Síndrome de Churg-Strauss vs Síndrome Hipereosinofílico Primario

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24 de Octubre 2014

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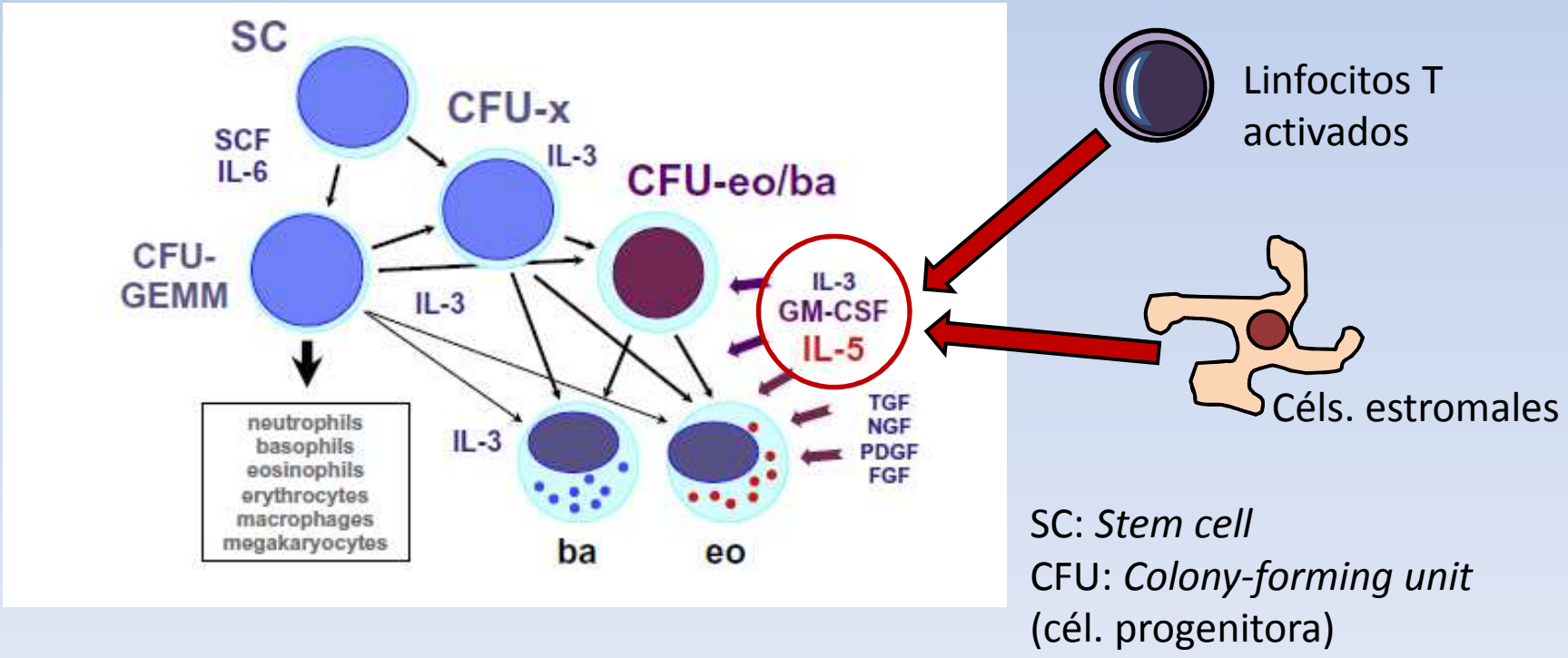
2. Sde de Churg-Strauss (SCS) y síndrome hipereosinofílico (SHE): ¿dos enfermedades, un espectro clínico?
3. SCS y SHE similitudes más allá de la clínica

$$a^n+b^n=c^n\ ?$$

INDICE:

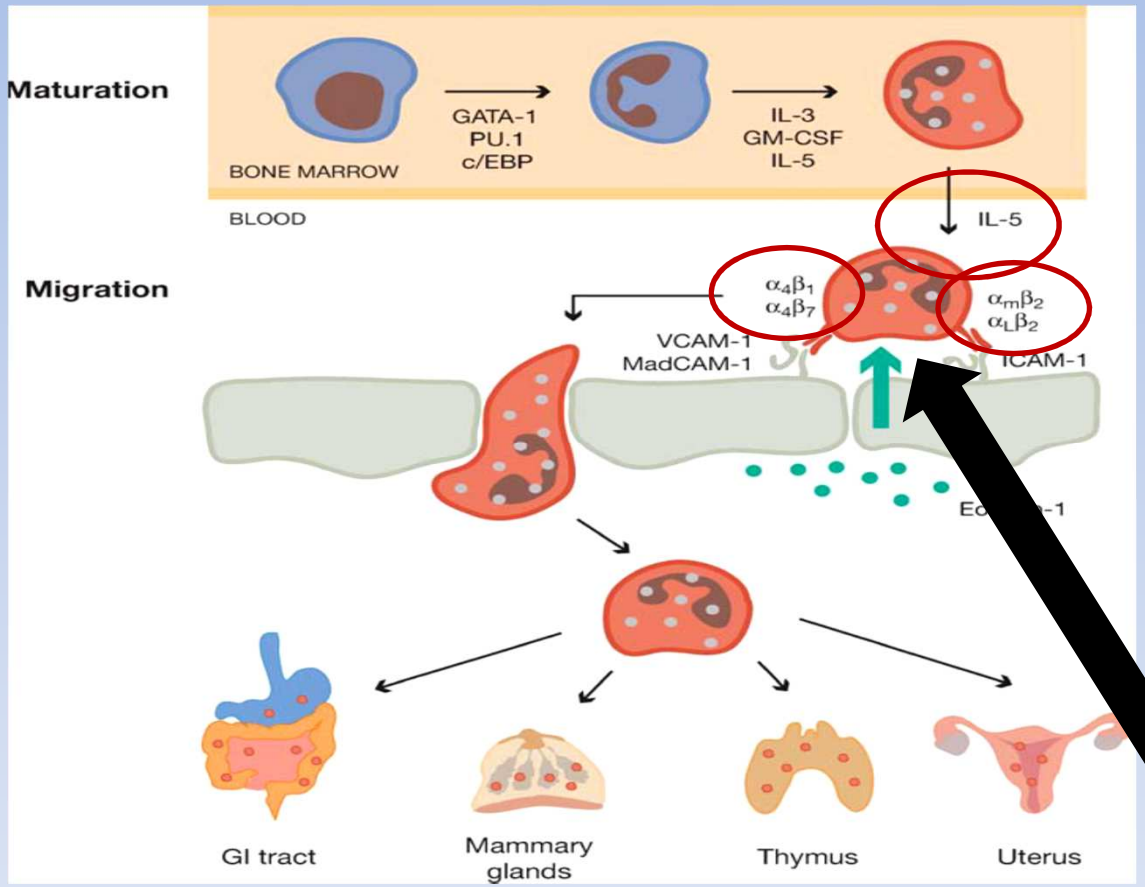
INTRODUCCIÓN: EL EOSINÓFILO

•Célula de estirpe mielopoiética derivada de la población de células hematopoiéticas CD34+ pluripotenciales sometidas a determinados estímulos: IL-5, GM-CSF, IL-3.



SC: *Stem cell*
CFU: *Colony-forming unit*
(cél. progenitora)

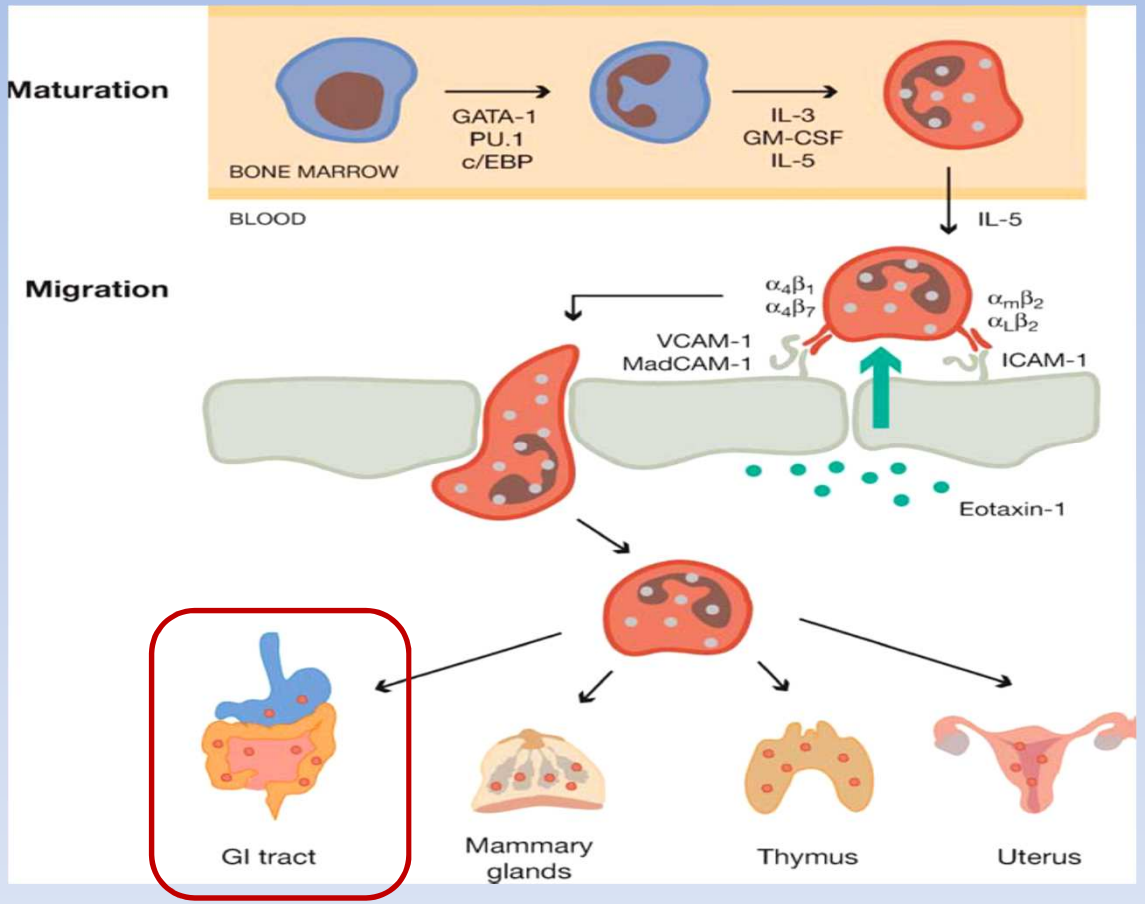
INTRODUCCIÓN: EL EOSINÓFILO



Vida media en SP: 12-20h
Valores normales:
350-500 cels/mm^3
3-5% de los leucos.

Receptores de adhesión:
- LFA-1 (CD11a-CD18)
- CR3 (CD11b-CD18)
- CR4 (CD11c-CD18)
- VLA4 (CD49d-CD29)
- CD44
- CD62L
- PSGL1
- CD34

INTRODUCCIÓN: EL EOSINÓFILO

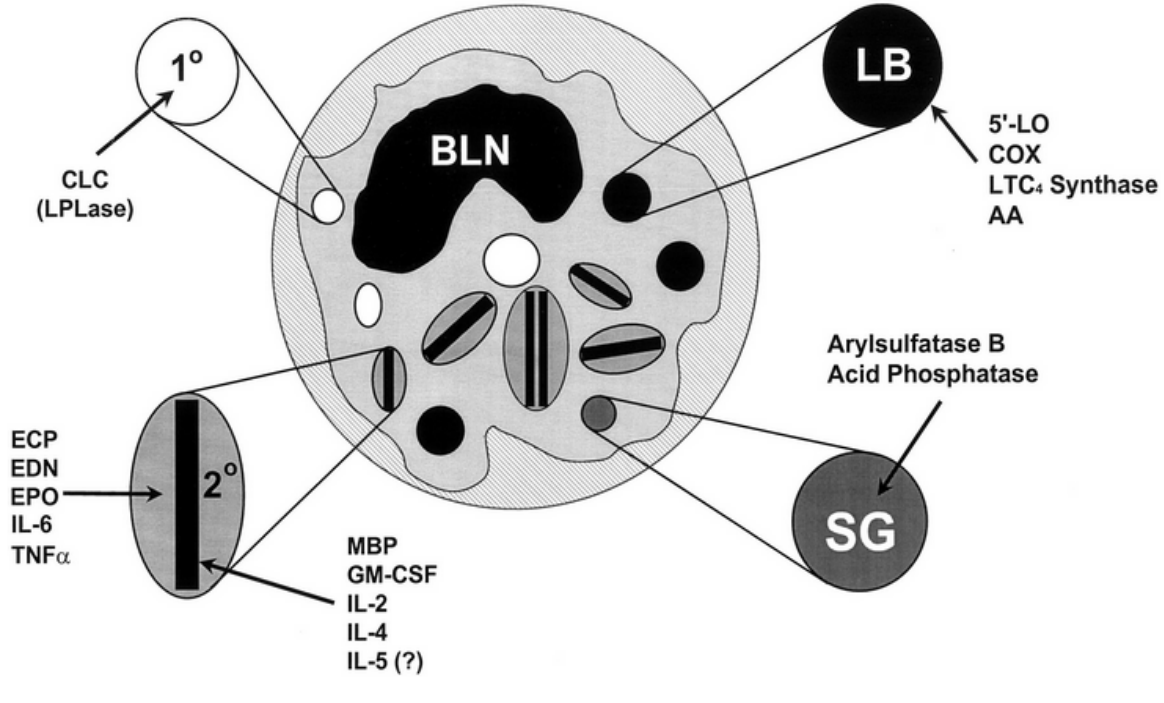


Vida media en SP: 12-20h
Valores normales:
350-500 cels/mm3
3-5% de los leucos.

Vida media en tejidos: 6 días-semanas
Población 100 veces más numerosa que en SP

INTRODUCCIÓN: EL EOSINÓFILO

Papel proinflamatorio:



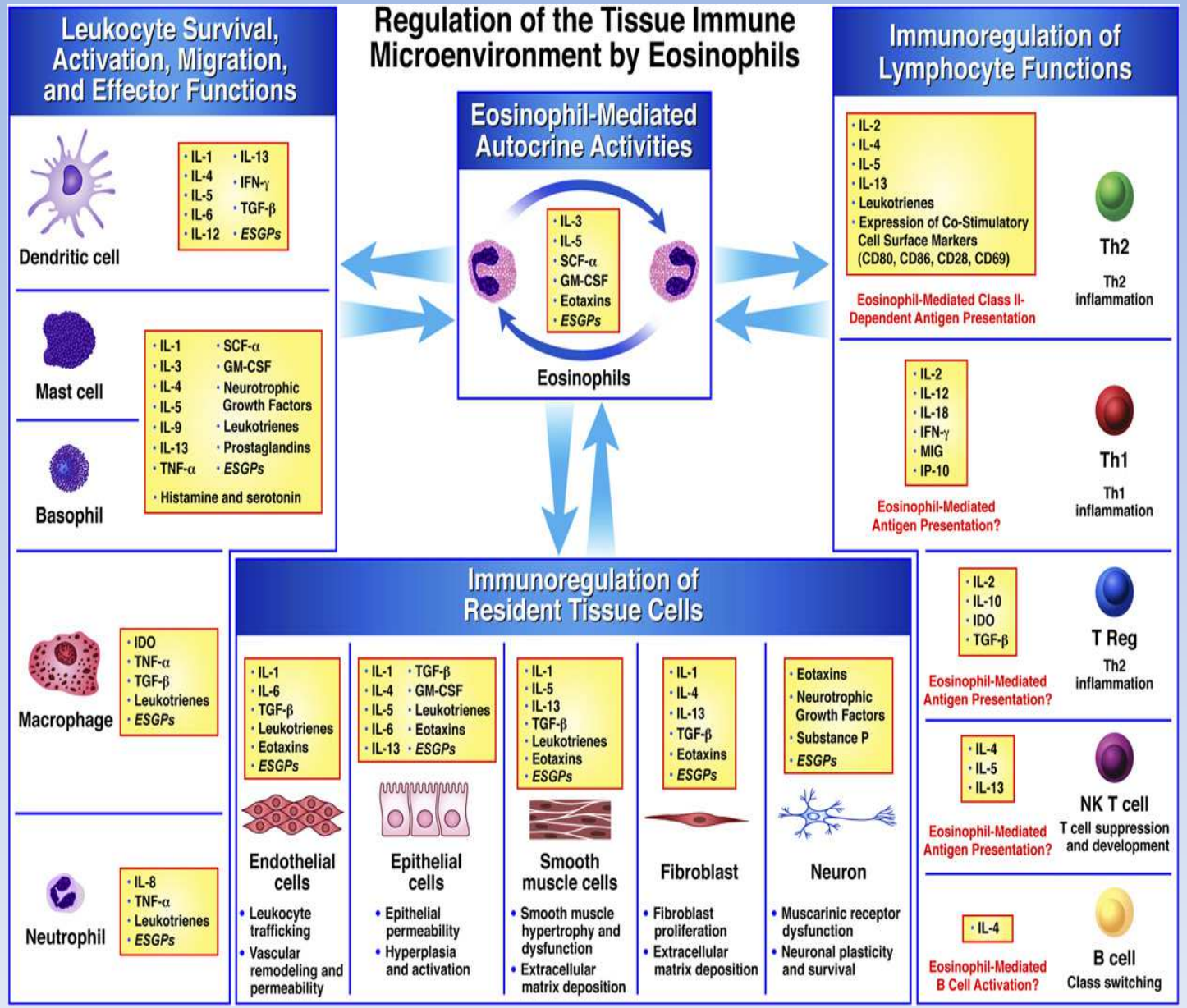
Giembyczi et al. Pharmacological Reviews.1999

Mediadores tóxicos:

- proteínas catiónicas básicas (MBP,ECP,EDN)
- mediadores lipídicos
- citoquinas, quimiocinas
- especies reactivas de oxígeno

- Papel efector crucial en la respuesta a parásitos, bacterias y células neoplásicas
- Mediador importante de las reacciones inmunoalérgicas
- La liberación excesiva de mediadores tóxicos proinflamatorios provoca daño tisular

INTRODUCCIÓN: EL EOSINÓFILO



Jacobsen et al. J Allergy Clin Immunol. 2007

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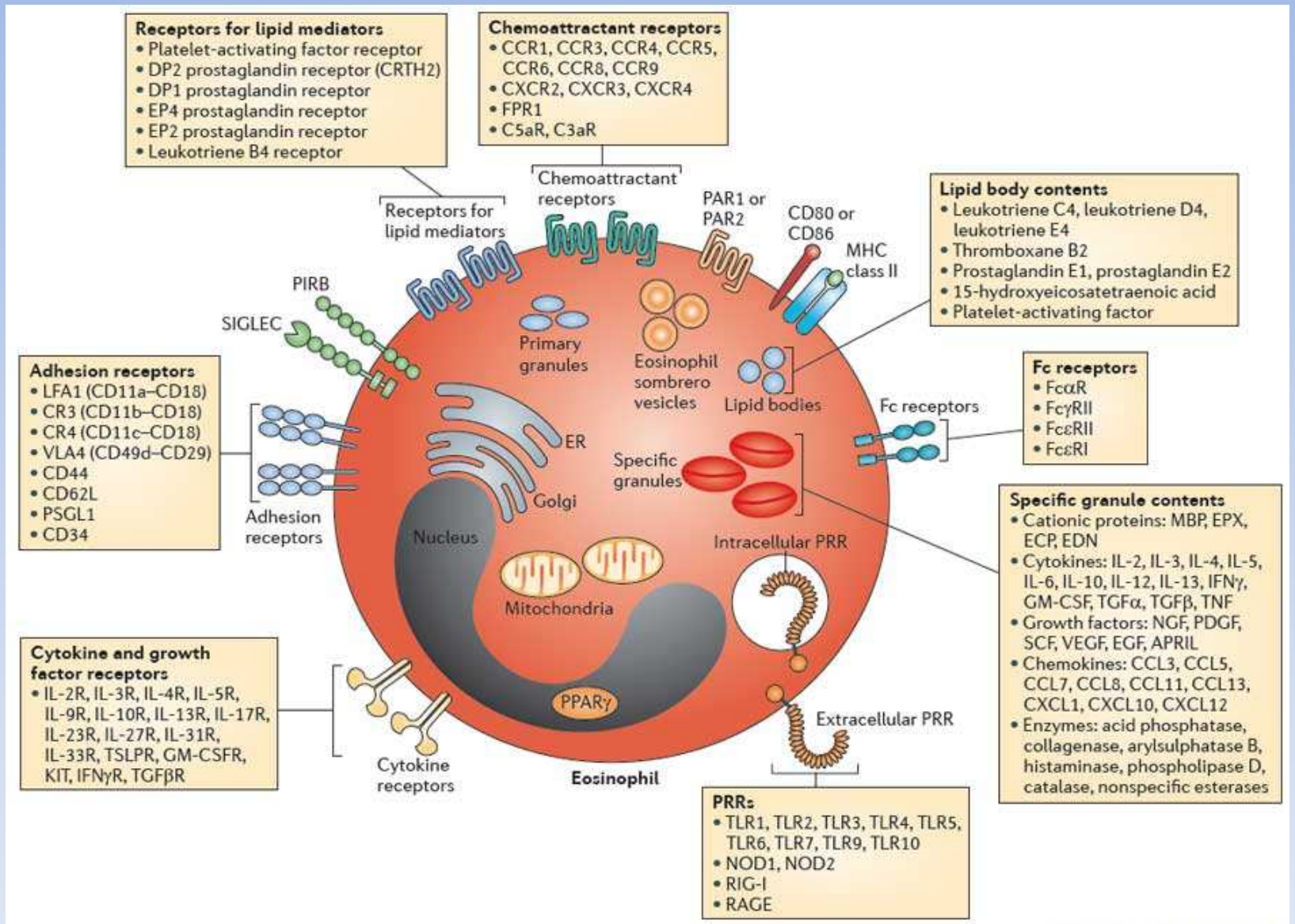

Helene F. Rosenberg, Nature Reviews Immunology, 2013

INDICE:

2. SCS y SHE: 2 enfermedades?

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

Peter Valent, MD,[a] Amy D. Klion, MD,[b] Hans-Peter Horny, MD,[c] Florence Roufosse, MD, PhD,[d] Jason Gotlib, MD,[e] Peter F. Weller, MD,[f] Andrzej Hellmann, MD,[g] Georgia Metzgeroth, MD,[h] Kristin M. Leiferman, MD,[i] Michel Arock, PharmD, PhD,[j] Joseph H. Butterfield, MD,[k] Wolfgang R. Sperr, MD,[a] Karl Sotlar, MD,[l] Peter Vandenberghe, MD, PhD,[m] Torsten Haferlach, MD,[n] Hans-Uwe Simon, MD, PhD,[o] Andreas Reiter, MD,[h] and Gerald J. Gleich, MD[i,p] *Vienna, Austria, Bethesda, Md, Ansbach, Mannheim, and Munich, Germany, Brussels and Leuven, Belgium, Stanford, Calif, Boston, Mass, Gdansk, Poland, Salt Lake City, Utah, Cachan, France, Rochester, Minn, and Bern, Switzerland*

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2. SCS y SHE: 2 enfermedades?

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

Proposed term	Definition and criteria
Hypereosinophilia (HE)	>1.500 Eo/mm^3 on 2 examinations (interval ≥ 1 m) **and/or tissue HE** defined by: 1. Percentage of eosinophils in BM sections >20% of all nucelated cells and/or 2. Pathologist opinion and/or 3. Marked deposition of Eo granule proteins
Hypereosinophilic syndrome (HES)	1. Criteria for peripheral blood HE fulfilled and **2. Organ damage and/or dysfunction attributable to tissue HE and** 3. Exclusion of other disorders or conditions as major reason for organ damage
Eosinophil-associated single-organ disease	1. Criteria of HE fulfilled and 2. Single-organ disease

2. SCS y SHE: 2 enfermedades?

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Hypereosinophilic syn	e
Eosinophil-associated single-organ disease	1. Criteria of HE fulfilled and 2. Single-organ disease

Daño orgánico secundario a eosinófilos:

- Disfunción asociada a marcada infiltración eosinofílica y/o presencia de productos derivados de los eosinófilos
- Formas:
  - Fibrosis (pulmón, corazón, tracto GI, piel...)
  - Trombosis
  - Eritema cutáneo, edema/angioedema, eccema, prurito
  - Neuropatía central o periférica
  - Otras menos frecuentes (hígado, riñón, páncreas...)

2. SCS y SHE: 2 enfermedades?

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

TABLE II. Classification of HE

Proposed terminology	Proposed abbreviation	Pathogenesis/definition
Hereditary (familial) HE	HE_{FA}	Pathogenesis unknown; familial clustering, no signs or symptoms of hereditary immunodeficiency, and no evidence of a reactive or neoplastic condition/disorder underlying HE
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Primary (clonal/neoplastic) HE†	HE_{N}	Underlying stem cell, myeloid, or eosinophilic neoplasm, as classified by WHO criteria; eosinophils considered neoplastic cells*
Secondary (reactive) HE†	HE_{R}	Underlying condition/disease in which eosinophils are considered nonclonal cells‡; HE considered cytokine driven in most cases‡

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Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

- Hipereosinfilia sin clonalidad demostrable
- Causa aparente subyacente después de estudio clínico
- Por hiperproducción de citocinas eosinofilopoiéticas: IL-3 e **IL-5**

Table 1. Reactive causes of eosinophilia

Allergic/hypersensitivity diseases	
	Asthma, rhinitis, drug reactions, allergic bronchopulmonary aspergillosis, allergic gastroenteritis
Infections	
	Parasitic (strongyloidiasis, *Toxocara canis*, *Trichinella spiralis*, visceral larva migrans, filariasis, schistosomiasis, *Ancylostoma duodenale*, *Fasciola hepatica*, *Echinococcus*, *Toxoplasma*, other parasitic diseases)
	Bacterial/mycobacterial
	Fungal (coccidioidomycosis, cryptococcus)
	Viral (HIV, herpes simplex virus [HSV], human T-cell leukemia virus type [HTLV-2])
	Rickettsial
Connective tissue diseases	
	Churg-Strauss syndrome, Wegener granulomatosis, rheumatoid arthritis, polyarteritis nodosa, systemic lupus erythematosus, scleroderma, eosinophilic fasciitis/myositis
Pulmonary diseases	
	Bronchiectasis, cystic fibrosis, Loeffler syndrome, eosinophilic granuloma of the lung
Cardiac diseases	
	Tropical endocardial fibrosis, eosinophilic endomyocardial fibrosis or myocarditis
Skin diseases	
	Atopic dermatitis, urticaria, eczema, bullous pemphigoid, dermatitis herpetiformis, episodic angioedema with eosinophilia (Gleich syndrome)
Gastrointestinal diseases	
	Eosinophilic gastroenteritis, celiac disease
Malignancies	
	Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic leukemia, Langerhans cell histiocytosis, angiolymphoid hyperplasia with eosinophilia (Kimura disease), angioimmunoblastic lymphadenopathy, solid tumors (eg, renal, lung, breast, vascular neoplasms, female genital tract cancers)
Immune system diseases/abnormalities	
	Wiskott-Aldrich syndrome, hyper-IgE (Job) syndrome, hyper-IgM syndrome, IgA deficiency
Metabolic abnormalities	
	Adrenal insufficiency
Other	
	IL-2 therapy, L-tryptophan ingestion, toxic oil syndrome, renal graft rejection

Extraído de:
Gotlib J et al. Blood 2004; 103(8): 2879-91

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

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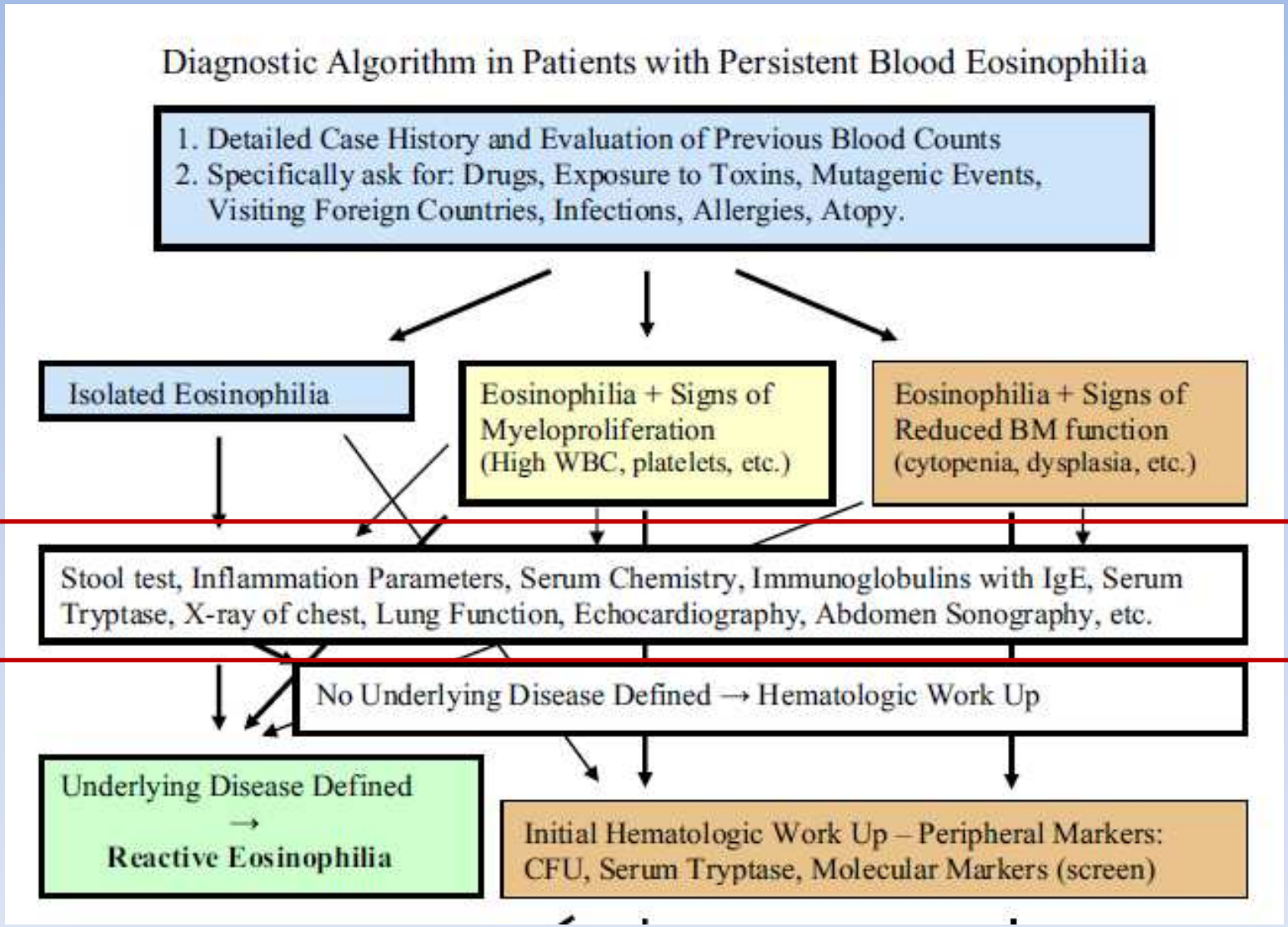
Transient
Infections
Allergic reactions
Drug reactions
Chronic/Persistent
Chronic helminth infections
Other chronic infections
Autoimmune diseases
cGvHD
Atopic diseases
Endocrinopathies
Solid tumors/cancer
B cell lymphoma/leukemia
T cell clones
T cell lymphoma/leukemia
Eosinophil syndromes – see Table 2

Causas de HE reactiva

Estudio de hipereosinofilia



Valent P et al. Blood Rev 2009: 157-165

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2. SCS y SHE: 2 enfermedades?

Hipereosinofilia primaria (o clonal):

- Los eosinófilos son consideradas células neoplásicas (HE monoclonal)
- Se considera clonalidad de HE cuando:
    - Puede demostrarse un defecto citogenético vinculado con la aparición de HE

2. SCS y SHE: 2 enfermedades?

Marcadores moleculares y defectos citogenéticos relacionados con hipereosinofilia clonal:

Molecular defect oncoprotein	Cytogenetic defect	Disorder/diagnosis
BCR/ABLp210	t(9;22)	CML
CBFβ/MYH11	inv(16)	AML M4-eo
FIP1L1/PDGFRA	del(4q12)	CEL, SM–CEL, CMML-eo, atypical/unclassifiable MPN-eo
BCR/PDGFRA	t(4;22)(q12;q11)	CEL, unclassifiable MPN-eo
KIF5B/PDGFRA	t(4;10)(q12;p11)	CEL
CDK5RAP2/PDGFRA	ins(9;4)(q33;q12q25)	CEL
ETV6/PDGFRB	t(5;12)(q33;p13)	CMML-eo, atypical MPN-eo, CEL
BABAPTIN5/PDGFRB	t(5;17)(q33;p13)	CMML-eo
HCMOGT1/PDGFRB	t(5;17)(q33;p11.2)	JMML-eo
CEV14/PDGFRB	t(5;14)(q33;q32)	AML-eo
NIN/PDGFRB	t(5;14)(q33;q24)	Atypical/unclassifiable MPN-eo
KIAA1509/PDGFRB	t(5;14)(q31;q32)	CMML-eo
TP53BP1/PDGFRB	t(5;15)(q33;q22)	Atypical/unclassifiable MPN-eo
PDE4DIP/PDGFRB	t(1;5)(q23;q33)	Atypical/unclassifiable MPN-eo
HIP1/PDGFRB	t(5;7)(q33;q11.2)	CMML-eo
H4/PDGFRB	t(5;10)(q33;q22)	Atypcial/unclassifiable MPN-eo
ZNF198/FGFR1	t(8;13)(p11;q12)	SCLL, atypical MPN-eo, CEL
FOP/FGFR1	t(6;8)(p27;p11)	SCLL
TIF1/FGFR1	t(7;8)(q34;p11)	SCLL
MYO18A/FGFR1	t(8;17)(p11;q23)	SCLL
HERVK/FGFR1	t(8;19)(p12;q13.3)	SCLL
BCR/FGFR1	t(8;22)(p11;q11)	Atypical MPN-eo (CML-like)
CEP110/FGFR1	t(8;9)(p12;q23)	SCLL
FGFR1OP2/PDGFRA	ins(12;8)(p11;p11p22)	SCLL
KIT D816V	–	SM-eo: (ISM-eo, SSM/ASM-eo) MCL-eo, SM–AHNMD
JAK2 V617F	–	Classical MPN: PV, ET, PMF

Valent P et al. Blood Rev 2009: 157-165

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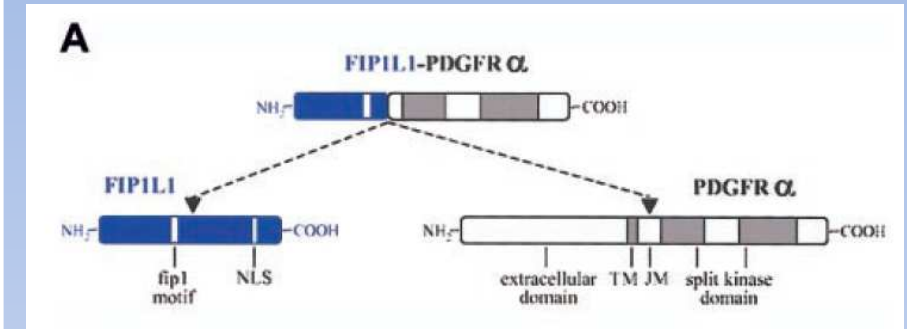
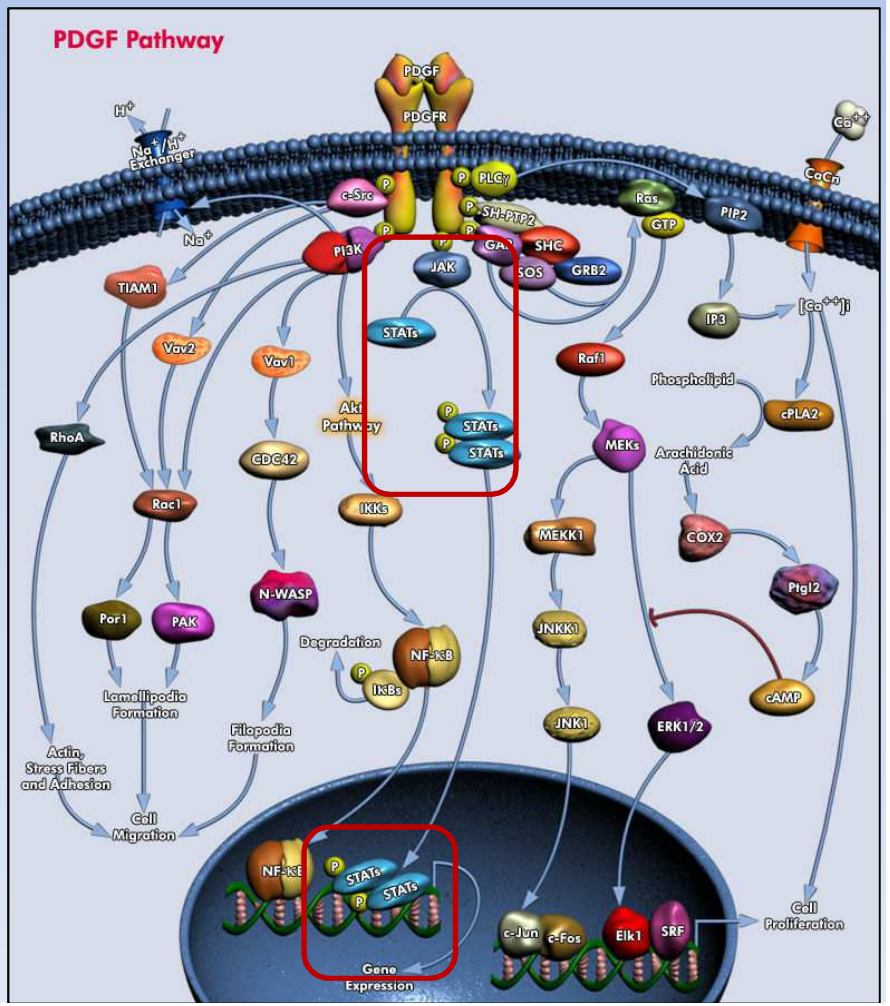


Proteína citosólica con actividad tirosin-kinasa constitutiva

STAT5 promueve la síntesis de genes relacionados con la proliferación celular, la aptosis y los procesos de diferenciación celular

Se considera que el producto de fusión de PDGFRA o PDFRB subyacen en el **50-60%** de los SHE primarios

Tasas de remisión completa sostenidas del 95% con **Imatinib**



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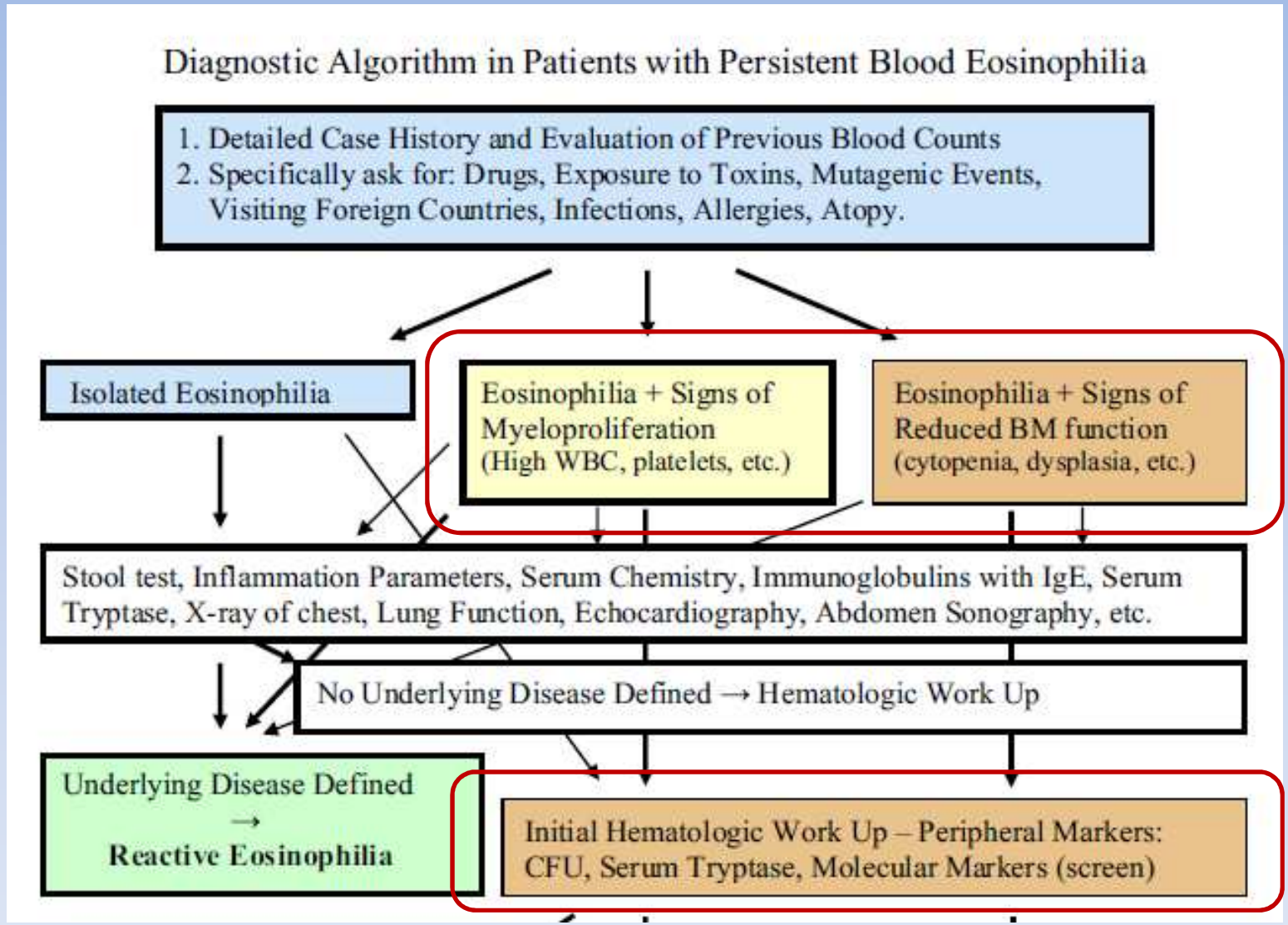
    - Puede demostrarse un defecto citogenético vinculado con la aparición de HE
    - Puede demostrarse una neoplasia mieloide asociada a la presencia de HE

1. Acute myeloid leukemia and related disorders
2. Myeloproliferative neoplasms (MPN)
   - Chronic myelogenous leukemia, *BCR-ABL1* positive
   - Chronic neutrophilic leukemia
   - Polycythemia vera
   - Primary myelofibrosis
   - Essential thrombocythemia
   - Chronic eosinophilic leukemia, not otherwise specified
   - Mastocytosis
   - Myeloproliferative neoplasms, unclassifiable
3. Myelodysplastic syndromes (MDS)
   - Refractory cytopenia with uni-lineage dysplasia
     - Refractory anemia
     - Refractory neutropenia
     - Refractory thrombocytopenia
   - Refractory anemia with ring sideroblasts
   - Refractory cytopenia with multilineage dysplasia
   - Refractory anemia with excess blasts (RAEB)
     - RAEB-1
     - RAEB-2
   - Myelodysplastic syndrome with isolated del(5q)
   - Myelodysplastic syndrome, unclassifiable
4. MDS/MPN
   Chronic myelomonocytic leukemia
     - CMML-1
     - CMML-2
   Atypical chronic myeloid leukemia, *BCR-ABL1* negative
   Juvenile myelomonocytic leukemia
   MDS/MPN, unclassifiable
     - Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)
5. Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*
   Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
   Myeloid neoplasms associated with *PDGFRB* rearrangement
   Myeloid and lymphoid neoplasms associated with *FGFR1* abnormalities.

Clasificación OMS 2008 de neoplasias mieloides

Estudio de hipereosinofilia



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HE de significado incierto

- HE sin criterios clínicos o de laboratorio, y en ausencia de síntomas asociadas, que sugieran agregación familiar, un proceso reactivo, una enfermedad de causa inmunológica o una enfermedad neoplásica
- No es bien conocida su historia natural. Se recomienda un seguimiento con reevaluaciones periódicas (descartar enf. subyacente o desarrollo de SHE)
- Únicamente entre el 30-48% de los pacientes con SHE, tienen causa molecular demostrable.

2. SCS y SHE: 2 enfermedades?

HE sin daño tisular atribuible a eosinófilos	HE con daño tislar mediado por eosinófilos - sde hipereosinofílico (SHE)
HE familiar (HE_{FA})	SHE familiar (?)
HE de significado incierto (He_{US})	SHE idiopático Enfermedad de un solo órgano
HE primaria o clonal (HE_N)	SHE primario
HE reactiva (HE_R)	SHE secundario

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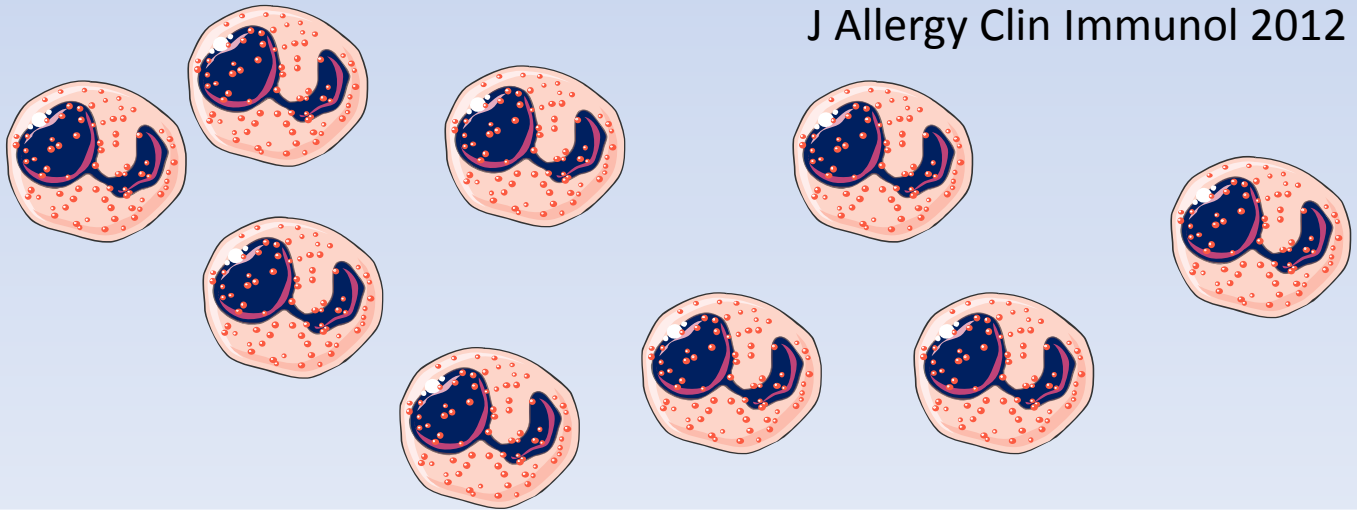

2. SCS y SHE: 2 enfermedades?

Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

TABLE III. Classification of syndromes and conditions accompanied by HE

Variant	Typical findings
HES*	
Idiopathic HES	No underlying cause of HE, no evidence of a reactive or neoplastic condition/disorder underlying HE and end-organ damage attributable to HE
Primary (neoplastic) HES (HES_N)	Underlying stem cell, myeloid, or eosinophilic neoplasm classified according to WHO guidelines and end-organ damage attributable to HE, and eosinophils are considered (or shown) neoplastic (clonal) cells.†
Secondary (reactive) HES (HES_R)	Underlying condition/disease in which eosinophils are considered nonclonal cells; HE is considered cytokine driven, and end-organ damage is attributable to HE.
	Subvariant: lymphoid variant HES (clonal T cells identified as the only potential cause)‡
Other conditions and syndromes	
Specific syndromes accompanied by HE	Specific syndromes in which the effect of eosinophilia remains unclear but the clinical presentation is distinct and accompanied by HE; specific syndromes are listed in Table E3.
Other conditions accompanied by HE	Mostly organ-restricted conditions in which the effect of eosinophilia remains unclear; an overview of organ-restricted pathologies accompanied by HE is shown in Table E4, and that of skin disorders accompanied by eosinophilia is shown in Table E5.

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Primary (neoplastic) HES (HES_N)	
Secondary (reactive) HES (HES_R)	Underlying stem cell, myeloid, or eosinophilic neoplasm classified according to WHO guidelines and end-organ

TABLE E3. Selected defined syndromes associated with eosinophilia or HE

Gleich syndrome	Cyclic recurrent angioedema, HE, and increased IgM levels, often with clonal T cells (regarded as one of several possible clinical presentations of lymphoid HES by some of the faculty members)
Churg-Strauss syndrome	Multisystem disorder with HE and necrotizing vasculitis, often with lung infiltrates. $ANCA^+$ and $ANCA^-$ variants have been described
Eosinophilia myalgia syndrome	Recurrent severe myalgia and HE, often with neurologic symptoms and skin abnormalities; the epidemic variant has been described to be related to L-tryptophan exposure
Omenn syndrome	HE with associated severe combined immunodeficiency, often with skin rash, splenomegaly and/or lymphadenopathy; autosomal recessive genetic disease (*RAG1* or *RAG2* mutations)
Hyper-IgE syndrome	Inherited immune defect accompanied by HE and elevated IgE levels, often also by an eczema and by facial abnormalities. Identified gene mutations are: *STAT3* mutations in autosomal dominant hyper-IgE syndrome and *DOCK8* mutations in autosomal recessive hyper-IgE syndrome

ANCA, Antineutrophil cytoplasmic antibodies; *DOCK8*, dedicator of cytokinesis 8; *RAG*, recombination-activating gene; *STAT3*, signal transducer and activator of transcription 3.

012

2. SCS y SHE: 2 enfermedades?

Sde Hipereosinofílico

Sde de Churg-Strauss

TABLE 1. Clinical manifestations of Churg–Strauss syndrome

Clinical manifestation	At presentation No. (%)
Asthma	32 (100%)
Fever, weight loss	22 (68.8%)
Glomerulonephritis	1
Renal insufficiency	1
Haematuria	2
Hypertension	5 (15.6%)
Ophthalmic involvement	2 (6.3%)
Orbital pseudotumour	1
Sudden blindness	1
Arthralgia, myalgia	12 (37.5%)

Gotlib et al. Blood 2004; 103(8): 2879-91

Table 2. Organ involvement in hypereosinophilic syndrome

Organ system	Cumulative frequency from 3 studies, %*	Examples of organ-specific manifestations
Hematologic	100	Leukocytosis with eosinophilia; neutrophilia, basophilia, myeloid immaturity, immature and/or dysplastic eosinophils; anemia, thrombocytopenia or thrombocytosis, increased marrow blasts, myelofibrosis[19,21]
Cardiovascular	58	Cardiomyopathy,[28,29] constrictive pericarditis,[30,31] endomyocarditis,[32,33] mural thrombi,[27,34] valvular dysfunction,[27,35,36] endomyocardial fibrosis,[37,38] myocardial infarction[39]
Dermatologic	56	Angioedema,[40] urticaria,[40] papules/nodules,[40] plaques,[41] aquagenic pruritis,[42] erythroderma,[43] mucosal ulcers,[44] vesicobullous lesions,[45] microthrombi,[46,47] vasculitis,[48] Wells syndrome[49]
Neurologic	54	Thromboembolism,[50] peripheral neuropathy,[50,51] encephalopathy,[50,52] dementia,[53,54] epilepsy,[55] cerebellar disease,[56] eosinophilic meningitis[57]
Pulmonary	49	Pulmonary infiltrates,[9,58] effusions,[9,59] fibrosis,[4] emboli,[60] nodules/focal ground glass attenuation,[61] acute respiratory distress syndrome (ARDS)[62]
Splenic	43	Hypersplenism, infarct[63]
Liver/gallbladder	30	Hepatomegaly,[64] focal or diffuse hepatic lesions on imaging,[64] chronic active hepatitis,[65] hepatic necrosis,[66] Budd-Chiari syndrome,[67] sclerosing cholangitis,[68] cholecystitis,[69] cholestasis[70]
Ocular	23	Microthrombi,[71-73] choroidal infarcts,[72] retinal arteritis,[73] episcleritis,[74] keratoconjunctivitis sicca,[74] Adie syndrome (pupillotonia)[75]
Gastrointestinal	23	Ascites,[76] diarrhea,[77] gastritis,[78] colitis,[69,78] pancreatitis[77]
Musculoskeletal	N/A	Arthritis,[79,80] effusions,[80] bursitis,[81] synovitis,[82] Raynaud phenomena,[83] digital necrosis,[84] polymyositis/myopathy[85,86]
Renal	N/A	Acute renal failure with Charcot-Leyden crystalluria,[87] nephrotic syndrome,[88] immunotactoid glomerulopathy,[89] crescentic glomerulonephritis[90]

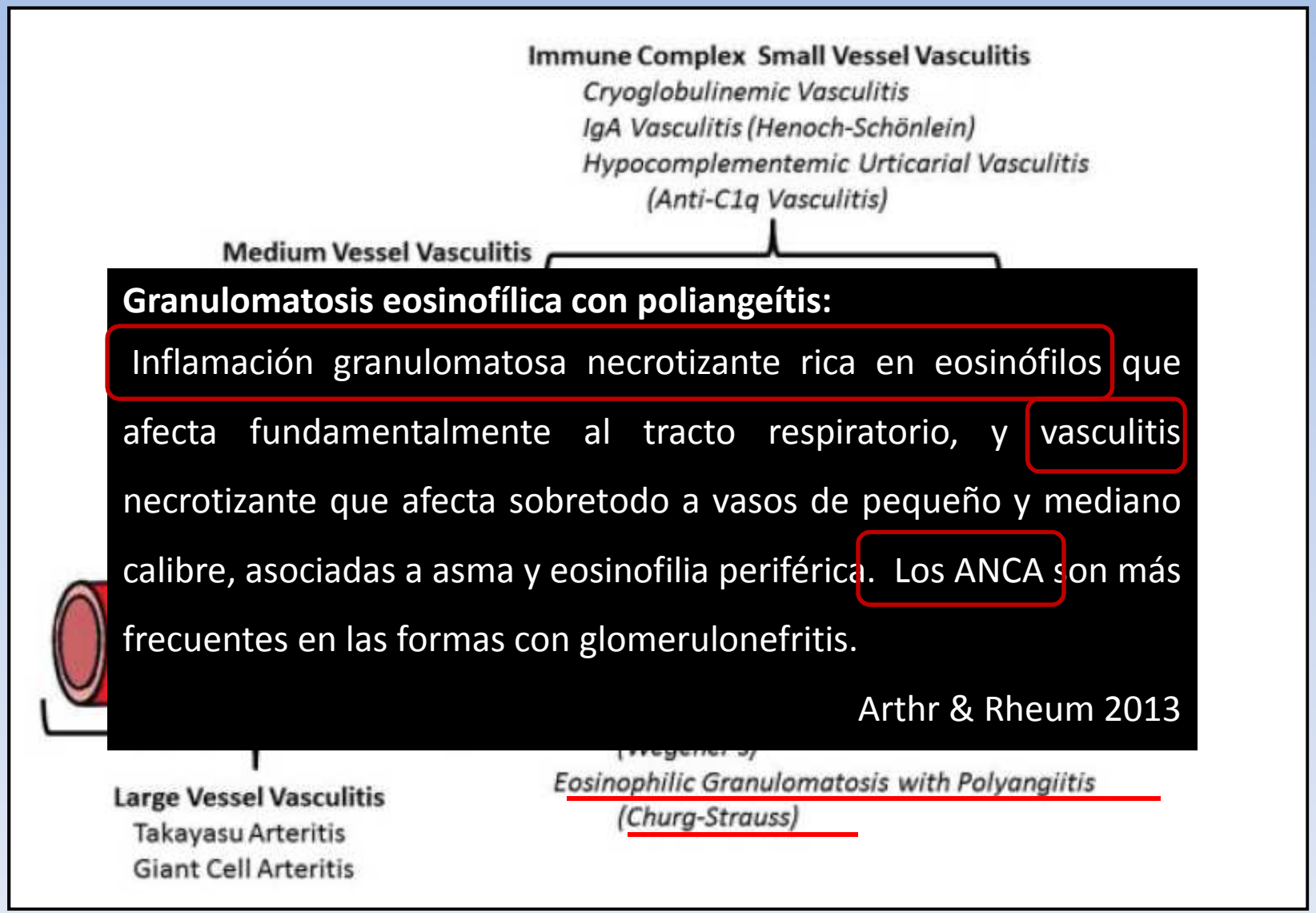
Solans et al. Rheumatol 2001; 40: 763-71

2. SCS y SHE: 2 enfermedades?

Afectación	Gotlib et al (SHE)	Solans et al (SCS)
Fiebre, cuadro tóxico	26%	68,8%
Pulmonar	49%	53,1%
Piel	56%	68,8%
Neurológica	54%	65%
Gastrointestinal	23%	37,5%
Cardíaca	58%	28,1%

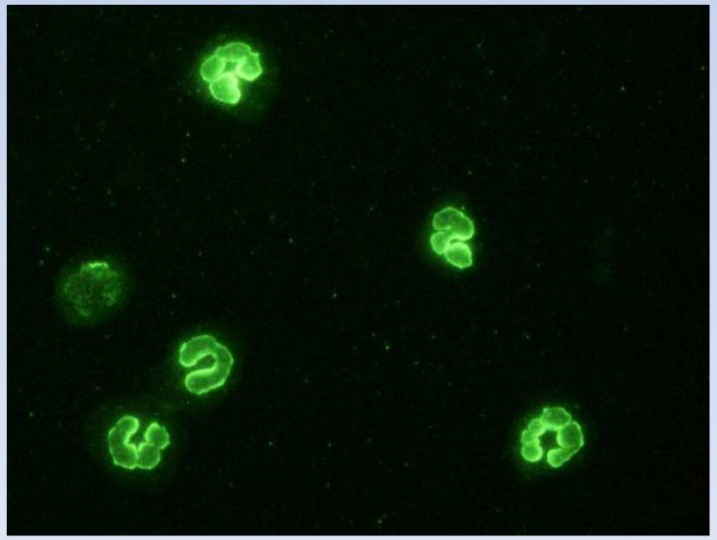
INDICE:

SCS y SHE: similitudes más allá de la clínica



SCS y SHE: similitudes más allá de la clínica

- La prevalencia de ANCA en el SCS se situa en torno al 40% (37.6%-47.6%)
- Más del 75% de pacientes ANCA positivos presentan especificidad por el enzima mieloperoxidasa



SCS y SHE: similitudes más allá de la clínica

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Table 4. Clinical features in ANCA-positive and ANCA-negative patients*

	ANCA positive (n = 35)	ANCA negative (n = 58)	P†
Asthma	34 (97.1)	55 (94.8)	1.00
Constitutional symptoms	30 (85.7)	33 (56.9)	0.006
Sinusitis	27 (77.1)	45 (77.6)	1.00
Skin involvement	21 (60.0)	28 (48.3)	0.29
Purpura	9 (25.7)	4 (6.9)	0.015
Lung involvement, all kinds	12 (34.3)	35 (60.3)	0.019
Pulmonary hemorrhage	7 (20.0)	0 (0.0)	0.001
Heart involvement	2 (5.7)	13 (22.4)	0.042
Gastrointestinal involvement	7 (20.0)	13 (22.4)	1.00
Peripheral neuropathy, all kinds	25 (71.4)	35 (60.3)	0.37
Mononeuritis multiplex	18 (51.4)	14 (24.1)	0.013
CNS involvement	6 (17.1)	7 (12.1)	0.54
Renal involvement	18 (51.4)	7 (12.1)	<0.001
RPGN	10 (28.6)	3 (5.2)	0.004
ACR criteria	30 (85.7)	55 (94.8)	0.15
Lanham's criteria	30 (85.7)	47 (81.0)	0.78
Eosinophilia >10%	32 (91.4)	56 (96.6)	0.36
Eosinophils/mm^3, median (range)	4,881 (1,074–28,815)	3,544 (600–25,637)	0.51
BVAS, 0–63, median (range)	22 (7–40)	17 (6–40)	0.15
DEI, 0–21, median (range)	6 (3–10)	6 (3–10)	0.85
VDI, 0–11, median (range)	0 (0–2)	0 (0–5)	0.30
FFS ≥2	9 (25.7)	7 (12.1)	0.15

Sinico RA et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005;52(9):2926-35.

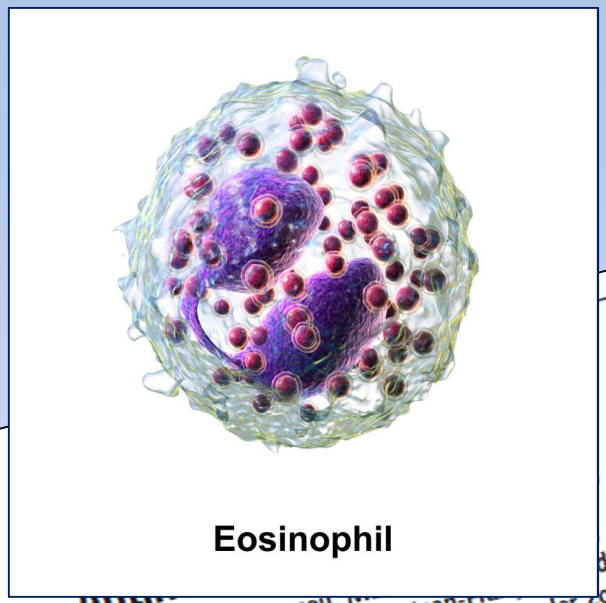
SCS y SHE: similitudes más allá de la clínica

Table 2 Comparisons between ANCA-positive and -negative patients with Churg–Strauss syndrome

	ANCA+	ANCA−	*p* value
Patients (*n*)	8	14	
Age (years)	67.1 ± 8.2	62.7 ± 10.9	0.4325
Sex (male/female)	3/5	6/8	
Duration from onset to biopsy (months)	2.8 ± 3.9	3.7 ± 8.4	0.5167
Disability score at biopsy	3.8 ± 0.7	3.1 ± 0.8	0.1332
CRP at biopsy (mg/dl)	4.6 ± 2.4	2.8 ± 2.4	0.056
MPO-ANCA titer, EU (range)	142 ± 157 (36–520)	<10	
Number of eosinophils (cells/μL)	7,250 ± 6,710 (2,190–19,040)	11,300 ± 6,100 (1,800–21,200)	0.1332
Pathological findings			
Necrotizing vasculitis	5/8 (63%)	3/14 (21%)	0.0815
Fibrinoid degeneration of vessels	4 (50%)	1 (7%)	0.0393
Eosinophilic granuloma	0	2 (14%)	0.5152
Massive infiltration of eosinophils	0	5 (36%)	0.1154
Endoneurial eosinophils	0	3 (21%)	0.2727

Oka N et al. Two subtypes of Churg-Strauss Syndrome neuropathy: the roles of eosinophils and ANCA. Mod Rheumatol 2011

SCS y SHE: similitudes más allá de la clínica



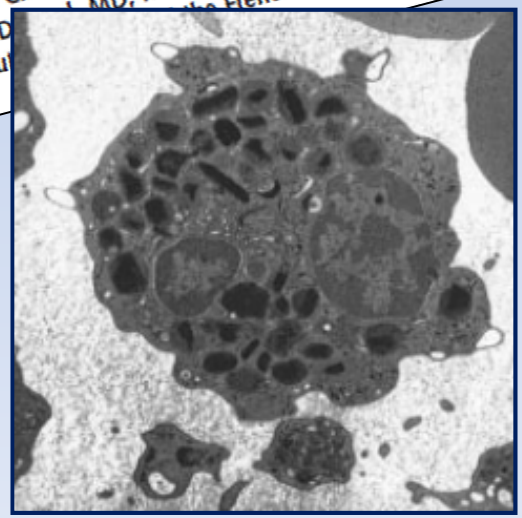
Eosinophil

ARTICLE

Antibodies and the Churg–Strauss Syndrome

Alfred Mahr, MD; Christian Pagnoux, MD; Luc Mouthon, MD, PhD; David Jayne, MD;
...MD; Xavier Puechal, MD, PhD; Dominique Lauque, MD;
...French Vasculitis Study Group*

Régis Sablé-Fourtassou, ...
Daniel Blockmans, MD, PhD; Jean-...
Jean-François Viallard, MD, PhD; Abdelkader Zoulim, MD; Loïc Gu...



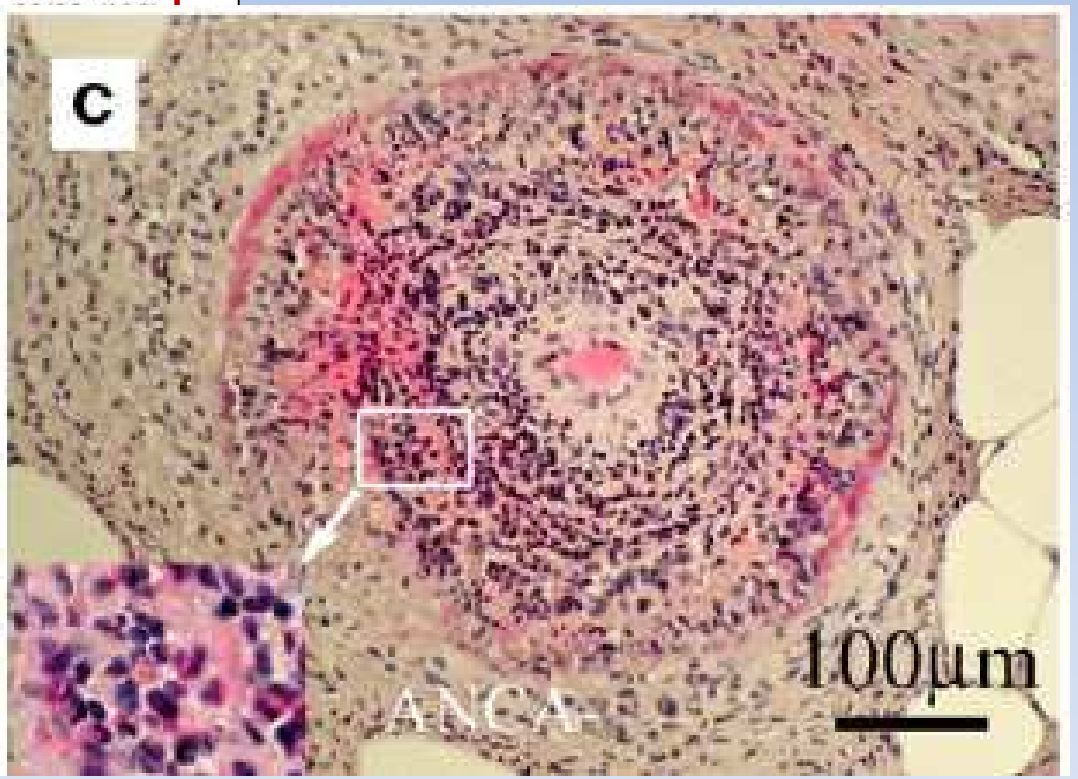
SCS y SHE: similitudes más allá de la clínica

TABLE 2. Laboratory findings in CSS patients

	No. patients (%)
Eosinophilia $>1500/mm^3$ 0% $>10\%$	
ESR $\geqslant 50$ mm in 1st h	
Antinuclear antibodies $>1/160$	
Rheumatoid factor titre $\geqslant 40$	
ANCA	
MPO-ANCA	
c-ANCA	
HBsAg	
Anti-HCV	

c-ANCA, ANCA with cytoplasmic pattern; HBsA
surface antigen; anti-HCV, antibodies to hepatitis C v

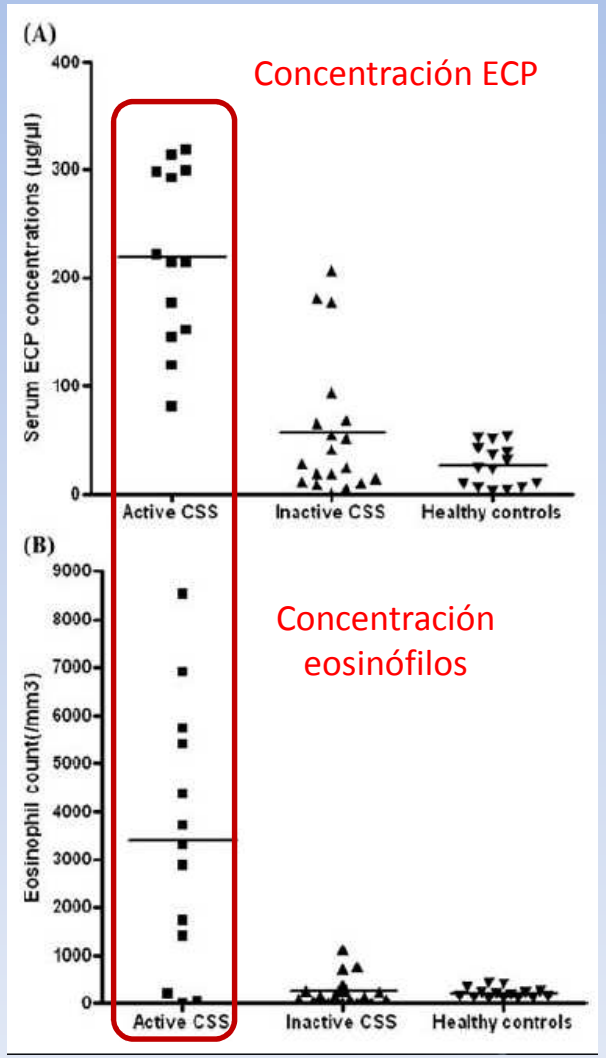
Solans et al. Churg-Strauss Syndrome: outcome
follow-up of 32 patients. Rheumatol 200



Oka N et al. Two subtypes of Churg-Strauss Syndrome with neuropathy: the roles of eosinophils and ANCA. Mod Rheumatol 2011; 21: 290-295

Serum Eosinophil Cationic Protein

A Marker of Disease Activity in Churg-Strauss Syndrome

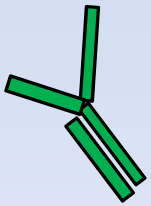


- Mean eosinophil count differed significantly between CSS patients with active disease or in clinical remission (3,407 ± 2,722/mm3 vs. 258 ± 300/mm3, *P = 0.0014).*
- Mean serum Eosinophil Cationic Protein (ECP) levels differed significantly between patients with active and inactive disease (219±80.6g/L vs. 56.8±63.8g/L; *P<0.0001)*
- **Both Eosinophil count and ECP levels did not differ significantly between patients with inactive disease and healthy controls**

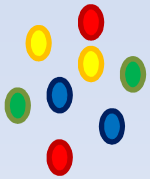
Guilpain et al. Ann NY Ac Sc 2007

SCS y SHE: similitudes más allá de la clínica

- Existen evidencias que indican que los eosinófilos activados son un mediador de daño tisular en el SCS:
    1. Se ha documentado en muestras tisulares depósito extravascular de ECP y MBP
    2. Se han detectado concentraciones elevadas de tanto ECP como MBP durante la fase activa de la enfermedad, tanto en sangre periférica como en líquido de lavado broncoalveolar
- ¿Existen vías de activación de eosfinófilos funcionalmente normales?



IgE
ANCA
otros



Microambiente citoquínico

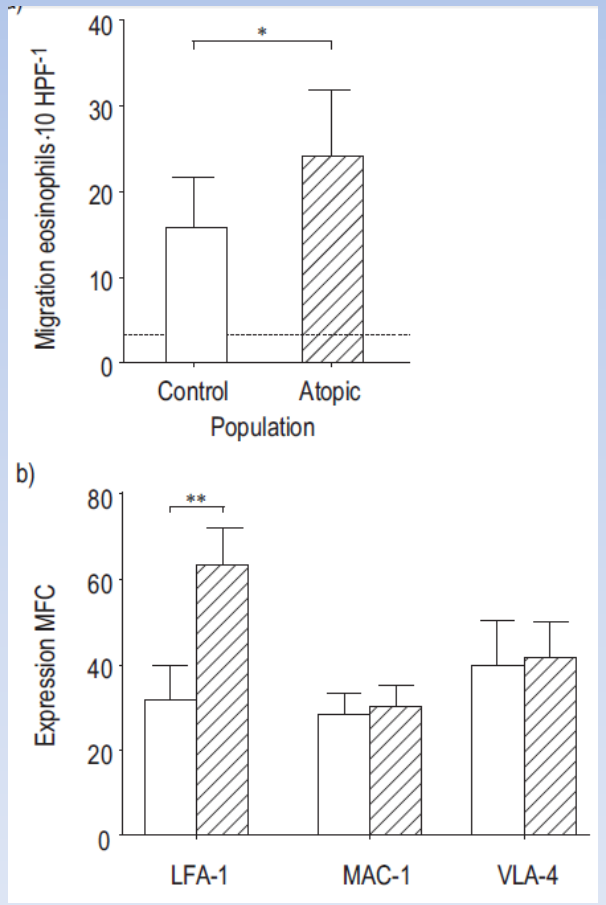
Antigeno tisular

SCS y SHE: similitudes más allá de la clínica

- Existen evidencias que indican que los eosinófilos activados son un mediador de daño tisular en el SCS:
    1. Se ha documentado en muestras tisulares depósito extravascular de ECP y MBP
    2. Se han detectado concentraciones elevadas de tanto ECP como MBP durante la fase activa de la enfermedad, tanto en sangre periférica como en líquido de lavado broncoalveolar
- ¿Existen vías de activación de eosfinófilos funcionalmente normales?
- ¿Existe una funcionalidad alterada del eosinófilo?

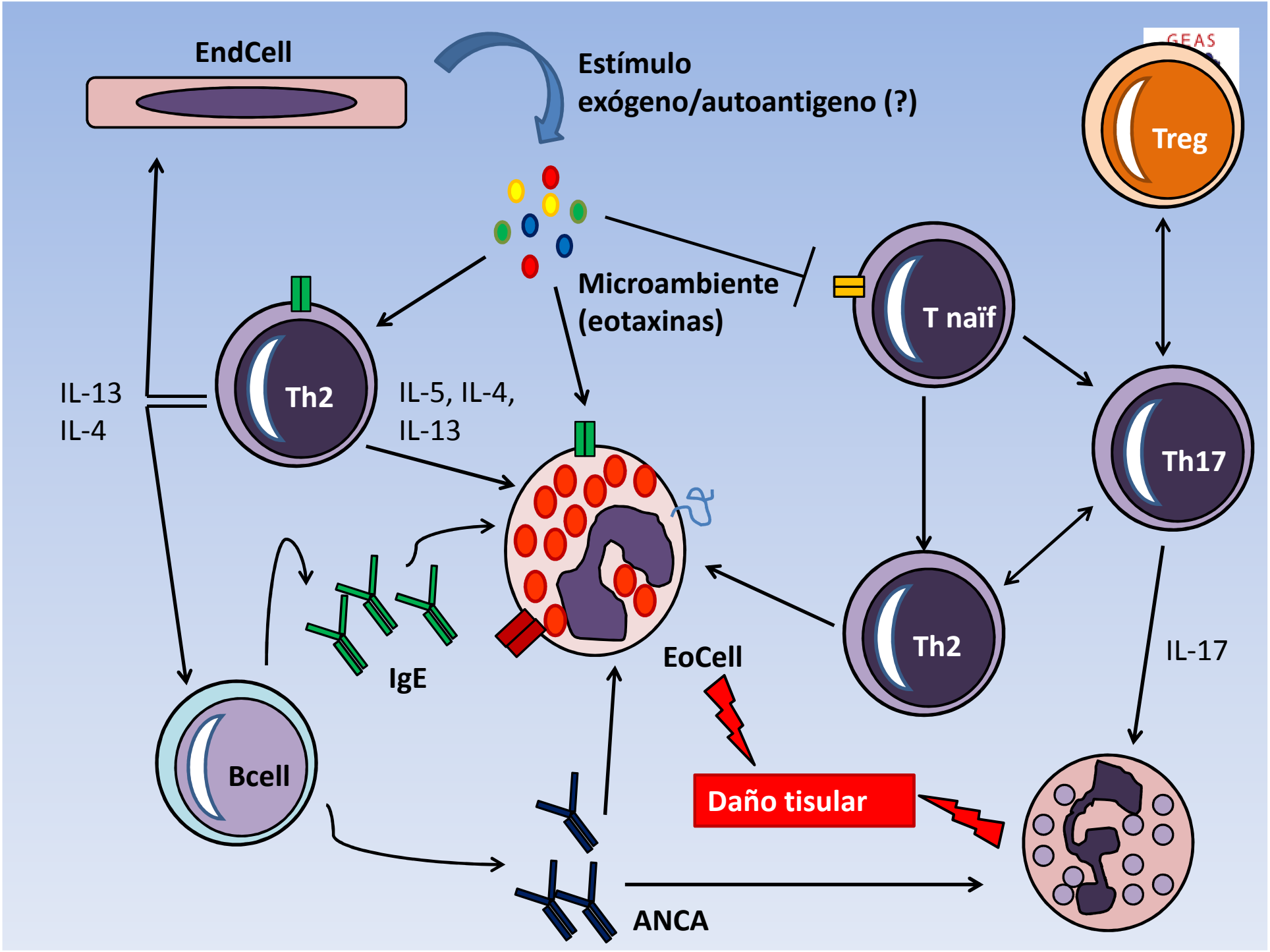
Stimulation of eosinophil IgE low-affinity receptor leads to increased adhesion molecule expression and cell migration

S. Lantero*, G. Alessandri**, D. Spallarossa*, L. Scarso***, G.A. Rossi*



- Los eosinófilos de pacientes atópicos mostraron mayor capacidad migratoria estimuladas con C5a en un modelo de HUVEC.
- Los eosinófilos de pacientes atópicos presentaban, comparados con controles sanos, aumento de expresión de *Lymphocyte function-associated antigen 1* (LFA-1)

Lantero et al. Eur Resp J 2000; 16:940-946


EndCell
Estímulo
exógeno/autoantigeno (?)
Treg
Microambiente
(eotaxinas)
T naïf
Th2
IL-13
IL-4
IL-5, IL-4,
IL-13
Th17
IgE
EoCell
Th2
IL-17
Bcell
Daño tisular
ANCA

blood

2010 116: 4523-4531
Prepublished online August 20, 2010:

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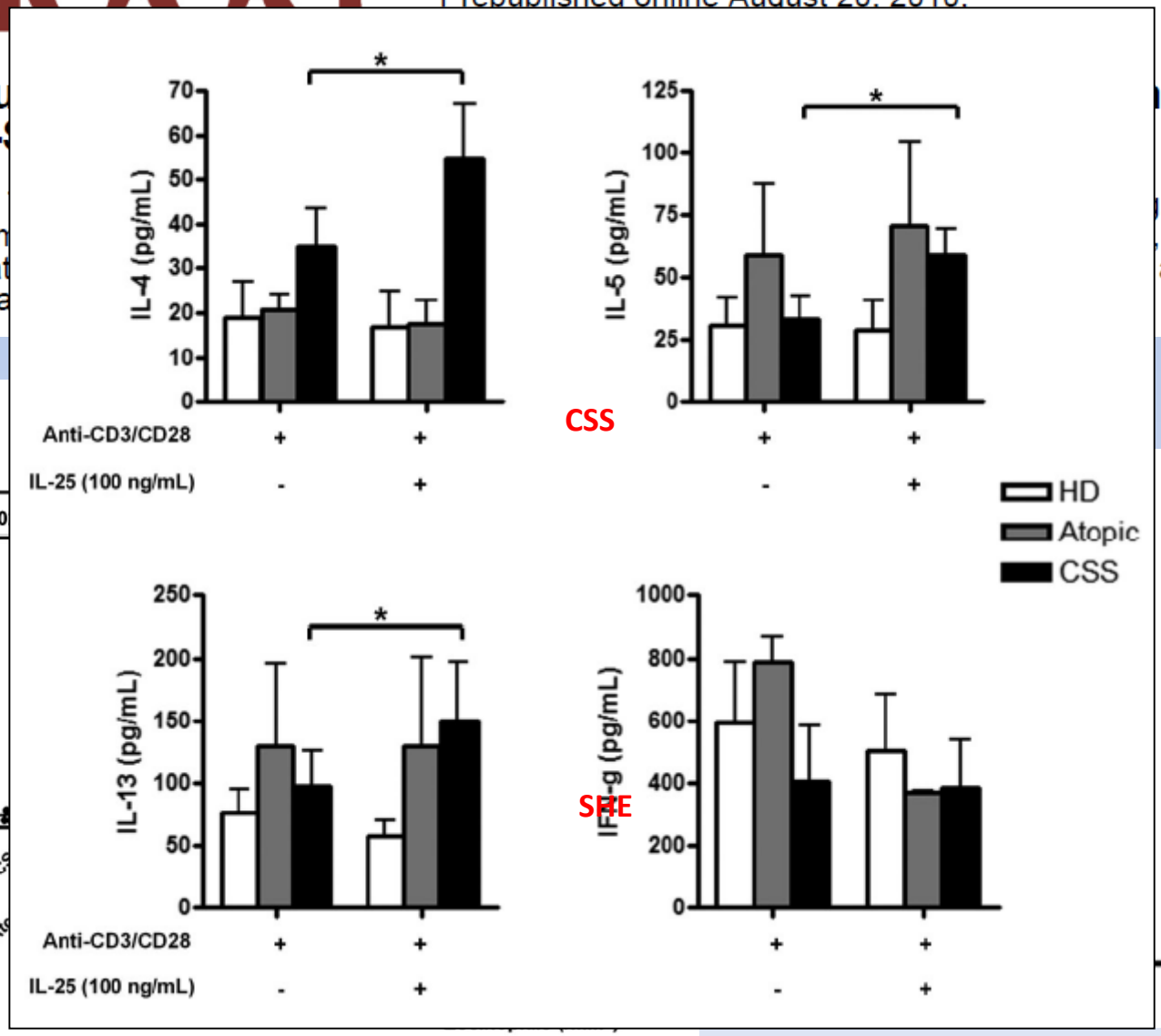
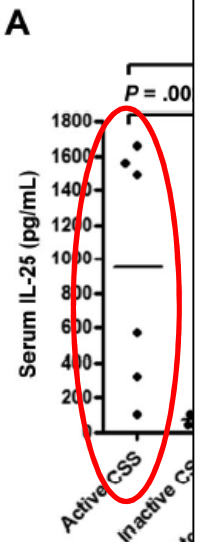




Rheumatology 2008;47:804–808
Advance Access publication 8 April 2008

doi:10.1093/rheumatology/ken033

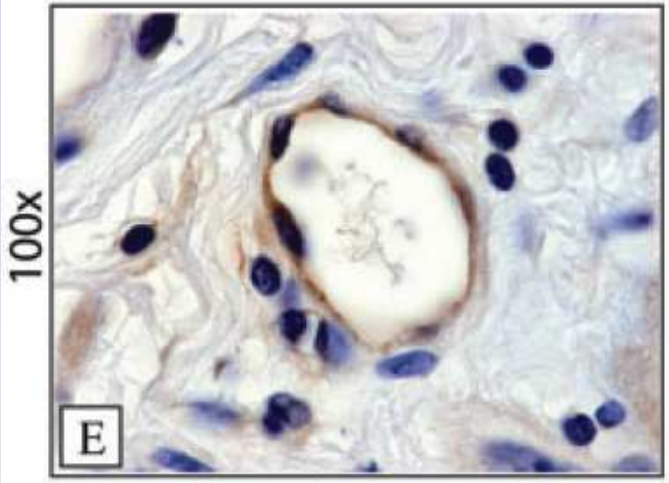
Eotaxin-3 is involved in Churg–Strauss syndrome – a serum marker closely correlating with disease activity

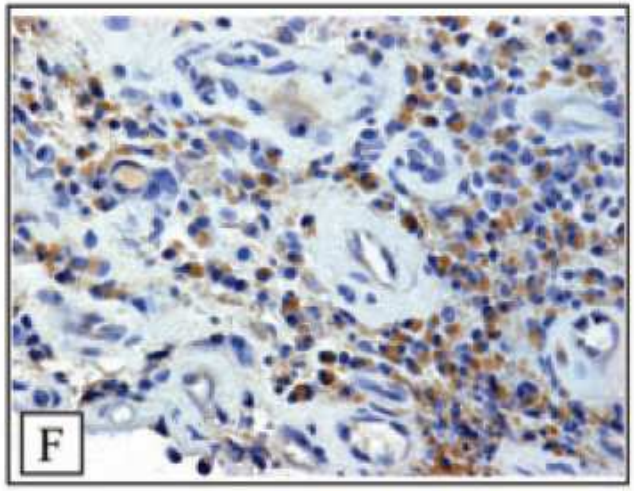
K. Polzer[1], T. Karonitsch[2], T. Neumann[3], G. Eger[1], C. Haberler[4], A. Soleiman[5], B. Hellmich[6], E. Csernok[6], J. Distler[1], B. Manger[1], K. Redlich[2], G. Schett[1] and J. Zwerina[1]

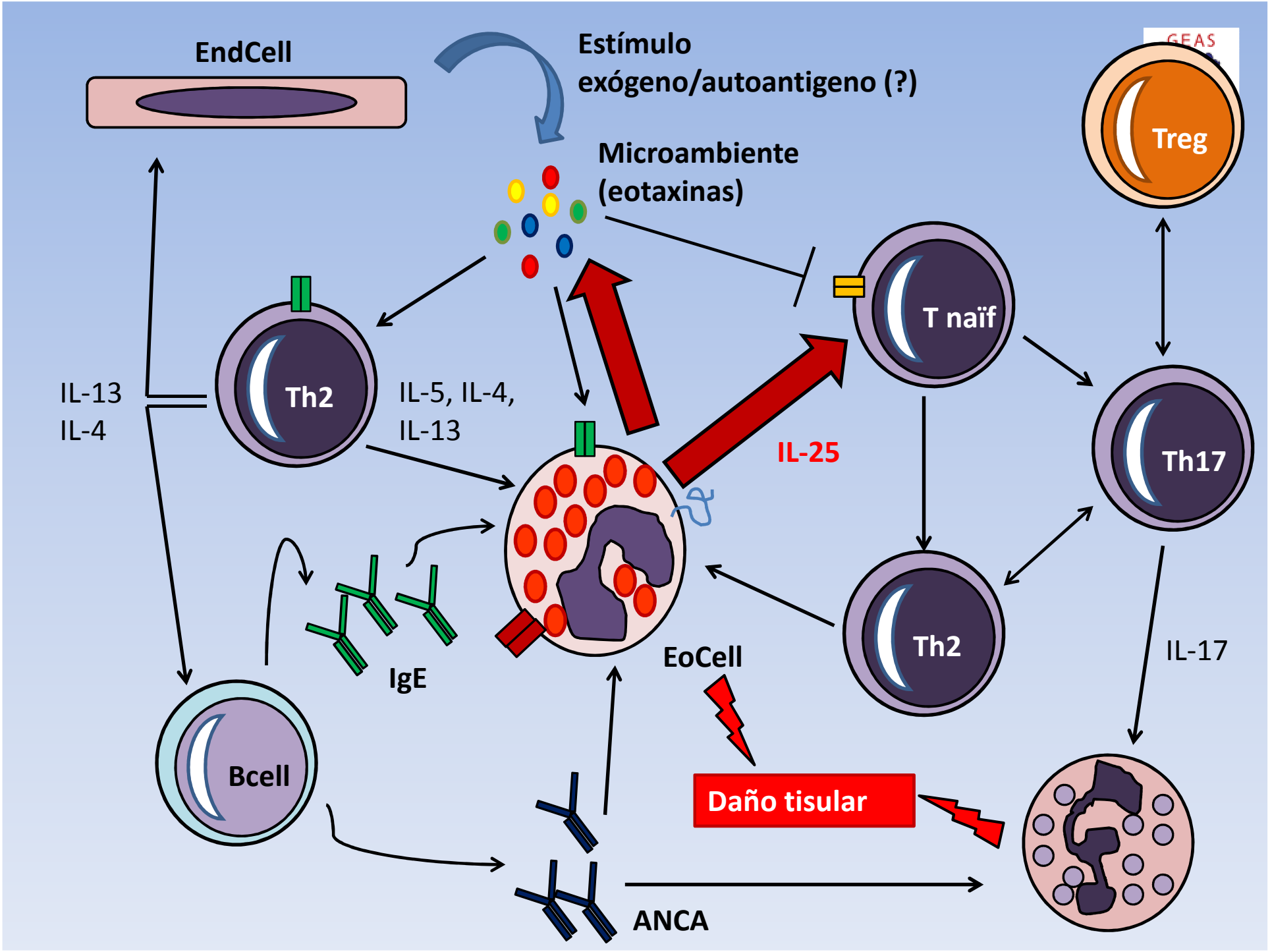
TABLE 3. Expression of eotaxin-3 in CSS tissue biopsies

Patient	Age	Biopsy site	Histopathological diagnosis	Eotaxin-3 expression			
				Endothelium	VSMC	Eosinophils	Epithelium
1	51	Nasal concha	Perivascular eosinophilia	+	–	+++	+
2	62	Gall bladder	Eosinophilic vasculitis	+++	+	++	+
3	37	Sural nerve	Eosinophilic vasculitis	++	NA	+	NA
4	22	Sural nerve	Eosinophilic vasculitis	+	NA	+	NA
5	33	Skeletal muscle	Perivascular eosinophilia	–	–	+++	NA
6	44	Maxillary sinus	Perivascular eosinophilia	+	–	++	++

NA: not assessed due to absent anatomical structures; VSMC: vascular smooth muscle cells.






EndCell
Estímulo
exógeno/autoantigeno (?)
Microambiente
(eotaxinas)
Treg
T naïf
Th2
IL-13
IL-4
IL-5, IL-4,
IL-13
IL-25
Th17
IgE
EoCell
Th2
IL-17
Bcell
Daño tisular
ANCA

CONCLUSIONES

1) El estudio de una hipereosinofilia engloba dos ópticas diferenciadas: estudio de causas subyacentes (HE_R) y el de un defecto citogenético (HE_N).

2) El Síndrome Hipereosinofílico primario es una neoplasia mieloide en la que se puede demostrar alguno de los defectos citogenéticos conocidos (ej: FIP1L1/PDGFRA) que pueden afectar únicamente a los eosinófilos o también a otras líneas celulares.

3) Puede ser difícil distinguir desde un punto de vista clínico (e incluso anatomopatológico) el Síndrome Hipereosinofílico idiopático y el Sde de Churg-Strauss en su forma ANCA negativa.

4) El eosinófilo probablemente juegue un papel central, y de momento poco conocido, en la amplificación de la respuesta inmunológica en el Sde. de Churg-Strauss.

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