed by bronchoalveolar lavage or biopsy
- EGPA vasculitis: small- and medium-sized arteries; perivascular eosinophilia early and granulomas and necrosis later; asthma often antecedent; extrapulmonary, for example, neurological, cutaneous, cardiac, or gastrointestinal vasculitic involvement likely
- Drug- and toxin-induced eosinophilic lung diseases
- Other: neoplasia, hypereosinophilic syndromes, bronchocentric granulomatosis

Skin and subcutaneous diseases

- Skin diseases—atopic dermatitis, blistering diseases, including bullous pemphigoid, urticarias, drug reactions
- Diseases of pregnancy: pruritic urticarial papules and plaques syndrome, herpes gestationis
- Eosinophilic pustular folliculitis
- Eosinophilic cellulitis (Wells' syndrome)
- Kimura's disease and angiolymphoid hyperplasia with eosinophilia
- Shulman's syndrome (eosinophilic fasciitis)
- Episodic angio-oedema with eosinophilia—recurrent periodic episodes with fever, angio-oedema, and secondary weight gain; may be longstanding without untoward cardiac dysfunction

Gastrointestinal diseases

- Eosinophilic gastroenteritis—(1) blood eosinophilia; (2) eosinophil cell infiltrates in the mucosa, muscularis, or serosa; (3) oedema of stomach or intestines; and (4) absence of extraintestinal involvement
- Inflammatory bowel disease and collagenous colitis—eosinophils in tissue lesions

Rheumatological diseases

- EGPA vasculitis
- Cutaneous necrotizing eosinophilic vasculitis

Endocrine disease

- Hypoadrenalism: Addison's disease, adrenal haemorrhage, hypopituitarism

Other causes of eosinophilia

- Atheromatous cholesterol embolization
- Hereditary
- Serosal surface irritation, including peritoneal dialysis and pleural eosinophilia

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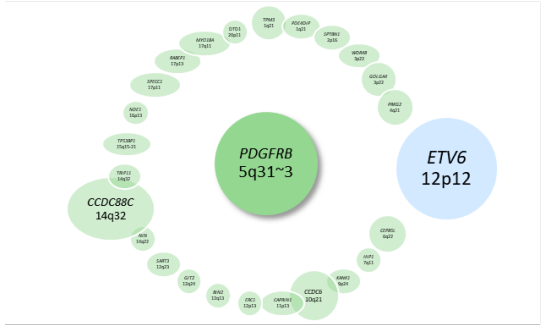
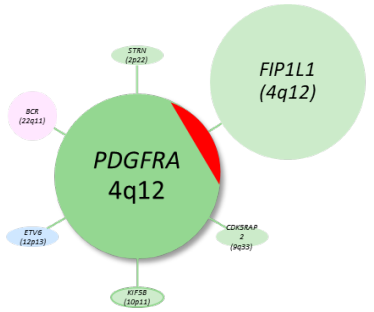
Bone marrow biopsy
Cytogenetic and molecular analysis





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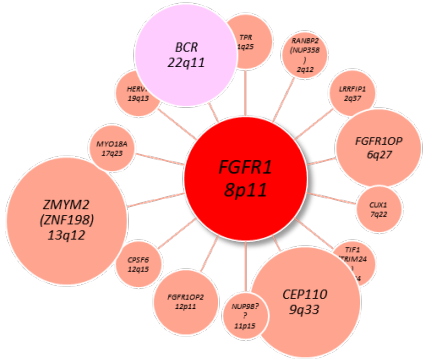

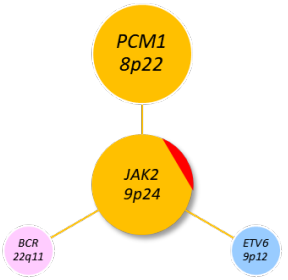

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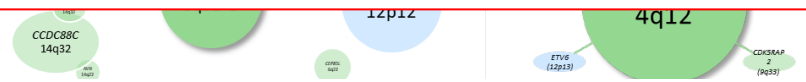

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PDGFRA rearrangement
PDGFRB rearrangement
FGFR1 rearrangement
JAK2 rearrangement
FLT3 rearrangement
ETV6::ABL1 fusion
Other defined tyrosine kinase fusions:
ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET

Case 1

2011, M, 30y

Allergies : penicillin, house dust mite, horses, hay fever

3/2011: DVT vena subclavia en vena axillaris.

5/2011: eosinophilia, splenomegaly, DVT

7/2011: Bone marrow cytology: DD reactive - MPN/iHES. DD… to be correlated with cytogenetics, molecular

Normal karyotype (fragile site @ 12q24). FISH 4q12 normal, WGS : no mutations in TKI genes.

01/2012

Hb 11,6 g/dl; WBC 25 10^9/L, Eosinophils 13 10^9/L

Splenomegaly

01/2012

Hyperviscosity syndrome

Hypertrophic cardiomyopathy and apical thrombus

Left hemiparesis

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Case 2

2016. F, 26j

Allergic rhinitis and asthma since 1 y

Progressive SOB, myalgia, skin lesions.

Hb 14g/dl, WBC 21 x 10^9/L, AEC 9 x 10^9/L, platelets 335 x 10^9/L

Cardiac MR: mild LV hypertrophy, diffuse myocardial edema/inflammation; ↑ troponins

Chest CT: airtrapping, otherwise normaal

Skin biopsy: Well's syndrome versus skin localisation of eosinophilic leukemia

BM-BB: 45% eosinophils, DD… to be correlated with cytogenetics, molecular

CME: 46,XX. FISH 4q12 normaal, no *FIP1L1::PDGFRA* transcript

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Definition of eosinophilia/hypereosinophilia (HE)

- Peripheral blood
  - Eosinophilia: > 0,5 * 10^9/L
  - Hypereosinophilia: > 1,5 * 10^9/L and eosinophilia > 10%
    - severe > 5,0 * 10^9/L and eosinophilia > 10%
    - Sustained elevation: at least two measurements 6m (WHO <2022)/4w (WHO 2022)/2w apart
- Tissue eosinophilia
  - Bone marrow: eosinophils > 20% ANC
  - Other tissues: lack of normal reference range, judgement of pathologist
  - Often in combination with PB eosinophilia

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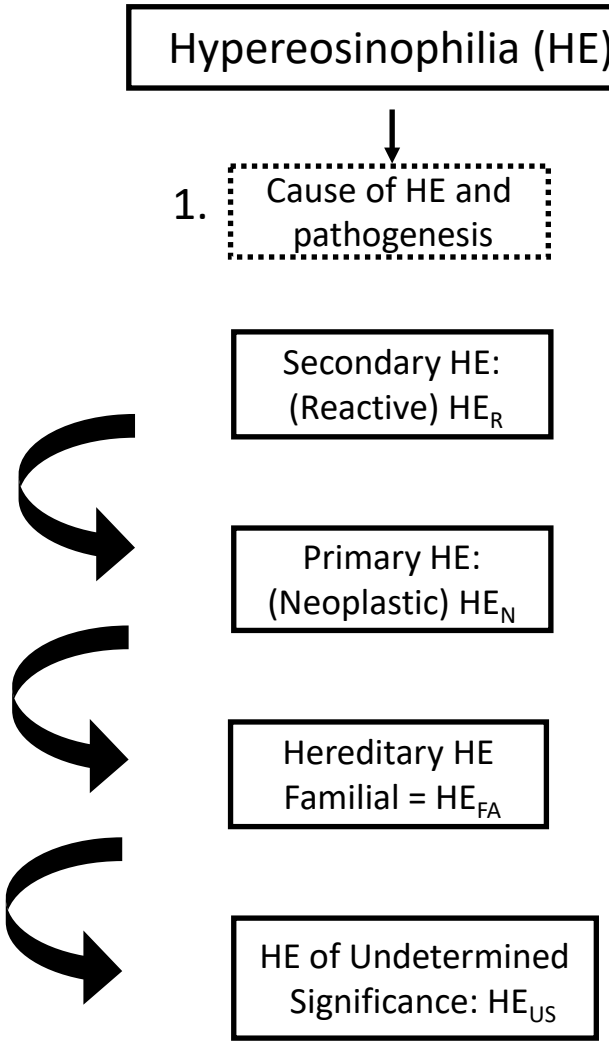
Approach to eosinophilia & hypereosinophilia (HE)



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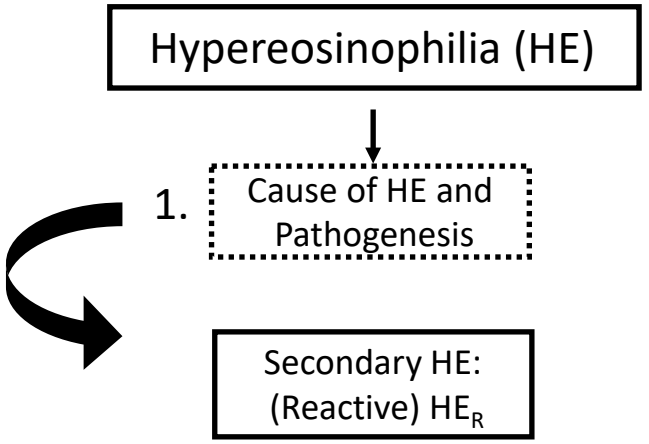

Infections, in particular helminth infections, more rarely fungal or viral	Travel history, stool exam, Strong. serology
Allergic and immunological reactions/diseases allergy and atopy drug allergy (DRESS) organ transplant Allergic Bronchopulmonary Aspergillosis	IgE Drug history Medical history Asp precipitins
Systemic diseases *EGPA* *SLE and other*	*ANCA (~50% sensitivity)* *Imaging (lung, heart)* *Biopsy*
Malignancy (HL, NHL, B-ALL, solid tumors)	
Lymphocytic HES (abnormal T-cell populations)	*Flow cytometry*
Skin diseases	
Pulmonary diseases parasitic eosinophilic pneumonias allergic bronchopulmonary aspergillosis	Aspergillus precipitins Endoscopy, BAL, biopsy
Gastrointestinal diseases IBD eosinophilic gastroenteritis	

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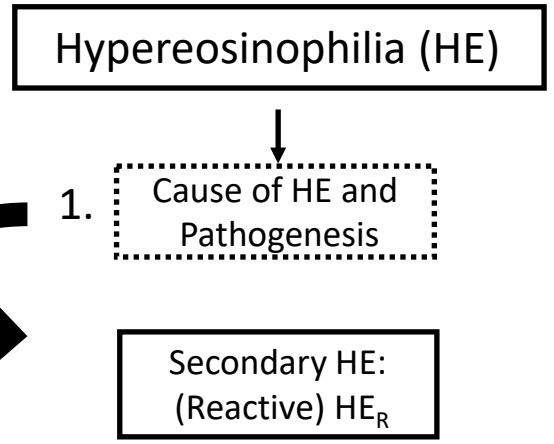

CBC and microscopic
WBC differential
Serum tryptase
Vitamin B_{12}
Abdominal US
~~FIP1L1-PDGFRA~~

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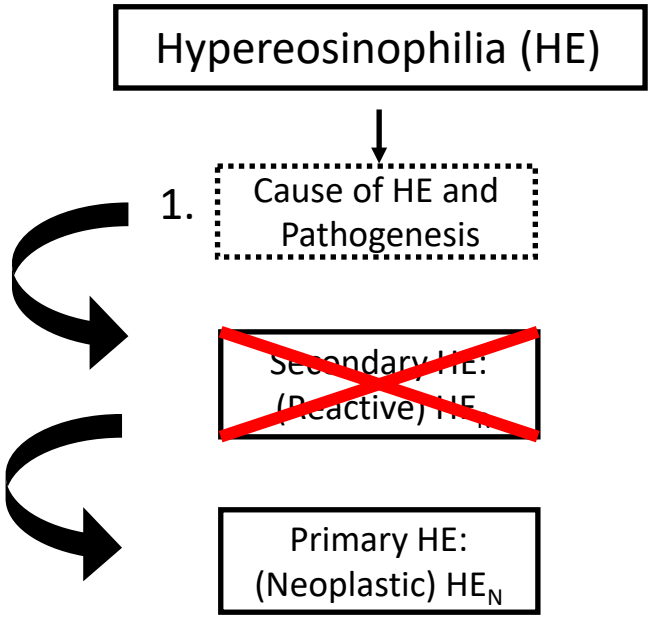

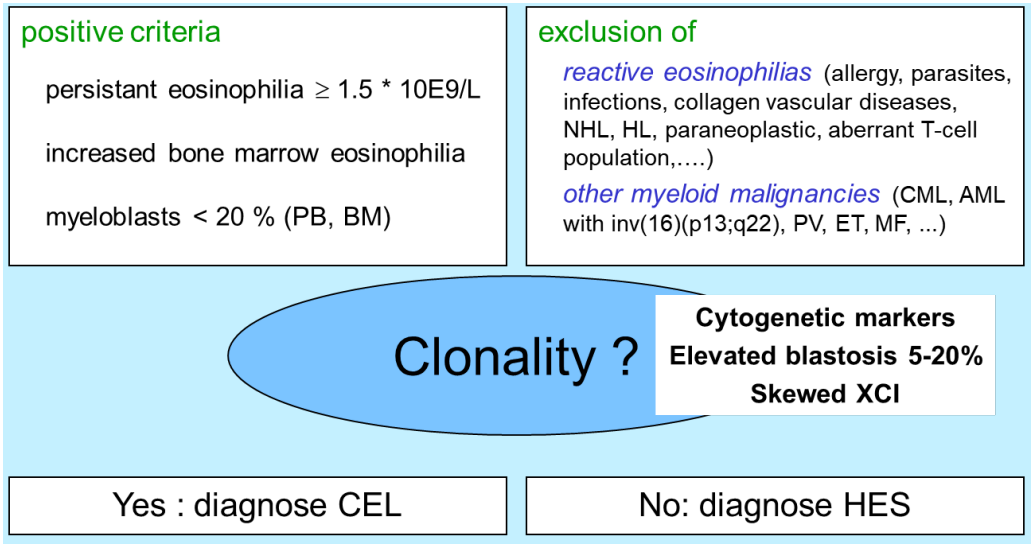

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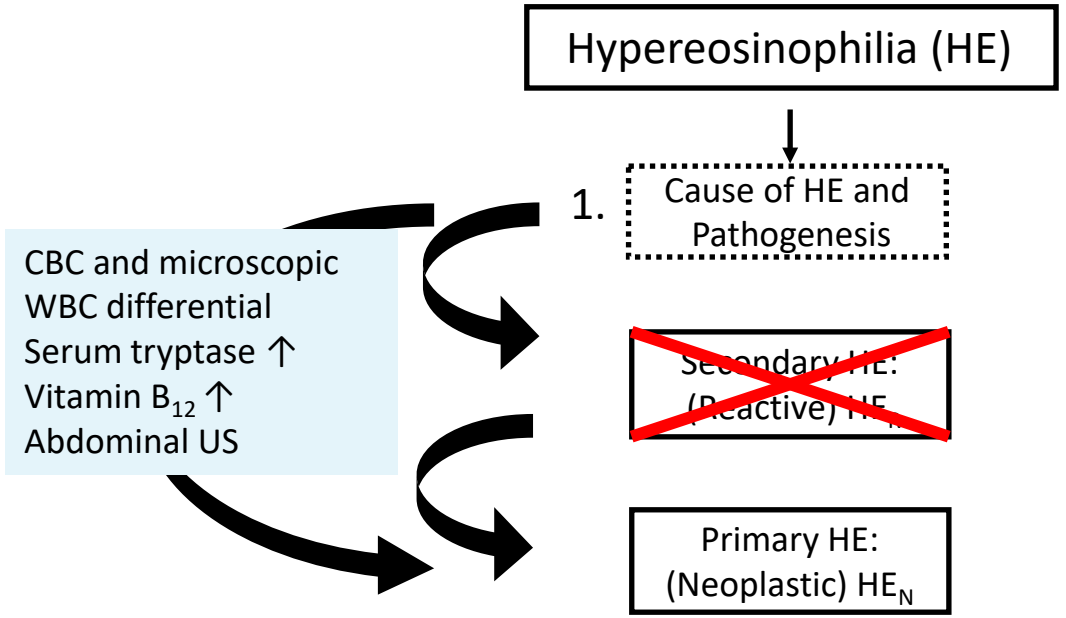

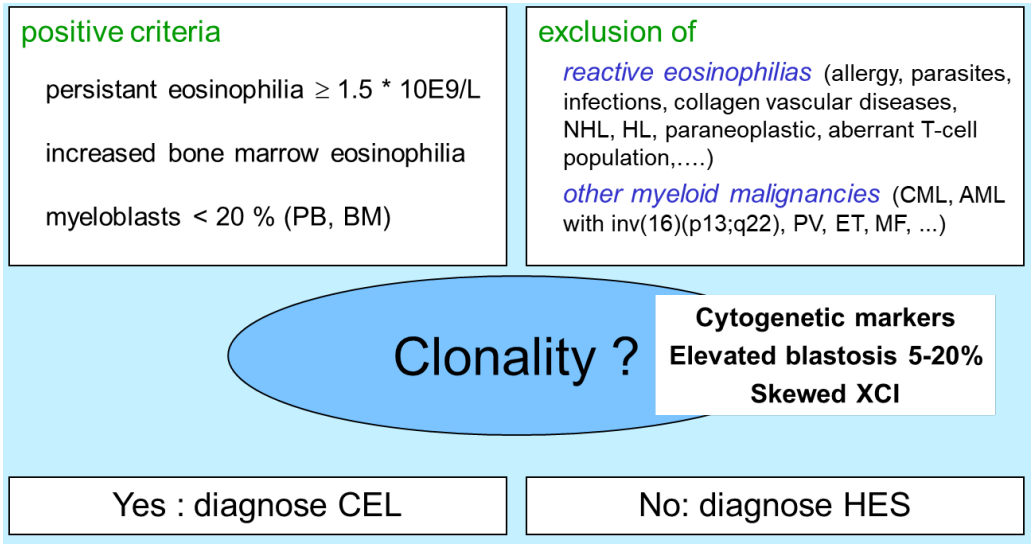

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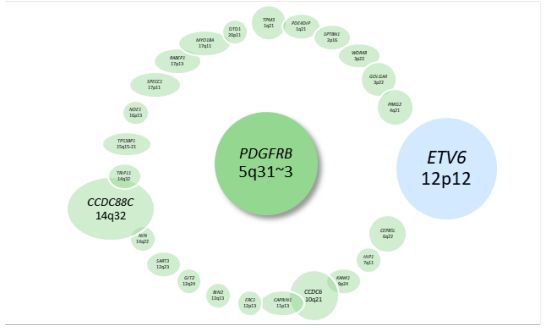

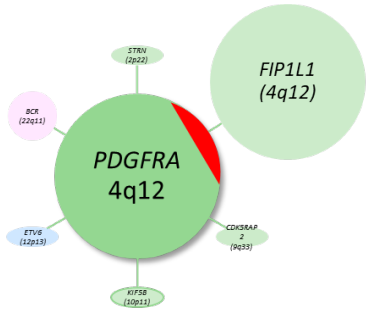

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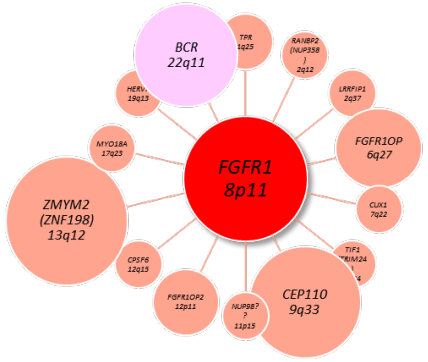

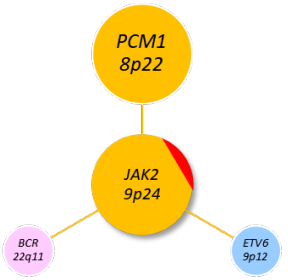

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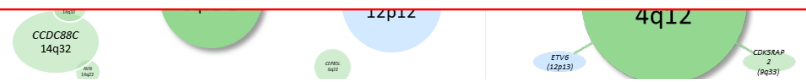

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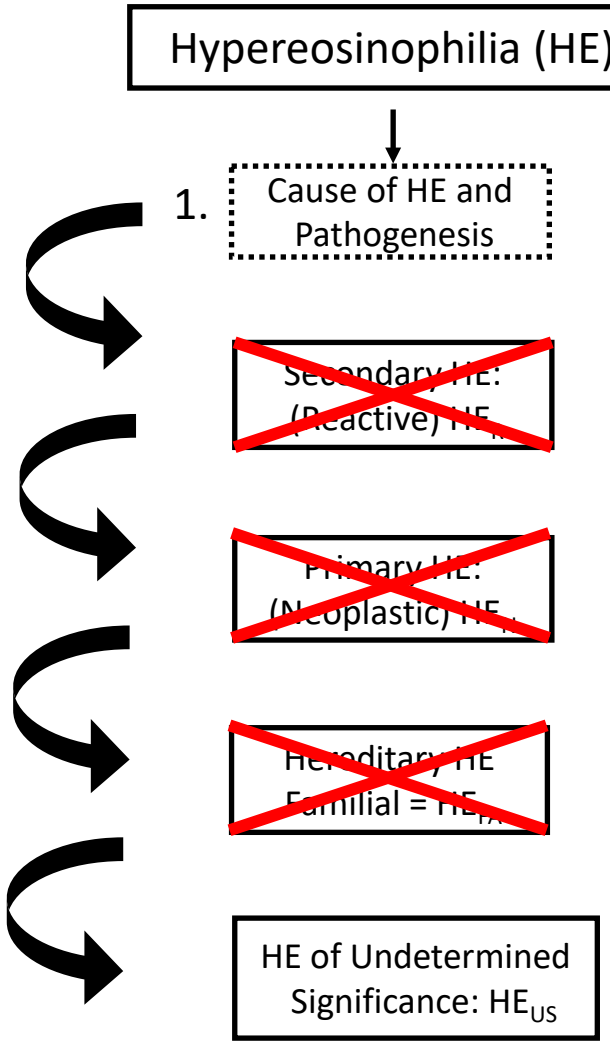

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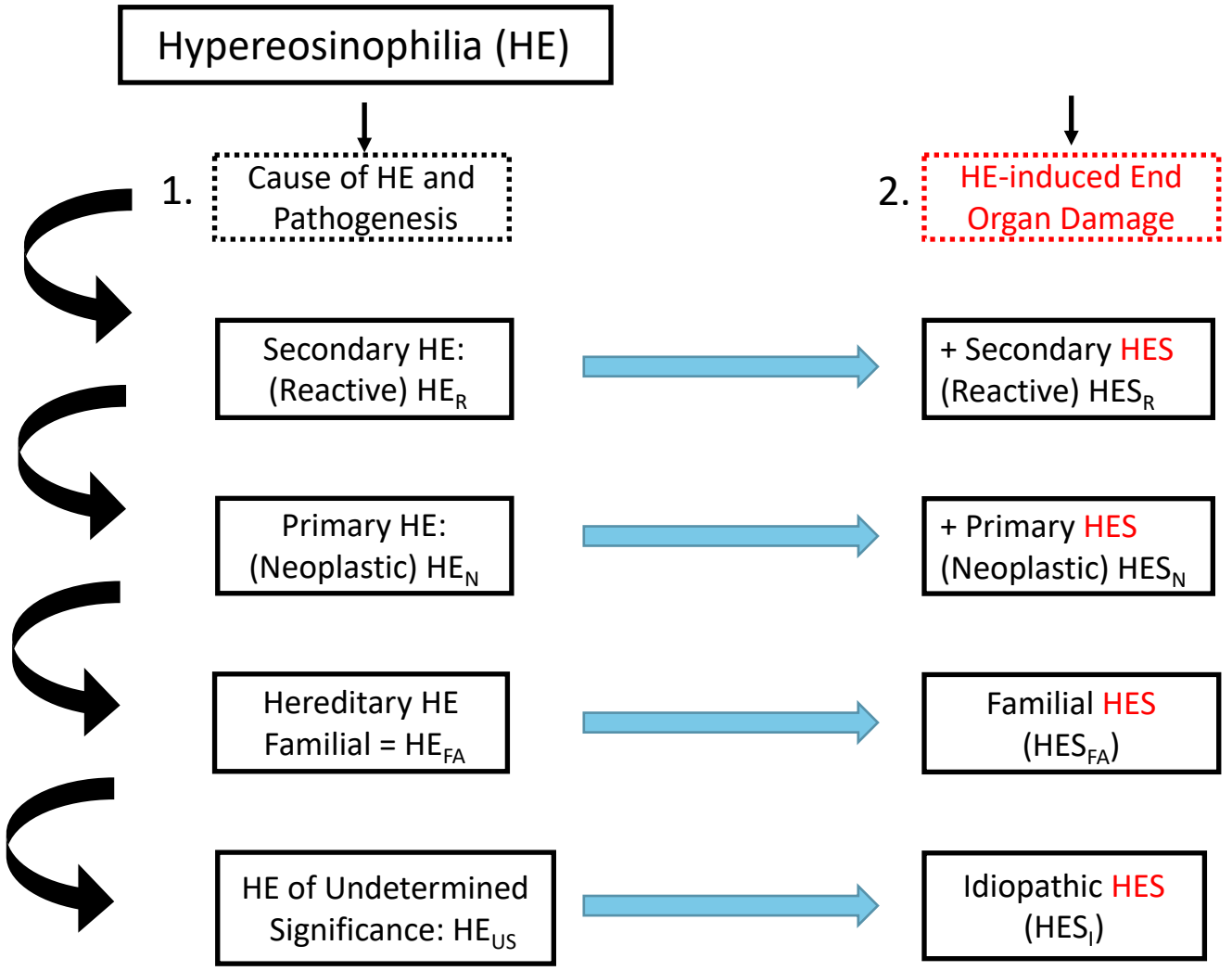

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Target organs in HES

- Heart (endomycardial biopsy, TTE, cardiac MRI, troponins)
- Skin (biopsy)
- Lung (imaging, endoscopy, biopsy, BAL)
- Central nervous system
- Gastrointestinal tract

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Single organ involvement and PB eosinophilia HE_R or HES_R ?

- In HES, eosinophils cause organ damage per *se*, by infiltration and/or degranulation.
- In HE_R, organ pathology induces local as well as PB eosinophilia as bystander

- Atopic dermatitis and PB HE
- Pulmonary infiltrates and eosinophilia (PIE)
- Eosinophilic esophagitis
- …

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HE: therapy

Hypereosinophilia (HE)

1. Cause of HE and Pathogenesis

Secondary HE: (Reactive) HE_R	*Underlying disease, if needed*	*Anti-IL5 (mepolizumab (Nucala®), reslizumab (Cinqaero®)* *Anti-IL5R (benralizumab (Fasenra®) (difficult asthma)*
Primary HE: (Neoplastic) HE_N	*Underlying disease, always*	*TKI* *Hydroxyurea, IFNa* *Allogeneic Stx*
HE of Undetermined Significance: HE_{US}	*Follow-up :* *reclassify as HE_R or HE_N or resolution* *evolution to organ damage*	

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Acute therapy for HES

Hypereosinophilia (HE)

1. Cause of HE and Pathogenesis

HE-induced End Organ Damage

Secondary HE: (Reactive) HE_R

+ Secondary HES (Reactive) HES_R

Primary HE: (Neoplastic) HE_N

+ Primary HES (Neoplastic) HES_N

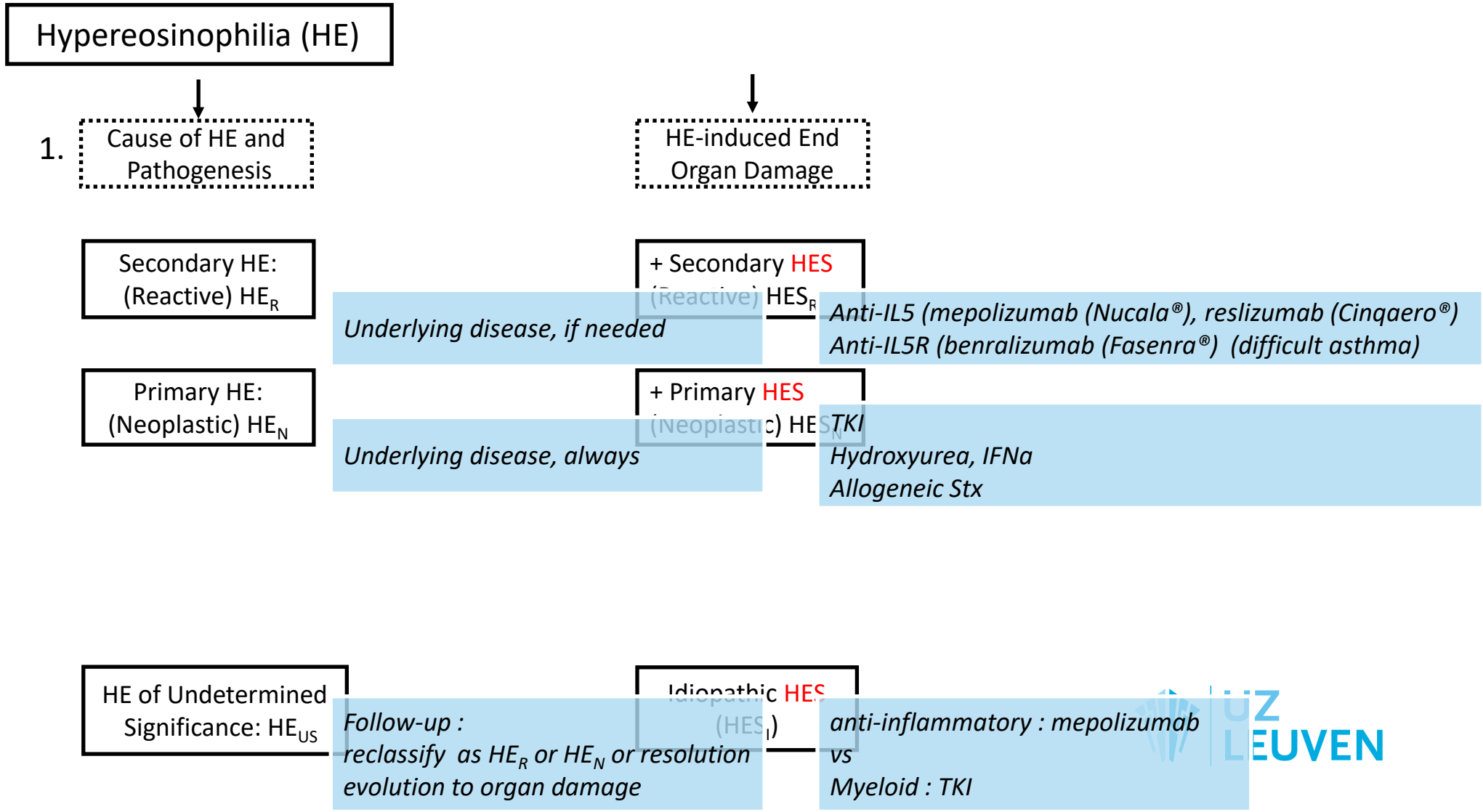
HE of Undetermined Significance: HE_{US}

Idiopathic HES (HES_I)

Acute phase/Emergency

Corticosteroids (prednisone 1mg/kg)

Chronic /maintenance therapy for HE and HES



Case 1

2011, M, 30y

Allergies : penicillin, house dust mite, horses, hay fever

3/2011: DVT vena subclavia en vena axillaris.

5/2011: eosinophilia, splenomegaly, DVT

7/2011: Bone marrow cytology: DD reactive - MPN/iHES. DD… to be correlated with cytogenetics, molecular

Normal karyotype (fragile site @ 12q24). FISH 4q12 normal, WGS no mutations in TKI.

01/2012

Hb 11,6 g/dl; WBC 25 10^9/L, Eosinophils 13 10^9/L

IgE normal, tryptase 60 (<11 ug/L), Vit B12 > 2000 ng/L

Splenomegaly

01/2012

Hyperviscosity syndrome

Hypertrophic cardiomyopathy and apical thrombus

Left hemiparesis

Idiopathic hypereosinophilic syndrome Started on imatinib

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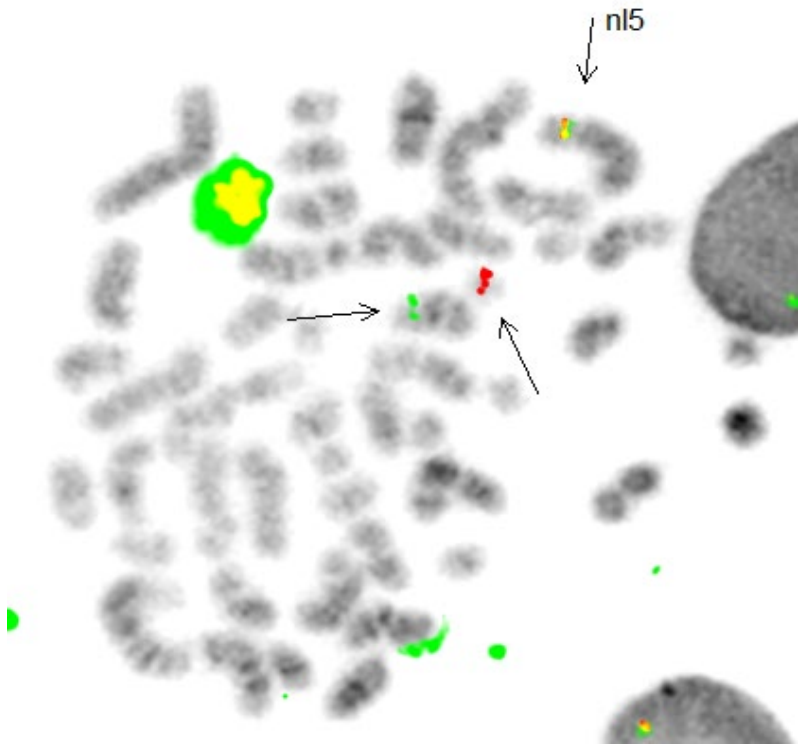
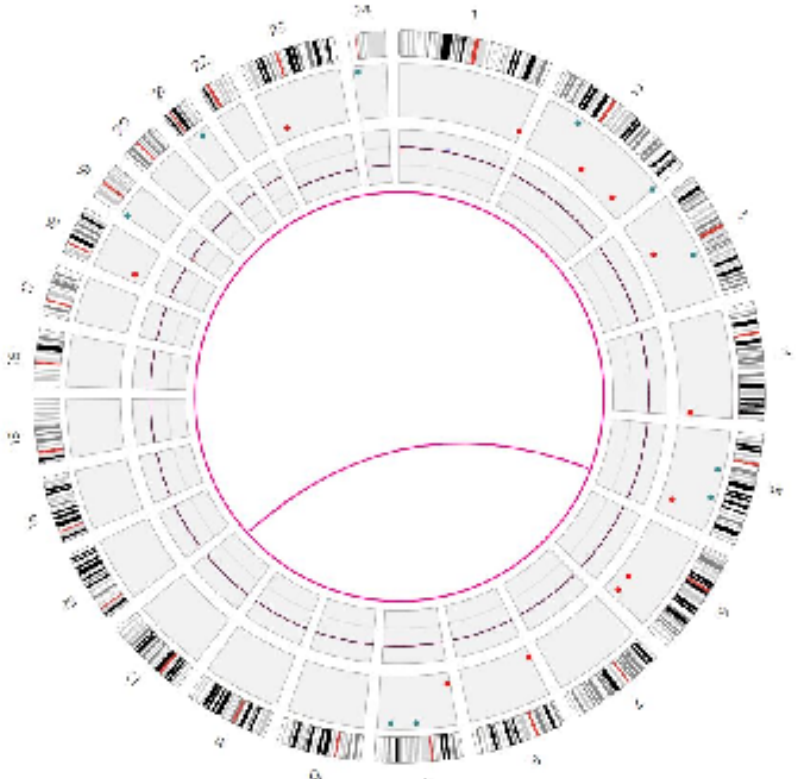
Case 1

karyotype



FISH *PDGFRB* 5q32



Optical genome mapping

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SART3:PDGFRB t(5;12)(q32;q23)

Case 2

2016. F, 26j

Allergic rhinitis and asthma since 1 y

Progressive SOB, myalgia, skin lesions.

Hb 14g/dl, WBC 21 x 10^9/L, AEC 9 x 10^9/L, platelets 335 x 10^9/L

Cardiac MR: mild LV hypertrophy, diffuse myocardial edema/inflammation; ↑ troponins

Chest CT: airtrapping, otherwise normaal

Skin biopsy: Well's syndrome versus skin localisation of eosinophilic leukemia

BM-BB: 45% eosinophils, DD… to be correlated with cytogenetics, molecular

CME: 46,XX. FISH 4q12 normaal, no FIP1L1::PDGFRA transcript

IgE ↑ 873 kU/L, ANCA negative, Vitamin B_{12} 526 ng/L (-), tryptase normal

iHES, most likely reactive or ANCA negative EGPA: tapering corticosteroids (x3), stable w/o steroids since mepolizumab

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Thank you

CME

L. Michaux, J. De Bie, Q. Van Thillo

J. Cools, E. Lierman, S. Smits, P. Marynen

EU-US Multicenter Cooperative Initiative to Standardize Parameters of Disease and Diagnostics for Practice and Clinical Trials in Eosinophil Disorders (led by Peter Valent)

J Allergy Clin Immunol. 2012 Sep;130(3):607-612

World Allergy Organ J. 2012 Dec;5(12):174-81

Allergy, 2022 in press

SAMEN GRENZEN VERLEGGEN

Invitation

A Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Patients With Hypereosinophilic Syndrome (HES) (NATRON)