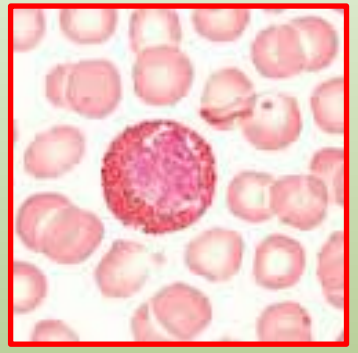


EOZİNOFİLİYE YAKLAŞIM

Dr. Dilek Keskin

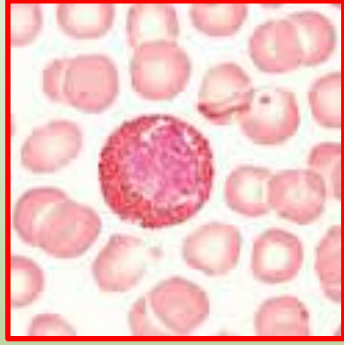
09.09.2023

Kanuni Sultan Süleyman
EAH Hematoloji BD.

Sunum planı

- Eozinofil nedir? Ne işlerden sorumludur?
- Eozinofili nedir? Ne için olur?
- Eozinofili neden önemlidir?
- Eozinofili ile nasıl başa çıkarız?

Eozinofil?



- Granülositlerin içinde küçük bir grup oluştururlar
- Yoğun kristal yapıda granülleri nedeniyle kırılgandırlar
- Parazit enfeksiyonları ile baş ederler
- Allerjik olayların içindedirler
- Dokuda gezmeyi severler
- Aktive olunca yaramaz olabilirler

Kemik iliği

EOZİNOFİLOPOEZ

IL-3

IL-5

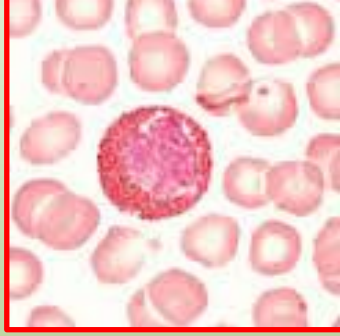
IL-2

CD34+
KÖK
HÜCRE

GM-CSF

MİKROÇEVRE

Eozinofili

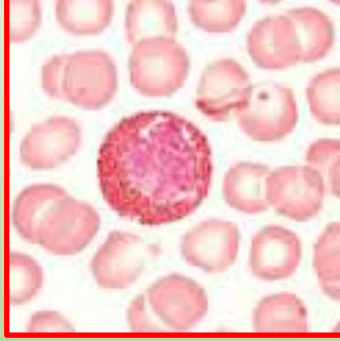


Normalde lökosit formulünün: % 3-5

350-500 mm^3

- Hafif 1500 mm^3
- Orta 1500-5000 mm^3
- Ağır 5000 mm^3

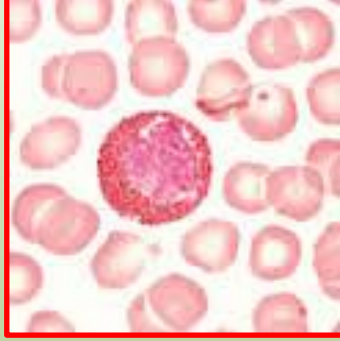
Eozinofili;



- Fibroz
- Tromboz
- Vaskülit
- Allerjik inflamasyon

} sorumlu olabilirler

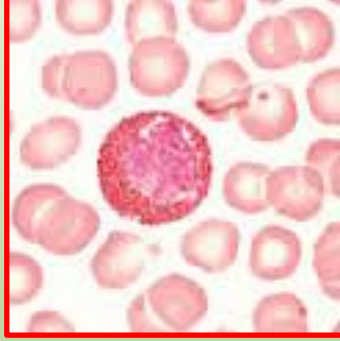
Ancak klinik;



- Eozinofil sayısına
- İnfiltre ettiği dokuya
- Aktivasyon şiddetine

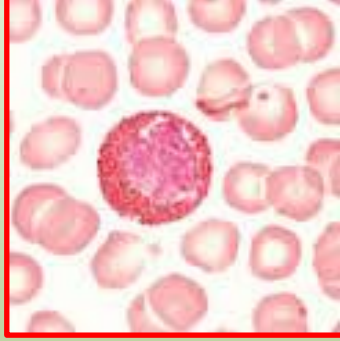
göre şekillenir

Tanımlar



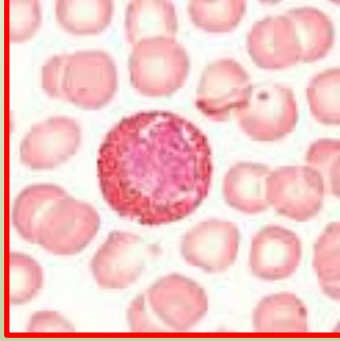
- **Kan eozinofilisi;** Eozinofil sayısı; 500-1500/mm^3
- **Hipereozinofili:** 1 ay ara ile iki ayrı ölçümde eozinofil sayısı; 1500/mm3 üzerinde olması yada dokuda eozinofilinin gösterilmesi
- **Hipereozinofilik sendrom:** Kan eozinofilisi ve doku tutulumu nedeniyle organ hasarı varlığı ve sekonder nedenlerin dışlanması
- **HES/organ spesfik eozinofilik hastalık:** Kan yada organ eozinofilisi ve tekli organ yada sistem tutulumu varlığı

Doku tutulumlu HE



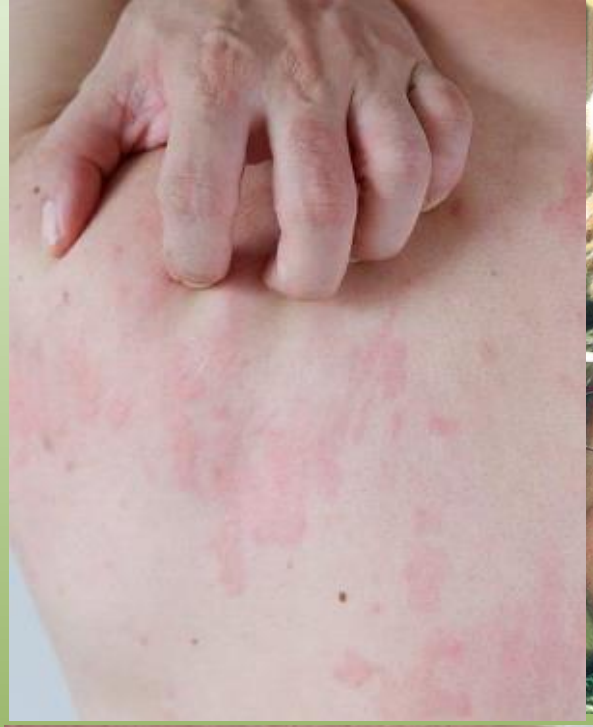
- Eozinofil hücre oranının kemik iliğinde %20>
- Deneyimli patoloğun dokuda belirgin eozinofil artışının olduğunu söylemesi
- İmmunhistokimyasal olarak eozinofil ve eozinofiliye ait proteinlerin ekstrasellüler alanda biriktiğinin gösterilmesi

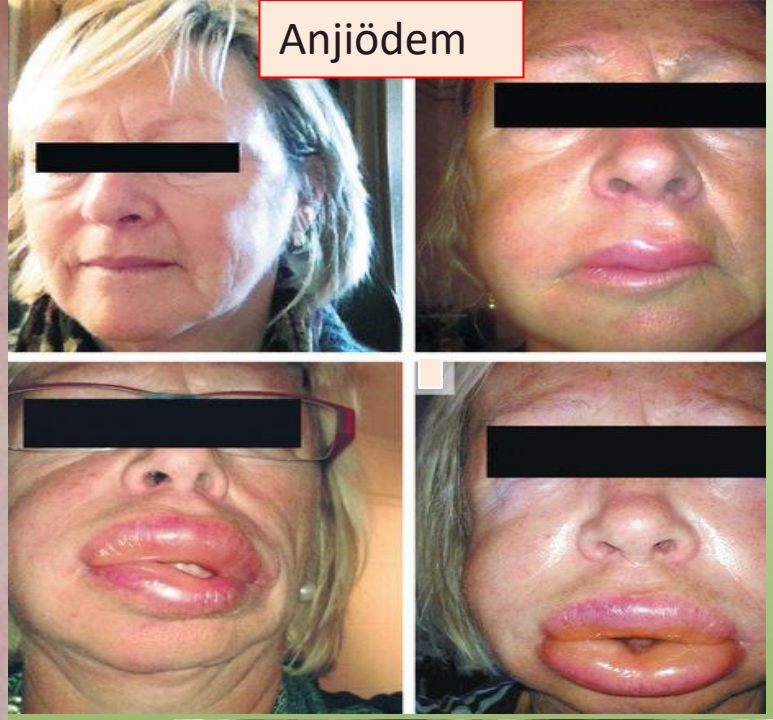
Hipereozinofili;



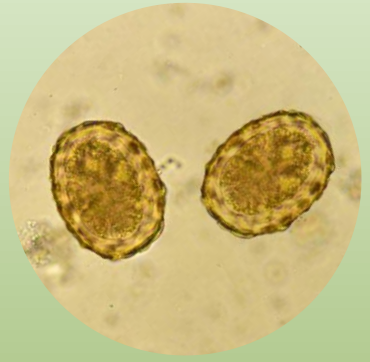
Sekonder/reaktif
(non-hematolojik)

Primer/klonal
(hematolojik)

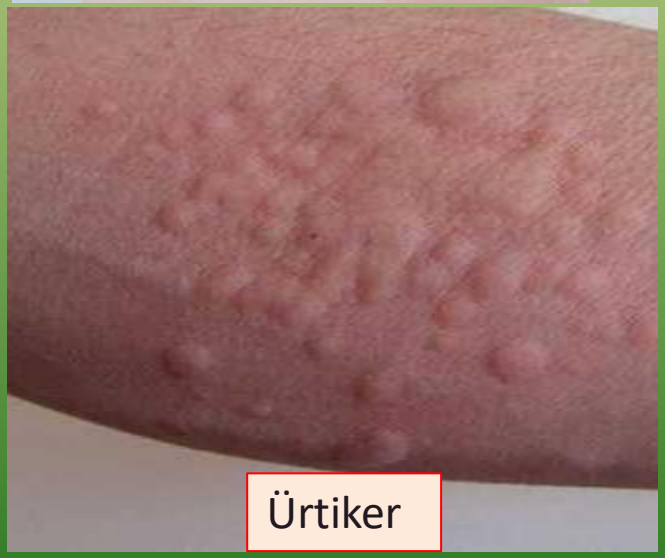




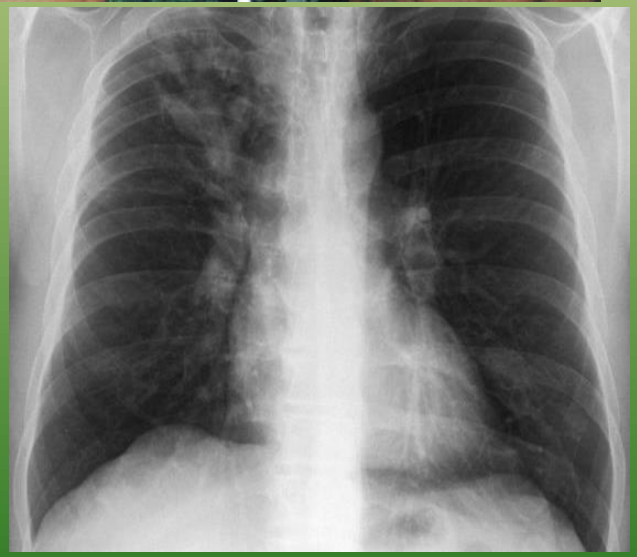
Anjiödem



Askariyazis



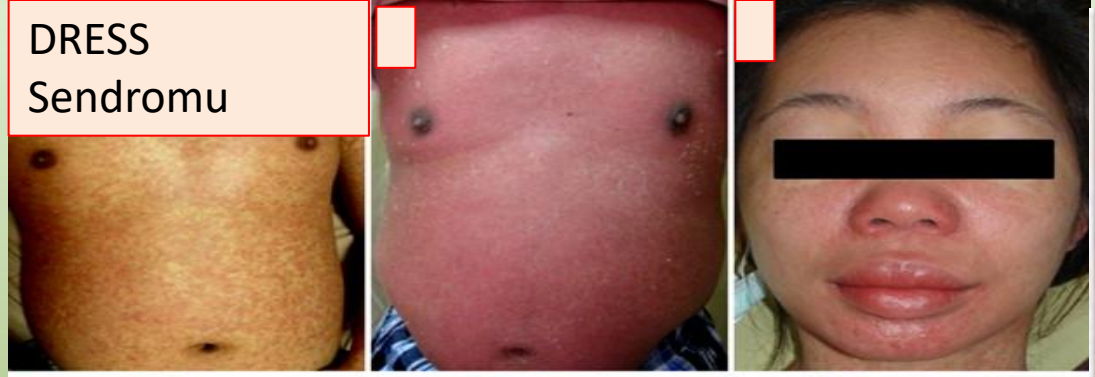
Ürtiker

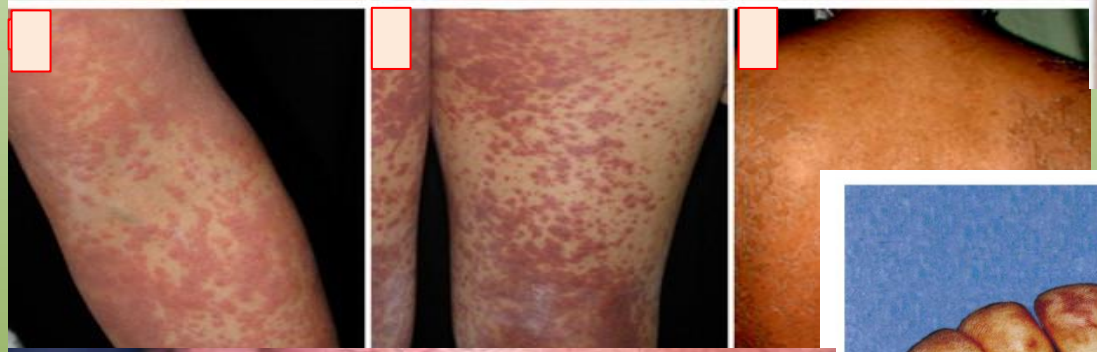


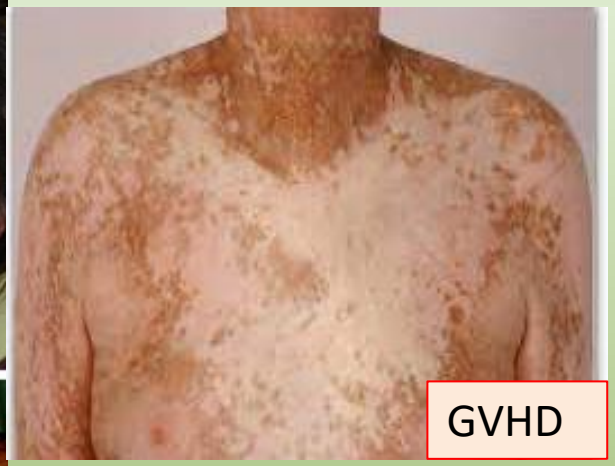
ABPA

Toksokariyazis

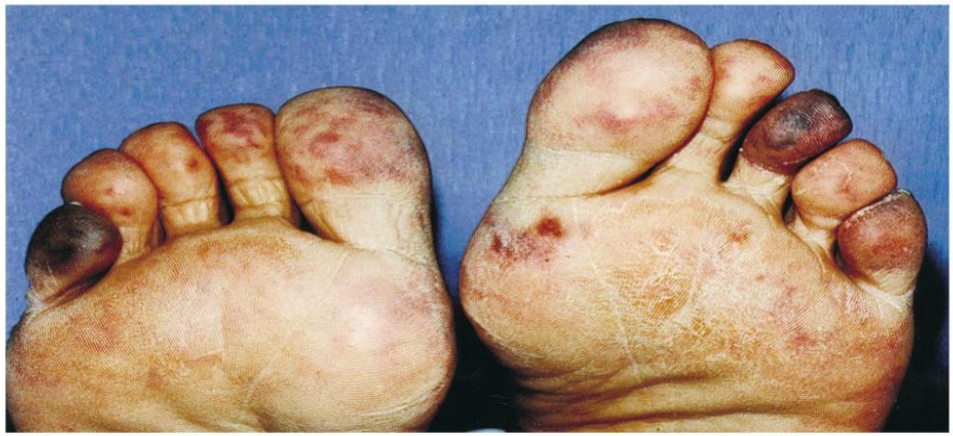
DRESS Sendromu

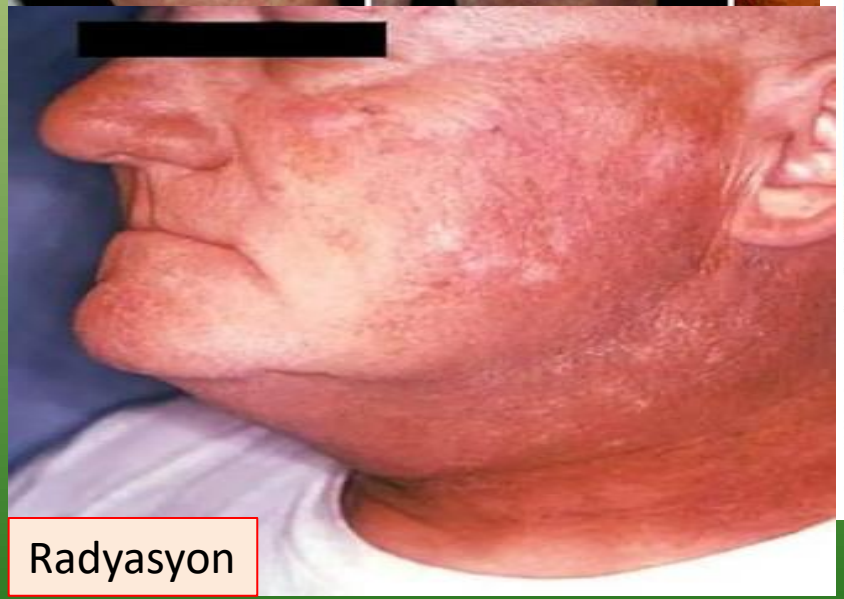




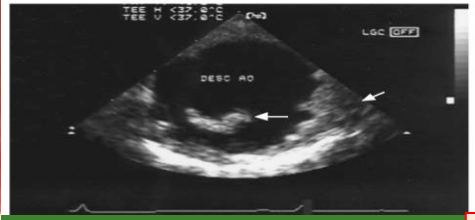


GVHD





Radyasyon



Ateroembolik hastalık

EOZİN**O**FİLİ NEDENLERİ

(ALLERGIC)

Adrenal yetmezlik (Addison hastalığı)

Lenfoma

L-triptofan eksikliği (Eozinofili miyalji sen.)

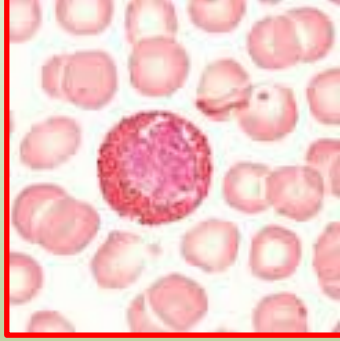
Egzema (Allerjik cilt hastalıkları,pemfigus, dermatitis herpetiformis)

Respiratuar nedenler (astım, ABPA vs.)

Gastroenterit (eozinofilik gastroenterit)

Infeksiyonlar (parazitler, mantarlar)

Collajen vasküler hastalıklar (SLE, EGPA)



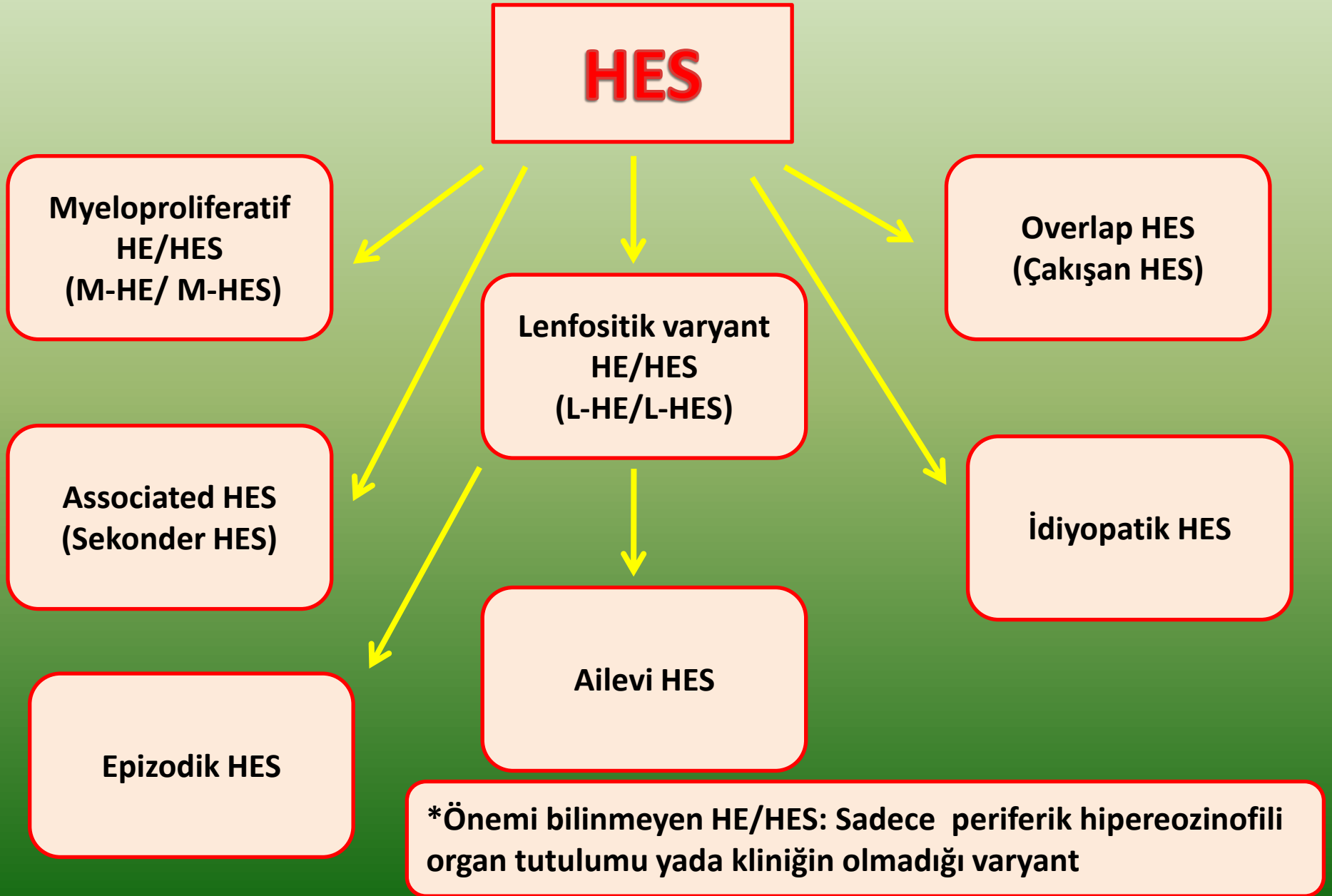
Hipereozinofilik Sendrom

En az 2 ölçümde PERİFERİK $1.5*10^9$ EOZİNOFİL/mL
Belirgin EOZİNOFİLİK DOKU infiltrasyonu

YA DA

Eozinofiliye atfedilebilecek klinik bulgu varlığı
(Açıklayacak başka nedeninin bulunmaması durumunda)

Hipereozinofilik Sendrom: Spektrum



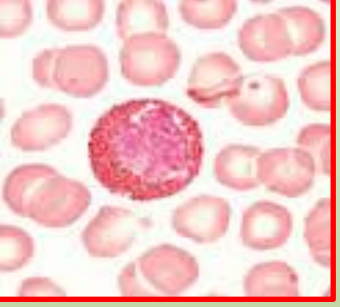
Tedavide dikkat edilecek hususlar

- Altta yatan helmint enfeksiyonları olmamalı

(Hiperinfeksiyon sendromundan kaçınmak için)

- Kardiak tutulum, trombotik olayda ve hipereozinofili (100 bin/mm^3) varlığında hızla tedavi başlanmalı
- Hasta için yapılacak tanısal işlemler tedavinin başlatılmasını geciktirmemeli

<u>Hemen her zaman ilk seçilecek tedavi kortikosteroid</u>



HES: Tedavi

✓Displazik eozinofili, periferde myeloid öncüller, anemi, trombositopeni
✓↑ B12 seviyesi, ↑triptaz
✓Splenomegali, lenfadenomegali
✓hipersellüler ki, kemik iliği fibrozu
✓atipik mast hücreleri

M-HE/HES*

PDGFR-alfa** pozitif vaka

1. basamak: 100-400 mg/gün imatinib mesilat!
✓Ekokardiyografide kardiak tutulum yada Troponin ↑
1 mg/kg Prednizolon yada ekivalanı

2.basamak:
Sorafenib, midostaurin, ponatinib

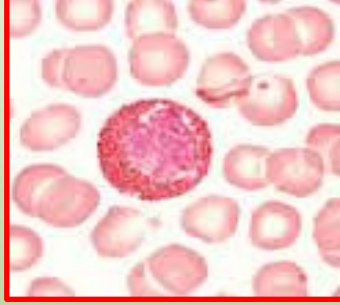
PDGFR-alfa*** negatif vaka

1. basamak:
Kortikosteroid

2.basamak:
Steroid dirençli vaka!
İmatinib
Hidroksiüre, IFN-alfa, SGTKIs
Allojeneik HKN

*% 20 lik kısmı oluşturur
**% 80'inde PDGFR-alfa pozitif

*** Jak2, KİT, FGFR1, PDGFRB pozitif olabilirler



✓Aberran ve/veya klonal lenfositoz
✓Cilt yada yumuşak doku tutulumunu daha yaygın
✓↑ IgE, ↑TARC

L-HE/HES*

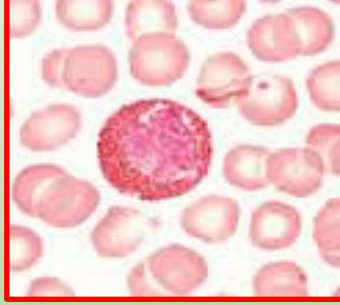
✓1. basamak: Orta yada yüksek doz kortikosteroide iyi yanıt alınır

✓2. basamak: Interferon-alfa

✓3. basamak: Metotreksat, siklosporin A, siklofosfamid, alemtuzumab

*Özellikle yeni beliren yada büyüyen LAM, Aberran T-hücre klonalitesinde artış, Tedaviye direnç, yeni gelişen sitogenetik özellikler, 6qdel varlığında

*Bu vakalar da %5-25 oranında HES dönüşümü ve lenfoma gelişimi olabilir



✓Tek organ yada sistemin eozinofilik infiltrasyonu, ör; eozinofilik kolit

Overlap HES

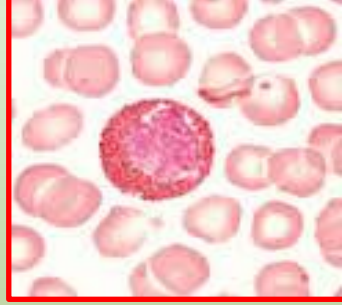
✓Tutulan organın kliniği ve mevcutsa eozinofili gerileyene değin kortikosteroid başlanır,devam edilir
Yavaş yavaş azaltılır (topikal/sistemik)
10 mg/gün altına düşülemeyen vakalar için ilave* düşünülebilir

Sekonder HES

✓Eozinofiliye neden olan başka bir sistemik hastalık var
Helmint enfeksiyonu, Churg-Strauss Sendromu, vb.

✓Allta yatan hastalık tedavi edilir

*Anti IL-5,Hidroksiüre 1-2 gr/gün ,IFN-alfa 1-3 milyonÜ/gün



Ailevi HES

✓OD geçişli
✓HES dönüşümü yaygın değil

✓Çoğunlukla tedavi ihtiyaçları olmaz

Epizodik HES

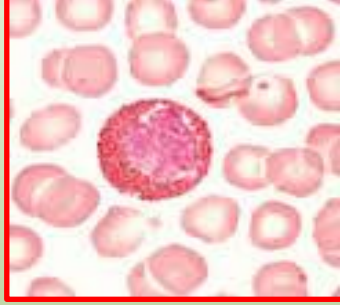
✓L-HES gibi tedavi edilebilirler

✓Herhangi bir kategoriye uymaz
✓Multisistemik tutulum

İdiyopatik HES

✓1.basamak:Kortikosteroid
*Steroid dirençli vakalarda
HU, IFN-alfa, TKIs, Anti-IgE tedaviler

Yeni terapiler



Anti- IL5 (reseptör üzerinden etkinler)

Mepolizumab, Reslizumab, Benralizumab

Dirençli PDGFR-alfa negatif vakalar

Mortal seyirli HES, L-HES vakaları

Reslizumab: IV

Mepolizumab, Benralizumab: SC

EOZİNOFİLİ

İlk İş: Uç Organ Hasarı Ve Ciddi Komplikasyon?

1. AFR, kcft, bft
2. PA ac grafisi, spirometri, trop, NT-proBNP, EKG, Eko
3. HIV serolojisi
4. D-dimer

Ciddi organ hasarı var

HIV + ise yada Strongiloides + ise anti helmintik ver

Steroid başla

Cevap yoksa

Ciddi organ hasarı yok

Sekonder nedenleri ara ve dışla

1. Allerji (sor, test et)
2. İnfeksiyon (seroloji, dışkı paraziti bak)
3. Otoimmun (ANA, ANCA, anti DSDNA, C3,C4)
4. Serum IgE, vitamin B12
5. Serum triptaz
6. ECP
7. Tutulu organ bx

yok

var

Uygun tedavi ve takip

Primer HES düşün

1. Kemik iliği asp.bx
2. F/P mutasyonu ara
3. Flow, THR rearrajmanı
4. Tamamlayıcı testler

HES alt tipini bulduysan
Uygun tedaviyi ver

1. İmatinib
2. Steroid
3. HU

HES alt tipini bulamadıysan
Organ tutulumu aramaya devam

1. Kardiak MRI, endomiyokardiyal bx
2. Tüm vücut BT
3. Bronkoskopi, BAL, AC bx
4. Endoskopi, bx
5. Anijografi
6. Nörolojik testler

ALTTA YATAN HASTALIKTAN BAĞIMSIZ OLARAK

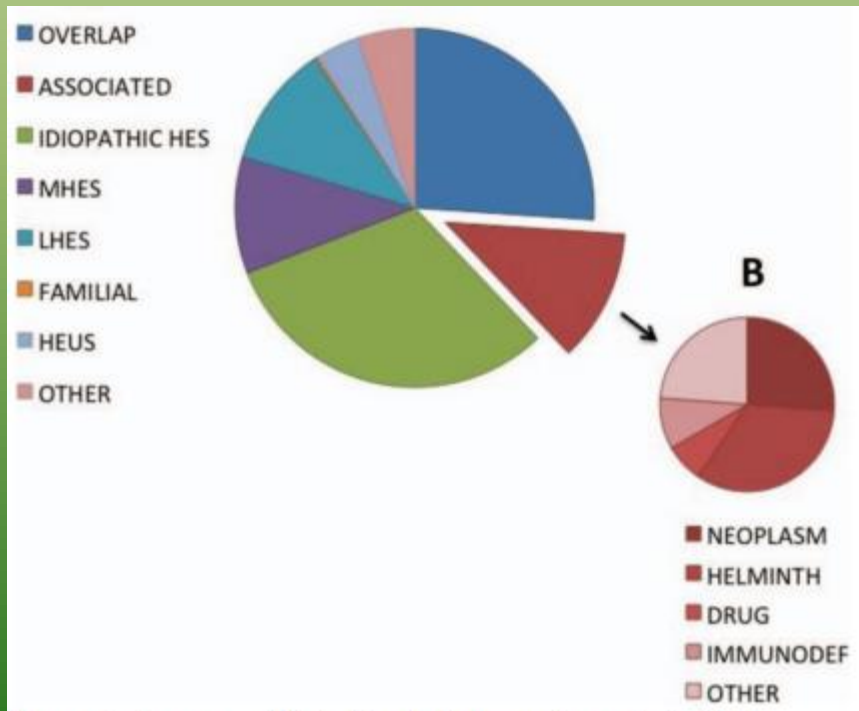
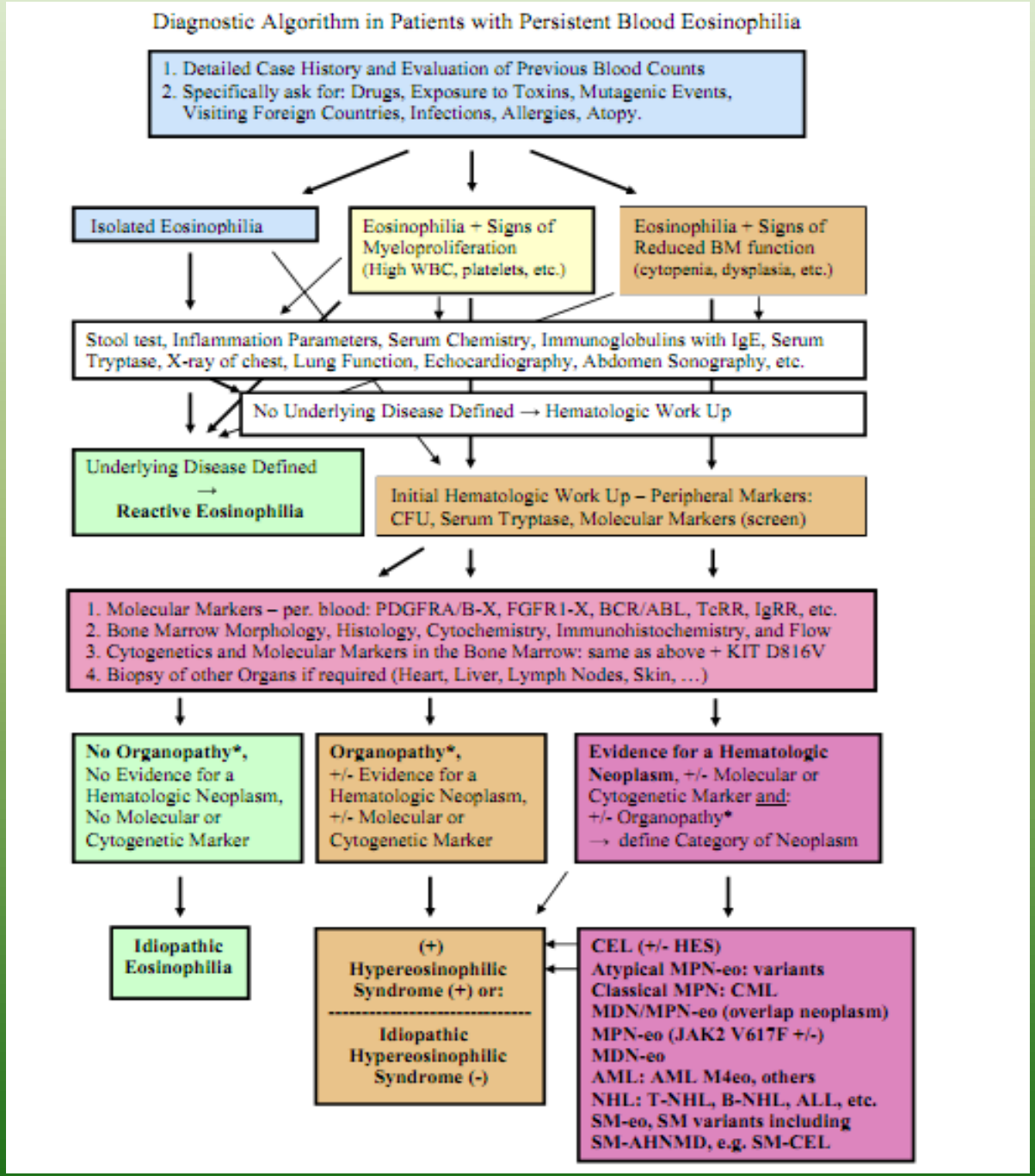
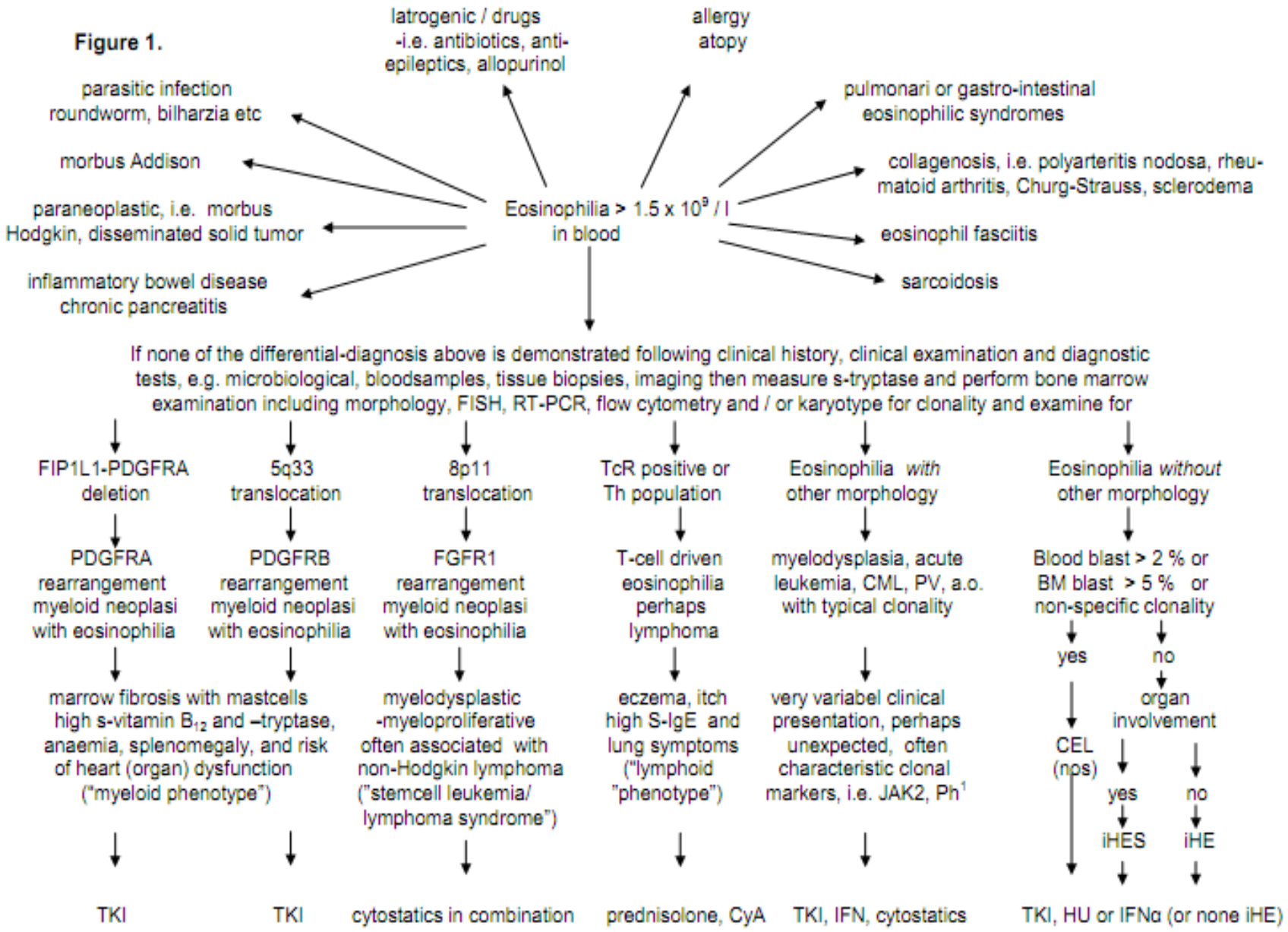


Figure 1. Frequency distribution of diagnoses in a cohort of 302 subjects referred for evaluation of unexplained hypereosinophilia. Adapted from Klion.[25]



Valent P, Blood Reviews, 2009

Figure 1.


Iatrogenic / drugs -i.e. antibiotics, anti-epileptics, allopurinol
allergy atopy
parasitic infection roundworm, bilharzia etc
pulmonari or gastro-intestinal eosinophilic syndromes
morbus Addison
collagenosis, i.e. polyarteritis nodosa, rheumatoid arthritis, Churg-Strauss, sclerodema
paraneoplastic, i.e. morbus Hodgkin, disseminated solid tumor
Eosinophilia > 1.5 x 10⁹ / l in blood
eosinophil fasciitis
inflammatory bowel disease chronic pancreatitis
sarcoidosis
If none of the differential-diagnosis above is demonstrated following clinical history, clinical examination and diagnostic tests, e.g. microbiological, bloodsamples, tissue biopsies, imaging then measure s-tryptase and perform bone marrow examination including morphology, FISH, RT-PCR, flow cytometry and / or karyotype for clonality and examine for
FIP1L1-PDGFRA deletion
5q33 translocation
8p11 translocation
TcR positive or Th population
Eosinophilia *with* other morphology
Eosinophilia *without* other morphology
PDGFRA rearrangement myeloid neoplasi with eosinophilia
PDGFRB rearrangement myeloid neoplasi with eosinophilia
FGFR1 rearrangement myeloid neoplasi with eosinophilia
T-cell driven eosinophilia perhaps lymphoma
myelodysplasia, acute leukemia, CML, PV, a.o. with typical clonality
Blood blast > 2 % or BM blast > 5 % or non-specific clonality
yes
no
marrow fibrosis with mastcells high s-vitamin B12 and –tryptase, anaemia, splenomegaly, and risk of heart (organ) dysfunction ("myeloid phenotype")
myelodysplastic -myeloproliferative often associated with non-Hodgkin lymphoma ("stemcell leukemia/ lymphoma syndrome")
eczema, itch high S-IgE and lung symptoms ("lymphoid "phenotype")
very variabel clinical presentation, perhaps unexpected, often characteristic clonal markers, i.e. JAK2, Ph1
organ involvement
CEL (nos)
yes
no
iHES
iHE
TKI
TKI
cytostatics in combination
prednisolone, CyA
TKI, IFN, cytostatics
TKI, HU or IFNα (or none iHE)

Organ	Symptoms
Heart	Myocardial necrosis (weeks), valvular involvement, thrombosis (months later) and fibrosis (end stage) (Loeffler's endocarditis and myocardial fibrosis in late stages) manifesting in congestive cardiac insufficiency, hypertrophy, dilation, arrhythmias, and pericardial effusion.
Nervous system	Cerebral thrombosis – mostly arterial, transient ischemia, embolic or local thrombus formation. Encephalopathy, in particular cognitive and / or upper neuron paresis. Peripheral neuropathies, symmetric or not, sensory or motoric or both.
Skin	Urticaria, angioedema, pruritus, papulous or nodulous lesions, mucocutaneous ulcera.
Pulmonary	Chronic, generally non-productive cough. Bronchial hyperactivity may be present in some, and some may have pulmonary symptoms secondary to heart affection.
Gastrointestinal	Diarrhoea, intermittent or persistent, but various abdominal symptoms may be experienced, also depending on a more selective localization in the gastrointestinal tract
Rheumatological	Arthralgia, mostly major joints, arthritis and myalgia. Raynaud's phenomenon. Autoimmune phenomena mostly develop in rheumatic disorders with eosinophilia,

Nordic Study Group- Guideline, 2012

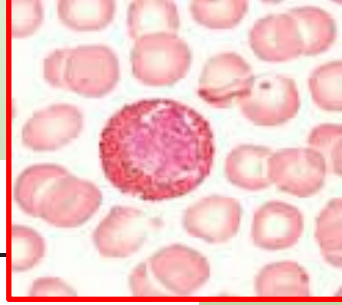


Table 1. Classification of hypereosinophilic syndromes

Clinical subtype	Definition	Examples	Features
M-HES	HES with documented or presumed clonal eosinophilic involvement	PDGFR-associated MPN CEL-NOS Idiopathic HES with myeloproliferative features*	Male predominance (in PDGFR-associated MPN) High mortality if untreated
L-HES	HES with a demonstrable clonal or phenotypically aberrant lymphocyte population producing cytokines that drive eosinophilia	CD3−CD4+ L-HES Episodic eosinophilia and angioedema† (Gleich's syndrome)	Equally common in men and women High prevalence of skin and soft tissue manifestations Elevated IgE and TARC Progression to lymphoma in 5%-25%
Overlap HES	Eosinophilic disease restricted to a single organ system accompanied by peripheral eosinophilia >1.5 × 10^9/L	Eosinophilic gastrointestinal disease Chronic eosinophilic pneumonia Eosinophilic granulomatosis with polyangiitis	Can be difficult to distinguish from idiopathic HES when AEC is elevated
Associated HES	Eosinophilia >1.5 × 10^9/L in the setting of a distinct diagnosis, in which eosinophilia has been described in a subset of affected patients	Primary immunodeficiency syndromes, such as autoimmune lymphoproliferative disease and hyper-IgE syndrome Sarcoidosis Inflammatory bowel disease	Treatment directed at underlying cause
Familial HES	HES occurring in multiple members of a single family	Autosomal dominant familial HE	Progression to HES uncommon
Idiopathic HES	HES of unknown cause that does not meet criteria for any of the other categories		Multisystem involvement

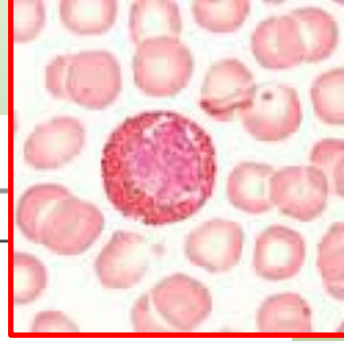


Table 2. Initial evaluation of HES

Test	Comment
All patients with HES	
Complete blood count*	
Routine chemistries, including liver function tests*	
Quantitative serum immunoglobulin levels, including IgE	
Serum troponin,* echocardiogram	If abnormal, cardiac MRI should be considered as this may show characteristic features of eosinophilic involvement; tissue involvement may be patchy limiting the utility of biopsy
Pulmonary function tests*	
Chest/abdomen/pelvis CT*	To assess for splenomegaly, lymphadenopathy and occult neoplasms
Bone marrow biopsy, including cytogenetics*	Recommended in all patients with AEC >5.0 × 10^9/L, features of M-HES or L-HES; should be considered in other patients
Biopsies of affected tissues (if possible)*	
Other testing as indicated by history, signs and symptoms	Including parasitic serologies, ANCA, and HIV
Serum tryptase and B12 levels	
FIP1L1/PDGFRA analysis by FISH or RT-PCR	Testing of peripheral blood is sufficient
T and B cell receptor rearrangement studies	
Lymphocyte phenotyping by flow cytometry*	At a minimum CD3, CD4, and CD8, and CD19 or 20 staining should be performed to assess for aberrant CD3−CD4+, CD3+CD4+CD8+, and CD3+CD4−CD8− populations and B cell lymphoproliferative disorders
Patients with features of M-HES	
Additional testing for *BCR-ABL1*, *PDGFRB*, *JAK2*, *FGFR1*, and *KIT* mutations by PCR, FISH or other methods, as appropriate	Testing should be guided by bone marrow findings
Patients with evidence of L-HES	
Consider PET scan,* lymph node biopsy*	
EBV viral load	

*Substantially affected by corticosteroid therapy.
Adapted from Klion.[25]