Universitat Autònoma de Barcelona

ESCLERODERMIA

Formas clínicas de presentación y características clinico-biológicas

XXX Congreso Nacional de la Sociedad Española de Medicina Interna
Línea Esclerodermia (Grupo Enfermedades Autoinmunes Sistémicas)
Valencia, 18 – 21 noviembre 2009

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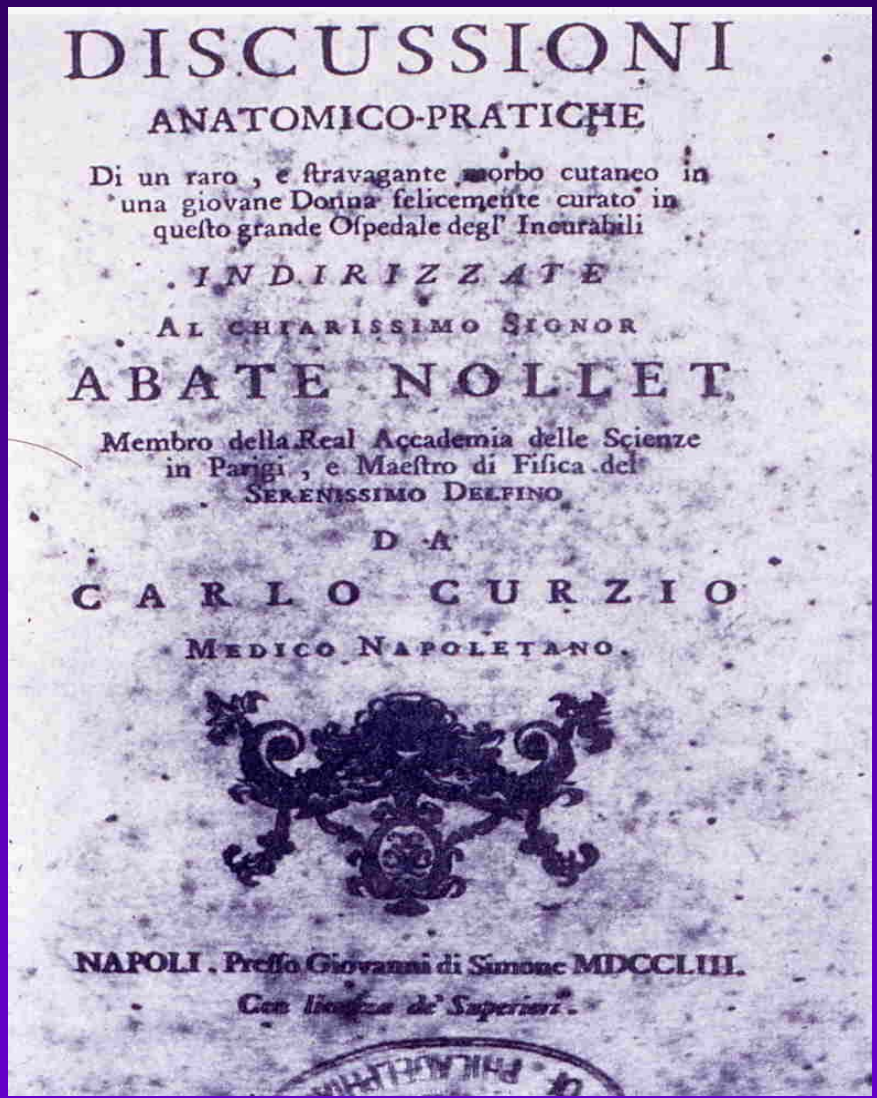
Servicio de Medicina Interna (Prof. M. Vilardell)
Hospital Universitario Vall d'Hebron. Barcelona

REGISTRO DE ESCLERODERMIA

R E S C L E

Gr cas

Sociedad Española de Medicina Interna


DISCUSSIONI
ANATOMICO-PRATICHE
Di un raro, e ſtravagante morbo cutaneo in una giovane Donna felicemente curato in queſto grande Oſpedale degl' Incurabili
INDIRIZZATE
AL CHIARISSIMO SIGNOR
ABATE NOLLET
Membro della Real Accademia delle Scienze in Parigi, e Maeſtro di Fiſica del SERENISSIMO DELFINO
DA
CARLO CURZIO
MEDICO NAPOLETANO
NAPOLI. Preſſo Giovanni di Simone MDCCLIII.
Con licenza de' Superiori.

DISCUSSIONI ANATOMICO-PRATICHE

Di un raro, e stravagante morbo cutaneo in una giovane Donna felicemente curato in questo grande Ospedale degl'Incurabili

Carlo Curzio, 1753
Medico Napolitano

ESCLEROSIS SISTÉMICA PROGRESIVA

C.R.E.S.T.

C.R.E.S.T.

ESCLERODERMIA

ESCLERODERMIA LOCALIZADA

Anti-topoisomerasa I

Anti-nucleolares

MORFEA

Síndrome de

Calcinosis

HTAP

SISTÉMICA

PROGRESIVA

Sistémica

PRIMARIO

MEGACAPILARES

ESCLEROSIS

ESCLERODERMIA. Criterios de clasificación

CRITERIO MAYOR

Esclerodermia proximal

CRITERIOS MENORES

Esclerodactilia

Cicatrices puntiformes en el pulpejo de los dedos

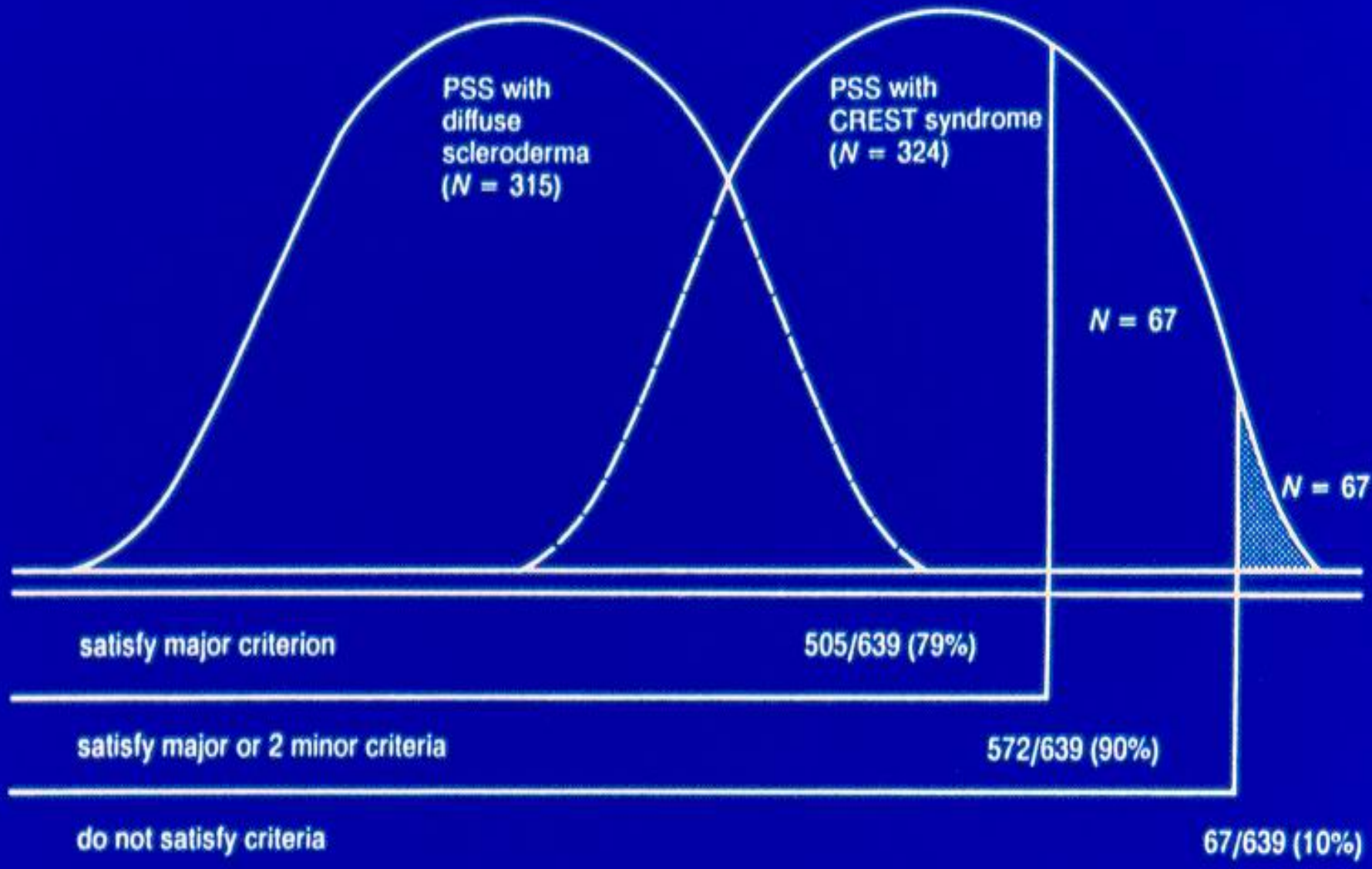
Fibrosis pulmonar bilateral

DIAGNÓSTICO

Criterio mayor o

Dos o más de menores

Arthtritis Rheum 1980;23:581-90


PSS with diffuse scleroderma (N = 315)
PSS with CREST syndrome (N = 324)
N = 67
N = 67
satisfy major criterion
505/639 (79%)
satisfy major or 2 minor criteria
572/639 (90%)
do not satisfy criteria
67/639 (10%)

Classification Criteria for Systemic Sclerosis Subsets

SINDHU R. JOHNSON, BRIAN M. FELDMAN, and GILLIAN A. HAWKER

J Rheumatol 2007;34:1855–63

Table 1. Classification of systemic sclerosis subsets.

Study	Classification Scheme	Number of Citations
Barnett[36]	3 subsets: limited, moderate, extensive, based on skin involvement of the fingers only, limbs and face, and involvement of the trunk, respectively	66
Ferri[30]	4 subsets: sine scleroderma SSc: absence of cutaneous involvement with visceral involvement, NC changes and autoantibodies; limited cutaneous: skin involvement of fingers with or without involvement of neck, face, and axillae; intermediate cutaneous: skin involvement of upper and lower limbs, neck and face without truncal involvement, diffuse cutaneous: distal and truncal skin involvement	52
Giordano[28]	6 subsets: I: sclerodactyly only; II: sclerodactyly and skin involvement of neck, lower eyelid, or axillae; III: skin involvement of hands and forearms ± legs ± face; IV: group III and arm and/or thigh skin involvement; V: group III and thorax; VI: group III and/or IV and/or V plus the abdomen	121
	3 subsets: limited: skin involvement of fingers, face, neck, axillae; intermediate: skin involvement proximal to fingers; diffuse: truncal skin involvement	121
Goetz[22]	2 subsets: acrosclerosis and diffuse: based on skin thickening limited to extremities or includes trunk	227
Holzmann[53]	5 subsets (Types I–IV) based on presence/absence of RP, sclerosis, extracutaneous manifestations, ANA	10
LeRoy[25]	2 subsets: diffuse cutaneous SSc: onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse GI disease, myocardial involvement; absence of ACA, abnormal ND; limited cutaneous SSc: RP for years, skin involvement limited to hands, face, feet, forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of ACA, abnormal NC	877
LeRoy and Medsger[41]	4 subsets: limited SSc (LSSc) consists of (1) objective RP plus any one of NC changes or SSc selective autoantibodies OR (2) subjective RP plus both NC changes and SSc selective autoantibodies; limited cutaneous SSc (lcSSc): criteria for LSSc plus distal cutaneous changes; diffuse cutaneous (dcSSc): criteria for lcSSc plus proximal cutaneous changes; diffuse fasciitis with eosinophilia: proximal cutaneous changes without criteria for lSSc or lcSSc	46
Maricq[6]	6 subsets: diffuse, intermediate, digital, scleroderma sine scleroderma, undifferentiated connective tissue disease with scleroderma, CREST syndrome	3
Masi[43]	3 subsets: digital: skin involvement of fingers or toes but not proximal extremity or trunk; proximal extremity: proximal extremities or face but not trunk; truncal: thorax or abdomen	42
Rodnan[2]	3 subsets: classical disease involving skin of the trunk, face and proximal extremities, and early involvement of esophagus, intestine, heart, lung and kidney; CREST syndrome; and overlap syndromes including sclerodermatomyositis and mixed connective tissue disease	79
Scussel-Lonzetti[39]	4 subsets: normal skin, limited: skin involvement restricted to fingers, with RP, calcinosis, esophageal involvement and telangiectasia; intermediate: skin involvement of arms proximal to metacarpophalangeal but not trunk; diffuse: skin involvement of the trunk	1
Tuffanelli and Winkelmann[35]	2 subsets: acrosclerosis: RP, acral skin involvement; diffuse SSc: no RP, skin involvement beginning centrally	42
Winterbauer[23]	CREST syndrome: calcinosis, RP, sclerodactyly, telangiectasia	176

RP: Raynaud's phenomenon; NC: nailfold capillary; ILD: interstitial lung diseases; GI: gastrointestinal; ACA: anticentromere antibodies; PAH: pulmonary arterial hypertension; LSSc: limited SSc.

Esclerodermia: Clasificación en subtipos, *según LeRoy*

TABLE 1. Some features of the LeRoy *et al.* 1988 [4] and LeRoy and Medsger [17] subsets of SSc

Diffuse cutaneous scleroderma (dcSSc)
- History of Raynaud's with onset within 1 yr
- Skin sclerosis extending proximal to the elbow; may involve truncal areas
- Tendon friction rubs may occur
- Early onset of pulmonary, renal and diffuse gastrointestinal involvement
- Rarely anticentromere antibodies but often antitopoisomerase 1 antibodies
- Nailfold capillary destruction

Limited cutaneous scleroderma (lcSSc)
- Skin involvement restricted to hands, face, forearms and feet
- Delayed but often severe onset of pulmonary arterial hypertension

Ectopic calcinosis, telangiectasias
- Anticentromere antibodies common but antitopoisomerase 1 very rare
- Dilated nailfold caps seen but no capillary destruction

Limited/unclassifiable/pre-SSc
- Raynaud's phenomenon objectively documented as well as *either* abnormal widefield nailfold capillaroscopy *or* SSc-selective autoantibodies (anticentromere antibodies, anti-topiisomerase 1, antifibrillin, anti-PM-Scl, anti-RNA polyisomerase I or III)
- Raynaud's phenomenon subjectively documented as well as abnormal widefield capillaroscopy *and* SSc selective autoantibodies

2 subsets: diffuse cutaneous SSc: onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse GI disease, myocardial involvement; absence of ACA, abnormal ND; limited cutaneous SSc: RP for years, skin involvement limited to hands, face, feet, forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of ACA, abnormal NC

ESCLEROSIS SISTEMICA: CLASIFICACION Y SUBTIPOS SEGUN UN ANALISIS DE LOS FACTORES PRONOSTICOS.

Carmen P. Simeón
Tesis Doctoral, 1991

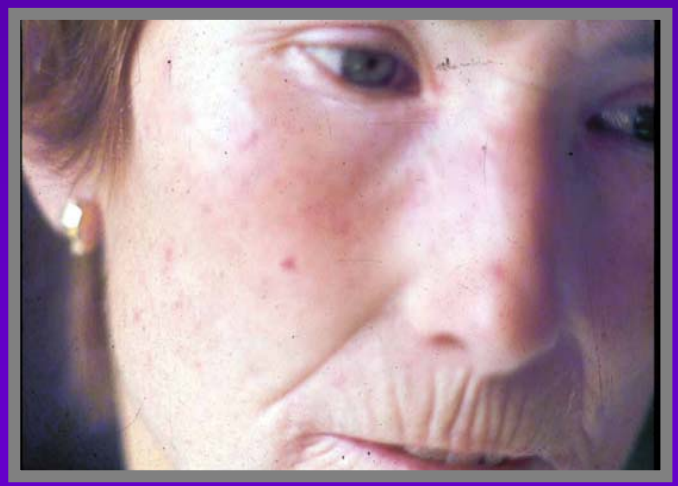
3.- Establecer diferentes grupos pronósticos con determinadas características clínico-biológicas.

4.- Establecer una clasificación de la ES según el estudio descriptivo y el análisis de los factores pronósticos.

2.- La magnitud de la afección cutánea permite distinguir dos grupos de enfermos con características clínicas y pronósticas homogéneas: 1) **ES difusa:** esclerosis cutánea proximal a codos y rodillas. 2) **ES limitada:** esclerosis cutánea distal a codos y rodillas.

Limitada

F. Raynaud > 5 a.
Afección cutánea distal
Telangiectasias, calcinosis
afección digestiva.HTP
Dilatación capilar
AAcentrómero (60-80%)



Difusa

F. Raynaud < 1 a.
Afección cutánea troncal y acra
Roces tendinosos
Afección visceral temprana
Pérdida capilar
Anti-Scl 70 (25-30%)

Cutaneous SSc Subsets and Clinical-epidemiologic features of the 916 Spanish patients with SSc

Disease manifestations	LcSSc (%)	DcSSc (%)
Number patients n (%)	562 (61.4%)	243 (26.5%)
Ratio Female: Male	8:1	4.6:1[b]
Age at onset (yrs)	45:97±15.57	43.99±15.32
Age at diagnosis (yrs)	53.36 ±14.41	46.76±15.51 [b*]
Time onset-diagosis (yrs)	7.37± 9.7	2.84± 5.96[b*]
ACR criteria fulfilled	367 (65.3)[a*]	243 (100)[b]
RP	533 (94.8)	215 (88.5)[b]
Digital Ulcers	219 (39)	155 (63.8)[b*]
Telangiectasias	207 (36.8)	90 (37)
Calcinosis	111 (19.8)	57 (23.5)
ANA positive	517 (92)	224 (92.2)
Scl70 positive	45 (9.4)	116 (52.7)[b*]
ACA positive	293 (58)	17 (8.4)[b*]

Línea Esclerodermia (GEAS)

Cutaneous SSc Subsets and Clinical-epidemiologic features of the 916 Spanish patients with SSc

Disease manifestations	LcSSc (%)	DcSSc (%)	
Osteomuscular	318 (56.6)	154 (63.4)	0.074
Arthritis	81 (14.4)	66 (27.2)	< 0.0001
Myositis	25 (4.4)	34 (14)	< 0.0001
Tendon Friction Rubs	14 (2.5)	28 (11.5)	< 0.0001
Acrosteolysis	46 (8.2)	37 (19.2)	0.0004
Digestive involvement	392 (69.8)	195 (80.2)	0.002
Oesophagus	322 (57.2)	173 (71.2)	<0.0001
Gastric	60 (10.7)	41 (16.9)	0.02
Malabsortion	9 (1.6)	13 (5.34)	0.004
PBC	24 (4.2)	0 (0)	<0.0001
Lung involvement	315 (56)	197 (81.1)	< 0.0001
Dyspnea	169 (30)	136 (56)	< 0.0001
ILD	221 (39.3)	170 (70)	< 0.0001
FVC $\leq$ 70%	70 (12.3)	87 (35.8)	< 0.0001
FVC (%) (mean $\pm$ SD)	90.72±22.69	74.93±22	< 0.0001
DLCO/VA (%) (mean $\pm$ SD)	76.45±23.16	74.84±22	ns
Ground-glass	62 (11)	77 (31.68)	< 0.0001
Reticular pattern	84 (13.0)	92 (38)	< 0.0001

Línea Esclerodermia (GEAS)

Cutaneous SSc Subsets and Clinical-epidemiologic features of the 916 Spanish patients with SSc

Predomina la forma limitada

La relación mujer/varón es diferente entre los 2 subtipos

El tiempo que transcurre desde el comienzo de la enfermedad hasta el diagnóstico es mayor en la forma limitada

En la forma limitada sólo un 65,3% cumplen los Criterios ACR

Las afecciones osteomuscular, digestiva, pulmonar, cardíaca y renal predominan en la forma difusa, con algunas peculiaridades como la exclusividad de la cirrosis biliar primaria en la forma limitada

El porcentaje de mortalidad es mayor en la forma difusa

Disease manifestations	LcSSc (%)	DcSSc (%)	
Sicca Syndrome	211 (37.5)	30 (33)	ns
Death	66 (11.7)	63 (26)	< 0.0001

Línea Esclerodermia (GEAS)

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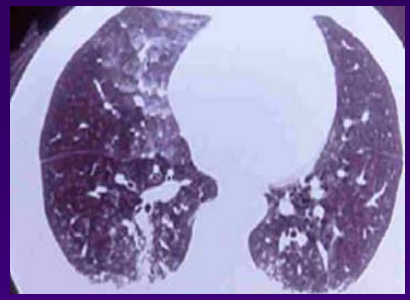
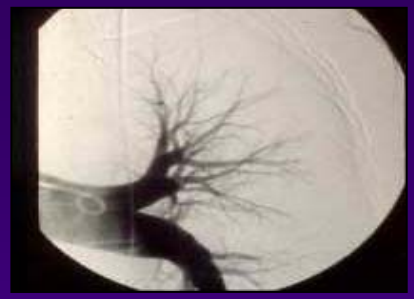
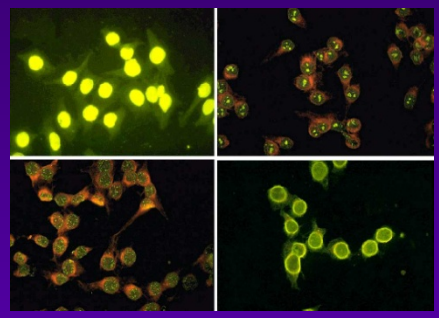
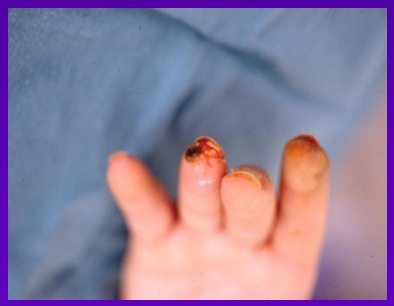
ESC *sine* esclerodermia

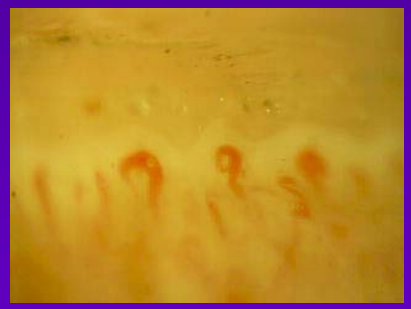
Fenómeno de Raynaud +/-
Afección visceral
AANs específicos
Sin afección cutánea

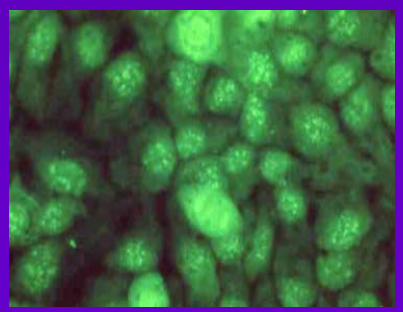












Pre-esclerodermia

Fenómeno de Raynaud
Úlceras digitales +/-
Alts. Capilaroscópicas
AANs específicos

Cutaneous SSc Subsets and Clinical-epidemiologic features of the 916 Spanish patients with SSc

	LcSSc	dcSSc	ssSSc	preSSc	total
Number patients n (%)	562 (61.4)	243 (26.5)	69 (7.5)	37 (4)	911
Ratio Female: Male	8:1	4.6:1[c]	8.8:1	17.5:1	7:1
Age at onse					5.02±15.23
Age at diagr					1.17±15.29
Time onset-					.16± 9.07
ACR criteria					620 (67.7)
First manife					
RP					678 (83.6)
Puffy hands					13 (1.6)
Arthralgia					50 (6.2)
Skin scleros					50 (6.2)
RP					49 (92.7)
Digital Ulce					94 (43.0)
Telangiecta					54 (60.5)
Calcinosis					74 (19.0)
ANA positiv					40 (91.7)
Scl70 positive	45 (9.4)	116 (52.7)[b*c*]	6 (9.5)	6 (18.8)	173 (18.9)
ACA positive	293 (58)[a]	17 (8.4)[b*c*]	27 (41.5)	19 (54.3)	356 (38.9)

Pre-esclerodermia

Predominan las mujeres

La edad de comienzo y la del diagnóstico son menores que las de los otros subtipos

El fenómeno de Raynaud está siempre presente y sólo ocasionalmente las otras manifestaciones

Los AANs son siempre positivos y en la mayoría ACA +

En la capilaroscopia predomina el patrón lento

SYSTEMIC SCLEROSIS SINE SCLERODERMA

Demographic, Clinical, and Serologic Features and Survival in Forty-Eight Patients

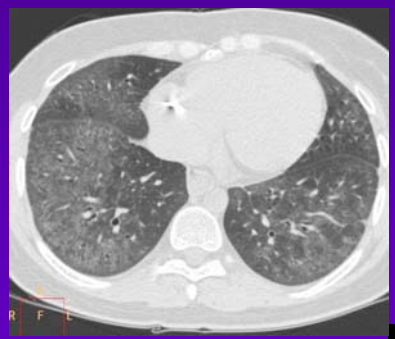
Poormoghim H et al. *Arthritis and Rheumatism*. 2000;43:444-51

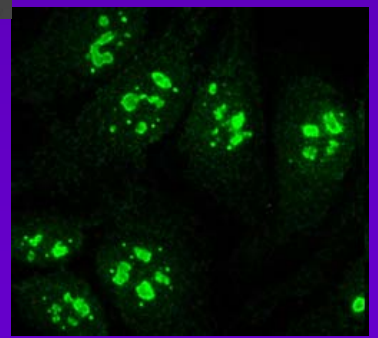
Table 1. Summary of organ system involvement in 48 patients with systemic sclerosis sine scleroderma (ssSSc) and 507 patients with SSc and limited cutaneous involvement (lcSSc)*

Organ system involvement	ssSSc	lcSSc	*P*
Peripheral vascular	47/48 (98)	502/507 (99)	NS
Articular	21/48 (44)	239/507 (47)	NS
Muscular	2/48 (4)	29/507 (6)	NS
Gastrointestinal	31/39 (79)	305/419 (73)	NS
Pulmonary	32/47 (68)	290/485 (60)	NS
Cardiac	4/45 (9)	41/472 (9)	NS
Renal	0/48 (0)	7/507 (1)	NS

* Values are the number (%). NS = not significant.

Fenómeno de Raynaud +/-
Afección visceral
AANs específicos
Sin afección cutánea





Conclusion. Systemic sclerosis sine scleroderma should be included in the spectrum of SSc with limited cutaneous involvement and should not be considered a distinct or separate disorder.

Clinical manifestations	a LcSSc (%)	b DcSSc (%)	c ssSSc (%)	p value a *vs* c	p value b *vs* c
Osteomuscular	318 (56.6)	154 (63.4)	36 (52.2)	ns	0.096
Arthritis	81 (14.4)	66 (27.2)	9 (13)	ns	0.016
Myositis	25 (4.4)	34 (14)	2 (2.9)	ns	0.09
Tendon Friction Ru				ns	0.008
Acrosteolysis				0.049	0.001
Digestive involvement				ns	ns
Oesophagus				0.05	<0.0001
Gastric				ns	ns
Malabsortion				ns	ns
PBC				ns	<0.0001
Lung involvement				0.020	< 0.094
Dyspnea				ns	ns
ILD				ns	< 0.0001
FVC ≤ 70%	70 (12.3)	87 (35.8)	115 (21.7)	0.091	0.042
FVC (%) (mean ± SD)	90.72±22.69	74.93±22	83.11±21.74	0.021	0.016
DLCO/VA (%) (mean ± SD)	76.45±23.16	74.84±22	70.07±18.29	0.091	ns
Ground-glass	62 (11)	77 (31.68)	9 (13.04)	ns	0.008
Reticular pattern	84 (13.0)	92 (38)	10 (149)	ns	<0.0001

Esclerodermia *sine* esclerodermia

Afección pulmonar
(respecto a la forma limitada)

FVC ≤ 70%

FVC(%) media*

DLCO

Clinical Manifestations	a LcSSc (%)	b DcSSc (%)	c ssSSc (%)	p value a *vs* c	p value b *vs* c
PAH	91 (16.2)	53 (21.8)	17 (24.6)	ns	ns
PAH isolated	30 (8.8)	10 (13.7)	3 (7.1)	ns	ns
PAPs (mmHg) (mean ± SD)	39.58±19.1	40.68±20.7	47.34±23.89	0.030	ns
PAPm (mean ± S				ns	ns
VTR (mean ± SD				0.08	ns
Hearth involvement				0.004	0.015
Pericarditis				ns	ns
Ischemia				0.007	0.004
Conduction Alteration				ns	ns
SRC	4 (0.7)	19 (7.8)	1 (1.4)	ns	ns
Sicca Syndrome	211(37.5)	80 (33)	10 (14.5)	<0.0001	0.003
Death	66 (11.7)	63 (26)	6 (8.7)	ns	0.002

Esclerodermia *sine* esclerodermia

Afección pulmonar
(respecto a la forma limitada)

FVC ≤ 70%
FVC(%) media*
DLCO
PAPs*
Afección cardíaca*
Síndrome seco*

Línea Esclerodermia (GEAS)

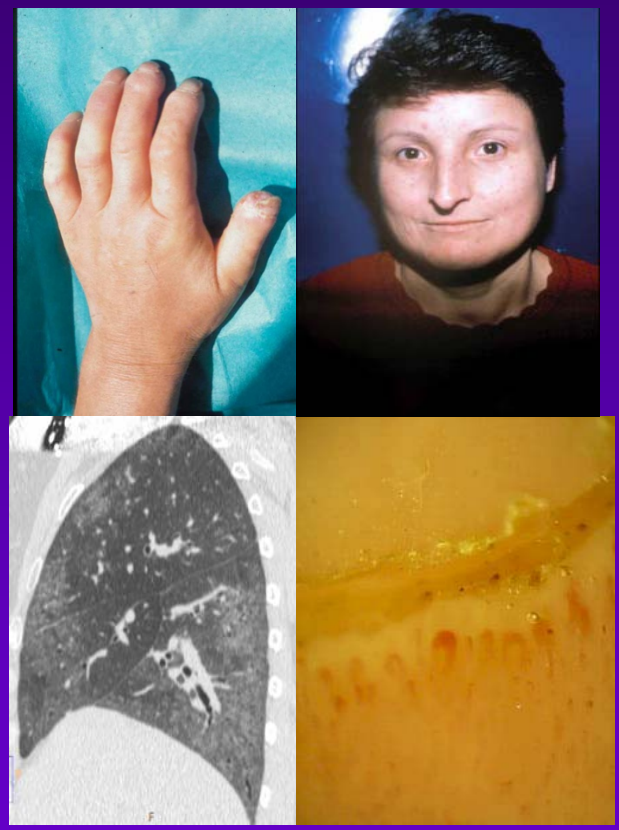
ESCLERODERMIA. Clasificación en subtipos

Forma difusa

F. Raynaud < 1 a.
Afec. cutánea troncal y acra
Roces tendinosos
Afección visceral temprana
Pérdida capilar
Anti-Scl 70 (25-30%)

Limitada

F. Raynaud > 5 a.
Afec. cutánea distal
Telangiectasias, a.diges.
Calcinosis,HTP
Dilatación capilar
AAcentrómero (60-80%)



ESC *sine* esclerodermia

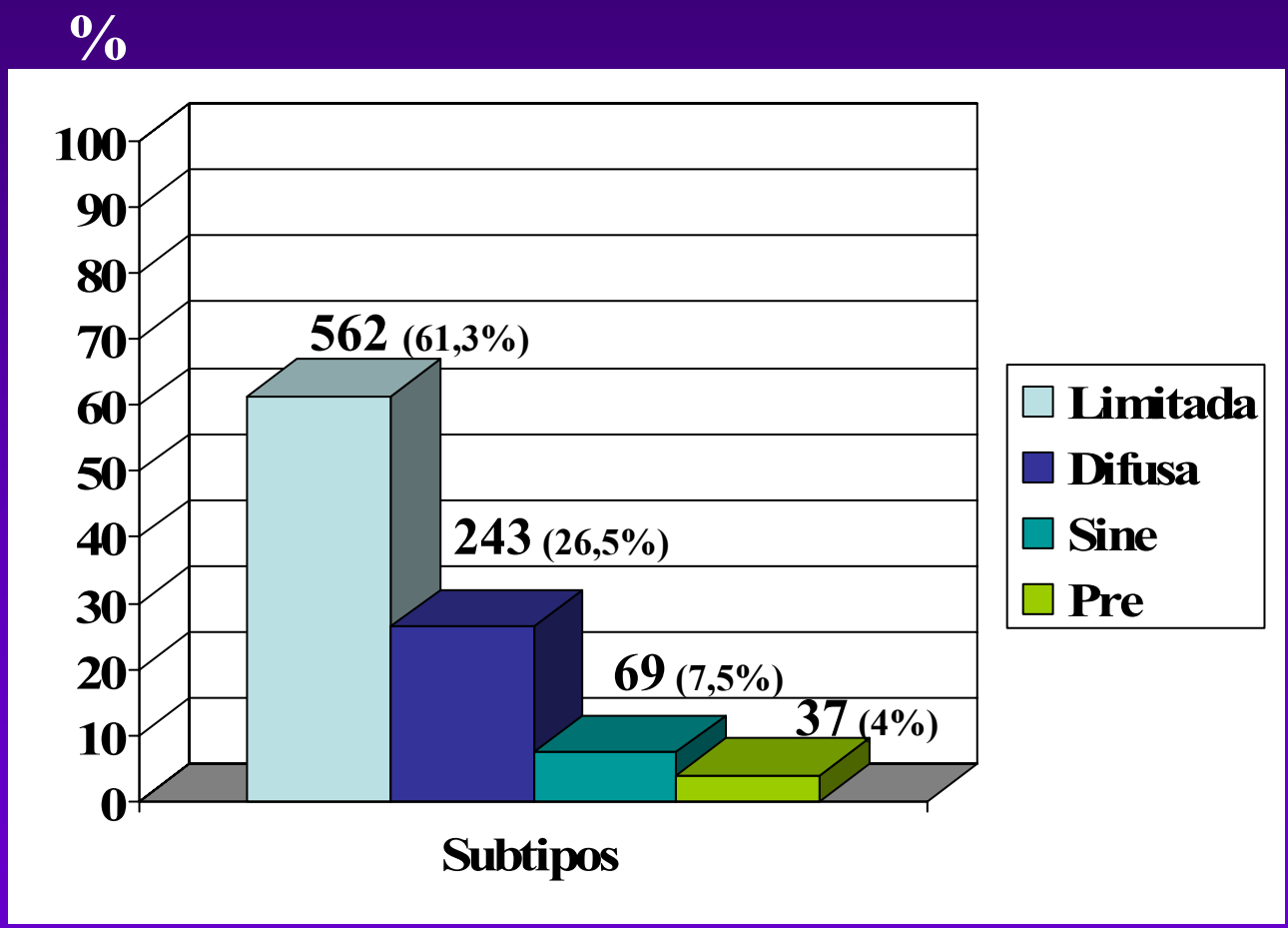
F. Raynaud +/-
Sin afección cutánea
Afección visceral
AANs específicos

Pre-esclerodermia

Fenómeno de Raynaud
Alts. capilaroscópicas
Úlceras digitales
AANs específicos

Características clínico-biológicas de una serie de 916 pacientes con esclerodermia:distribución según subtipos

Línea Esclerodermia. Grupo Enfermedades Autoinmunes Sistémicas. (Sociedad Española de Medicina Interna)

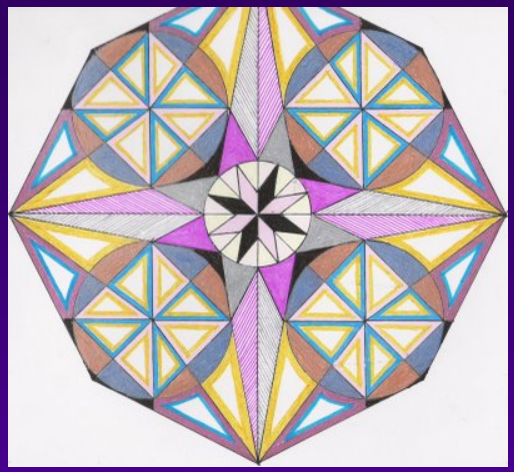


Demographic and clinical characteristics of the 916 Spanish patients with SSc

Ratio Female: Male	7:1
Age at onset (yrs)	45.02±15.23
Age at diagnosis (yrs)	51.17±15.29
Time onset-diagosis (yrs)	6.16± 9.07
ACR criteria fulfilled	620 (67.7)
First manifestation	
RP	678 (83.6)
Puffy hands	13 (1.6)
ArthralgiaS	50 (6.2)
skin sclerosis	50 (6.2)
RP	849 (92.7)
Digital Ulcers	394 (43.0)
Telangiectasias	554 (60.5)
Calcinosis	174 (19.0)

Osteomuscular	518 (56,6)
Digestive involvement	639 (69,8)
Lung Involvement) ILD PAH + ILD PAH isolate	570 (62,2) 421 (46) 161 (17.6) 43 (8,7)
Heart involvement	290 (31,7)
SRC	24 (2)
Sicca syndrome	306 (33,4)
Capillaroscopy Slow Active Not especific	600 (65) 339 (57,3) 199 (33.6) 54 (9)
ANA positive	840 (91.7)
Scl70 positive	173 (18.9)
ACA positive	356 (38.9)
Death	138 (15)

Línea Esclerodermia (GEAS)

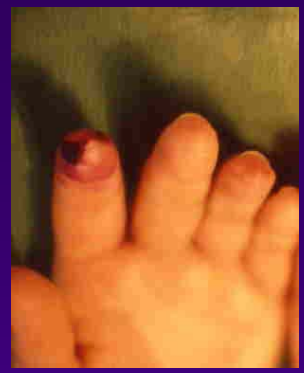


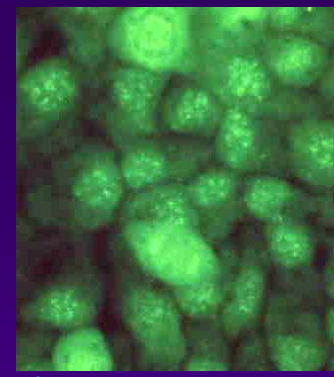
La esclerodermia: una enfermedad en calidoscopio

P.E.

Marzo 1990 (40 a.)

F. Raynaud: larga evolución
Úlceras digitales
Capilaroscopia: Megacapilares
AANs: + 1/160 moteado, ACA +

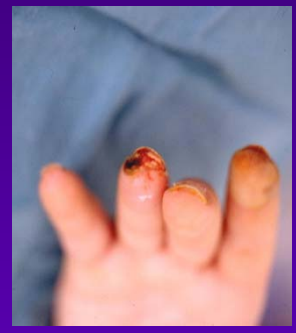




Diagnóstico: Pre-esclerodermia

Junio 1995 (45 a.)

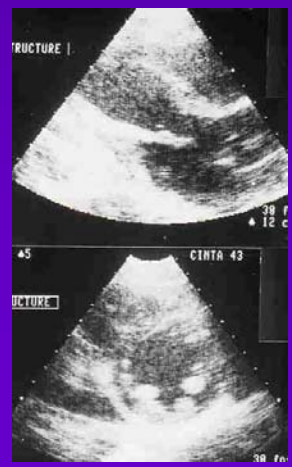
Úlceras digitales
Esclerodactilia
Hipomotilidad esofágica
AANs: 1/320 moteado, ACA+

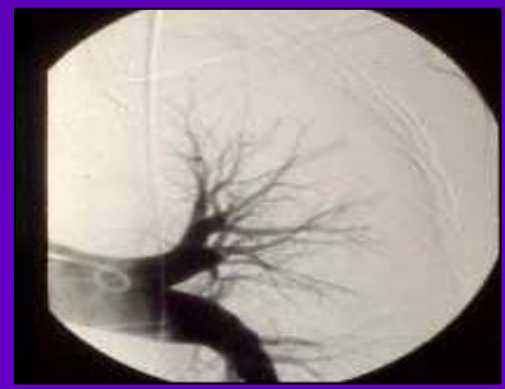



Diagnóstico : Esclerodermia limitada

Abril 2000 (50 a.)

Disnea progresiva,
ECO (abril 2000): PAPs 70 mmHg
Cateterismo: 84/40/55.





Agosto 2000

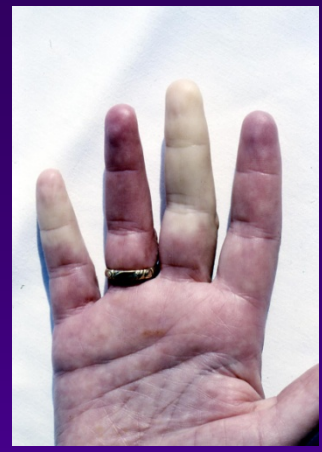
Disnea, ICD, hipotensión, oliguria,
Exitus (14/8/2000)

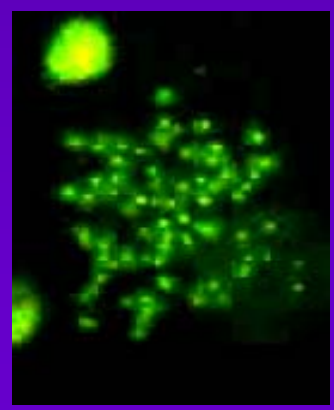
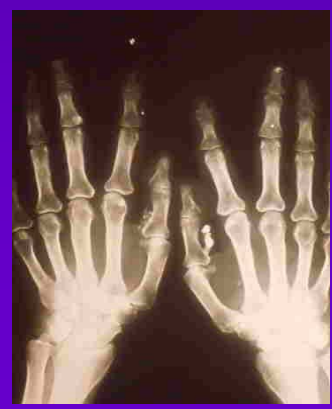
Diag: Esclerodermia limitada – Hipertensión arterial pulmonar

S.F.

1985 (42 a.)

F. Raynaud: larga evolución
Úlceras digitales/"Pitting"
Esclerodactilia / Telangiectasias
Hipomotilidad esofágica
Capilaroscopia: Dilataciones
Megacapilares
AANs: + 1/640 moteado, ACA +
Diag: Esclerodermia limitada

Evolución

F. Raynaud
Úlceras digitales
Calcinosis
PFRs: normales
Eco-Doppler cardíaco: normal
Esclerodermia limitada: estable

O.R.

1992 (39 a.)

F. Raynaud: < 1 año

Endurecimiento cutáneo difuso

Hipomotilidad esofágica

Capilaroscopia: Pérdida capilar

AANs: + 1/1.280 nucleolar

Diag: Esclerodermia difusa

1994 (41 a.)

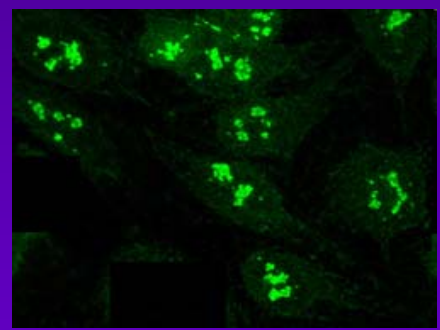
Hipertensión arterial maligna

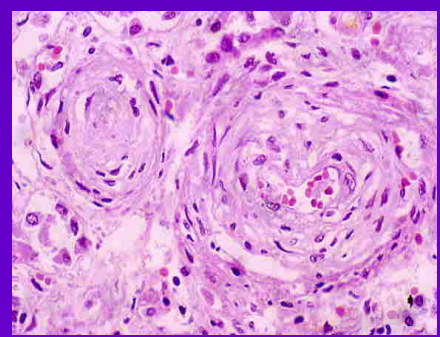
Insuficiencia renal progresiva

Exitus

Esclerodermia difusa:

Crisis renal esclerodérmica





E.P.

1986 (40 a.)

F. Raynaud: < 3 año

Endurecimiento cutáneo difuso

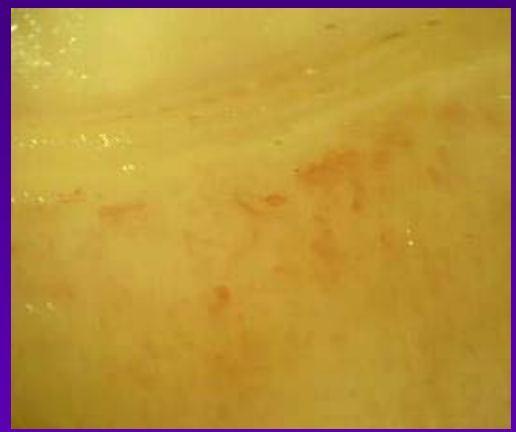
Hipomotilidad esofágica

Capilaroscopia: Pérdida capilar

AANs: + 1/640 moteado

Acs. Anti-topoisomersa 1 +

Diag: Esclerodermia difusa



Evolución

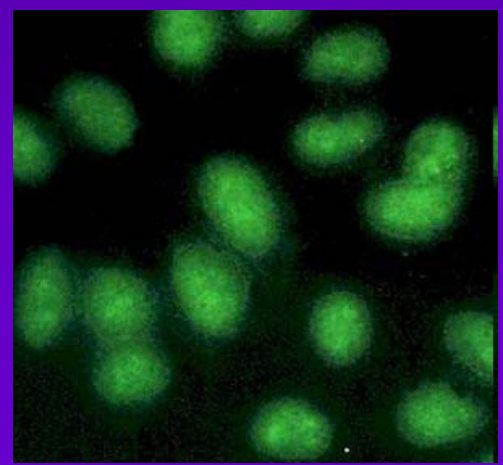
Reblandecimiento cutáneo troncular

Esclerodactilia / Retracciones

Úlceras digitales ocasionales

PFRs – Eco Doppler cardíaco: Normales

Esclerodermia difusa: estable



L.T.

1989 (38 a.)

F. Raynaud: < 3 año

Endurecimiento cutáneo difuso

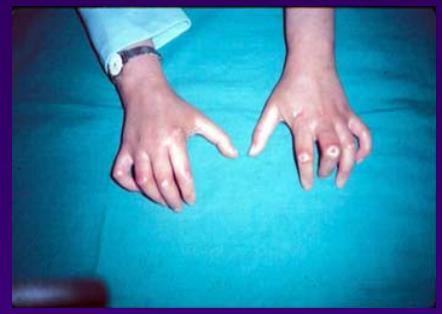
Úlceras digitales

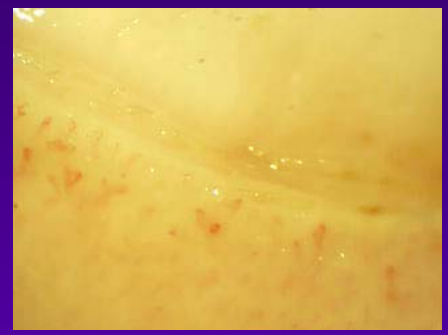
Capilaroscopia: Pérdida capilar

AANs: + 1/640 moteado

Acs. Antitopoisomerasa +

Diag: Esclerodermia difusa

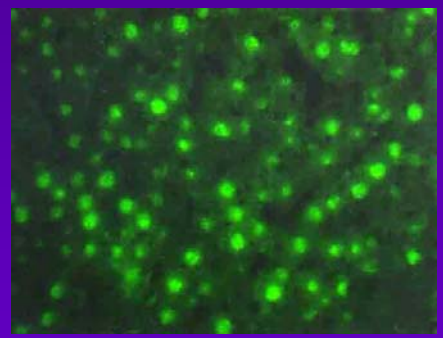




1998 (47 a.)

Disnea de esfuerzo

Fibrosis pulmonar

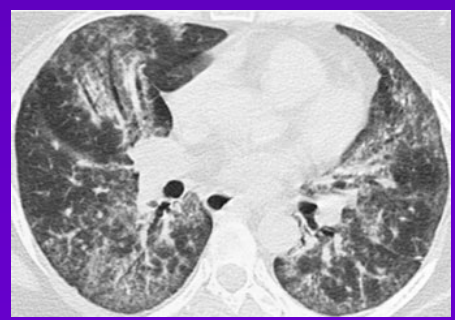


2005 (54 a.)

Insuficiencia respiratoria progresiva

Exitus

Esclerodermia difusa: Fibrosis pulmonar



ESCLERODERMIA: *..en busca de…..*

Clínico:difusa y limitada

Genético: polimorfismos

Vascular: capilaroscopia

Serológico: anticuerpos

The 670G>A polymorphism in the FAS gene
promoter region influences the susceptibili
systemic sclerosis
Polymorphic
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Systemic Sclerosis in Europ
Markers of the Fibrillin-1 Gene and
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Association of Polymorphisms in the IL1B and
Genes with Susceptibility and Severity of Sys
Sclerosis
As
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Cytokine
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Systemic
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Endothelin Axis P
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The PTPN22 620W Allele Confers Susceptibili
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CTGF
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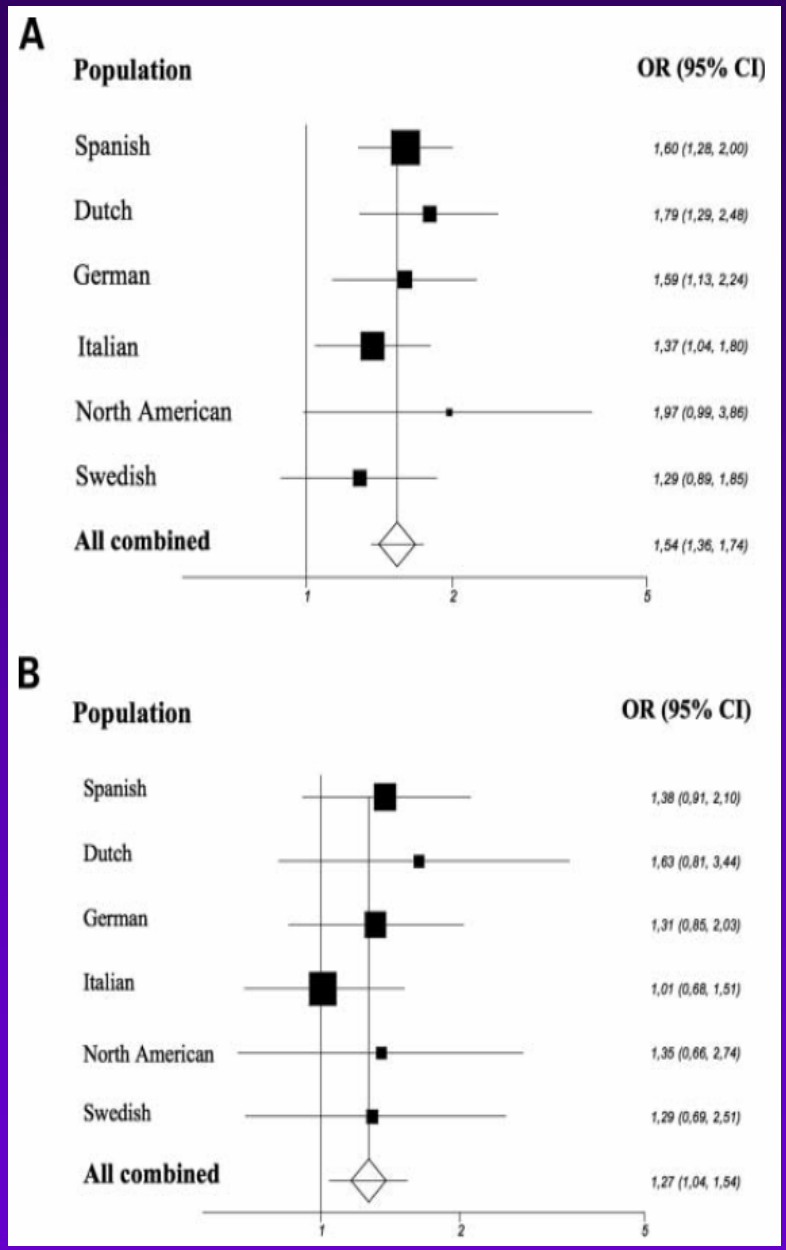


Human Molecular Genetics, 2009, Vol. 18, No. ? **1–7**
doi:10.1093/hmg/ddp119
Advance Access published on xxx

The *STAT4* gene influences the genetic predisposition to systemic sclerosis phenotype

B. Rueda[1], J. Broen[2], C. Simeon[4], R. Hesselstrand[5], B. Diaz[6], H. Sanchez[6], N. Ortego-Centeno[7], G. Riemekasten[8], V. Fonollosa[4], M.C. Vonk[2], F.H.J. van den Hoogen[9], J. Sanchez-Román[10], M.A. Aguirre-Zamorano[11], R. García-Portales[12], A. Pros[13], M.T. Camps[14], M.A. Gonzalez-Gay[15], M.J.H. Coenen[3], P. Airo[16], L. Beretta[17], R. Scorza[17], J. van Laar[18], M.F. Gonzalez-Escribano[19], J.L. Nelson[20], T.R.D.J. Radstake[2] and J. Martin[1,*]

RESULTS

STAT4 is associated with limited cutaneous SSc in the Spanish population

BANK1 Is a Genetic Risk Factor for Diffuse Cutaneous Systemic Sclerosis and Has Additive Effects With *IRF5* and *STAT4*

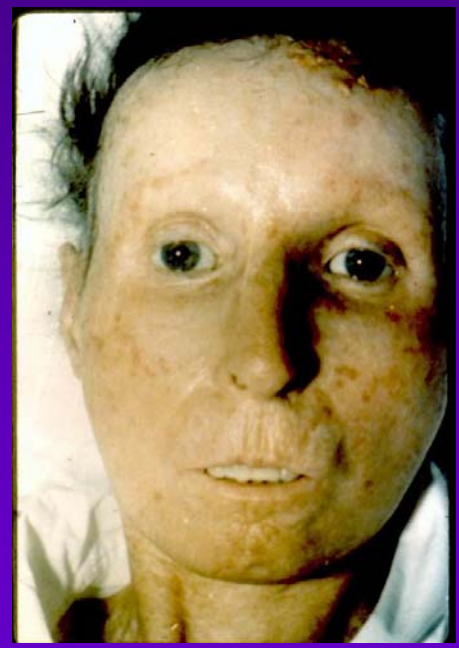
Diudé P et al. *Arthritis and Rheumatism*. 2009;60:3.447-454

Conclusion. Our results establish *BANK1* as a new SSc genetic susceptibility factor and show that *BANK1*, *IRF5*, and *STAT4* act with additive effects.

BANK1 functional variants are associated with susceptibility to diffuse systemic sclerosis in Caucasians

B Rueda, P Gourh, J Broen, S K Agarwal, C P Simeón, N Ortego-Centeno, M C Vonk, M Coenen, G Riemekasten, N Hunzelmann, R Hesselstrand, F K Tan, J D Reveille, S Assasi, F J Garcia-Hernandez, P Carreira, M Camps, A Fernandez-Nebro, P Garcia de la Peña, T Nearney, D Hilda, M A Gónzalez-Gay, P Airo, L Beretta, R Scorza, T RDJ Radstake, M Mayes, F C Arnett and J Martin

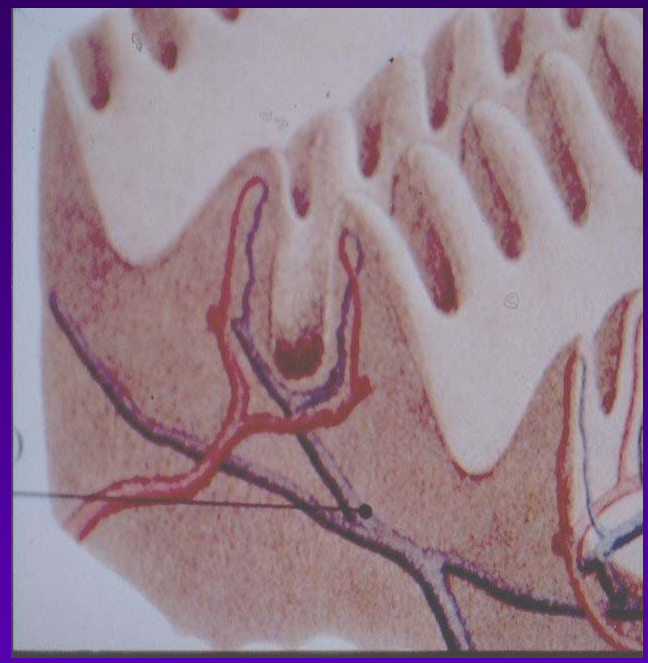
Ann Rheum Dis published online 8 Oct 2009;
doi:10.1136/ard.2009.118174



Conclusion: Our results suggest that *BANK1* gene confers susceptibility to SSc in general, and specifically to the dcSSc and anti-topoisomerase-I antibody subsets.

CAPILAROSCOPIA

Microcirculación cutánea
Porción venular
Porción arteriolar



Morfología capilar
Lecho periungueal

Maurice Raynaud

DE

L'ASPHYXIE LOCALE

ET DE

LA GANGRÈNE SYMÉTRIQUE

DES EXTRÉMITÉS,

PAR

MAURICE RAYNAUD,

Docteur en Médecine de la Faculté de Paris;
Licencié ès Lettres, Licencié ès Sciences;
Interne en Médecine et en Chirurgie des Hôpitaux et Hospices civils de Paris;
Lauréat des Hôpitaux (Médaille d'Argent, 1858; Médaille d'Or, 1860);
Lauréat de la Faculté de Médecine (grand Prix de l'École Pratique, Médaille d'Or, 1861);
ex-Médecin traitant aux Hôpitaux de l'Armée d'Italie, 1859 (Médaille d'Argent de 1re Classe);
Membre de la Société Anatomique.

La gangrène est à l'asphyxie locale ce que la mort est à l'asphyxie générale.
(Bouvier, *Traité des maladies chirurgicales*, t. I, p. 105.)

PARIS.

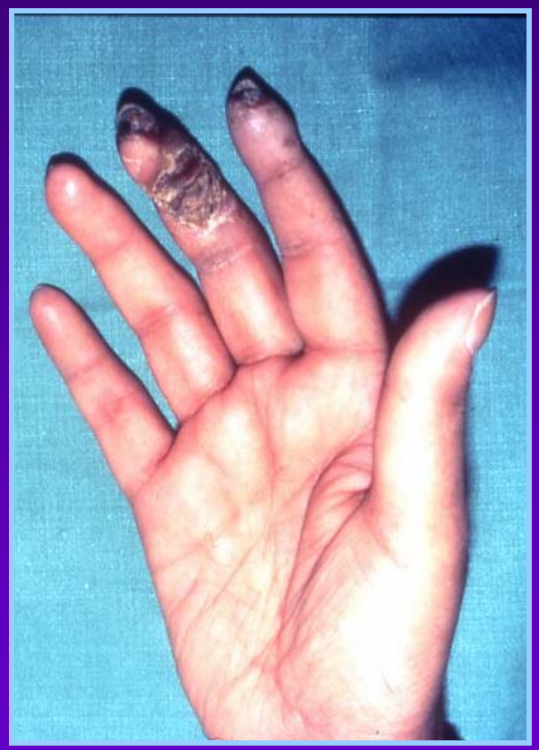
L. LECLERC, LIBRAIRE-ÉDITEUR,
rue de l'École-de-Médecine, 14.

1862

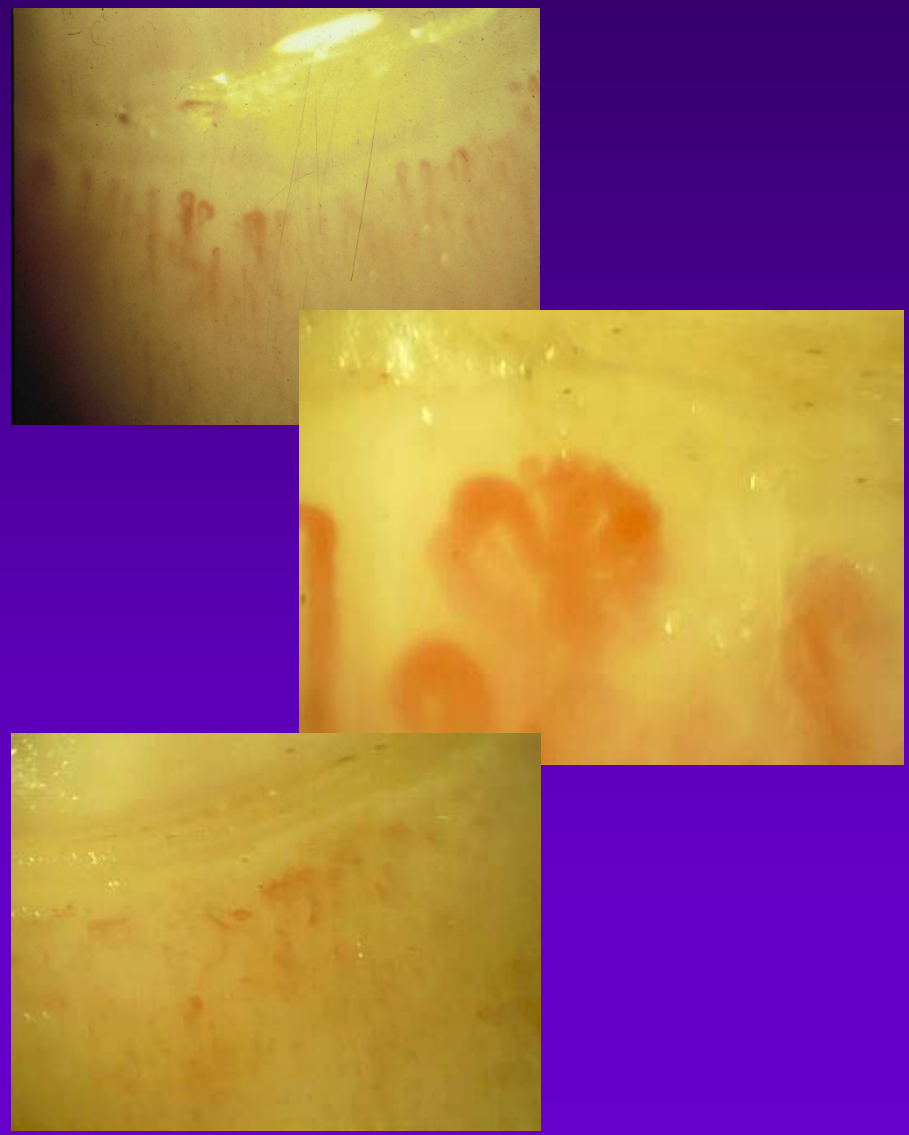
F.Raynaud. Clasificación

Primario

F.Raynaud. Clasificación



Secundario



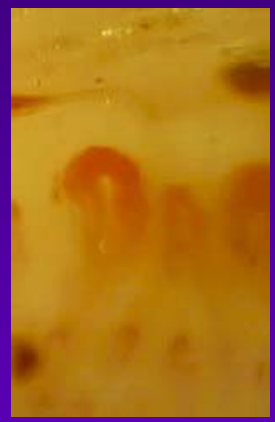
Prognostic Model Based on Nailfold Capillaroscopy for Identifying Raynaud's Phenomenon Patients at High Risk for the Development of a Scleroderma Spectrum Disorder

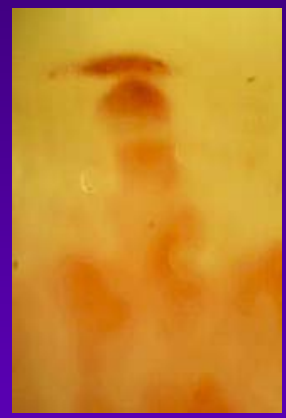
Ingegnoli F et al. *Arthritis and Rheumatism*. 2008;58:2.174-182

Table 2. Multivariate regression analysis of the 3 prognostically relevant capillaroscopy parameters*

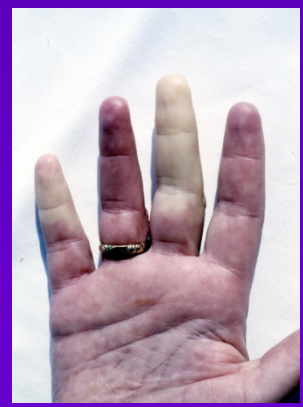
Prognostic variable	HR	95% CI	χ^2	*P*
Giant loops	1.58	0.6–4.14	0.86	0.355
Microhemorrhages	1.77	0.79–3.95	1.93	0.164
No. of capillaries				
Linear	0.66	0.45–0.98	4.15	0.042
Nonlinear	1.66	1.01–2.70	4.06	0.044

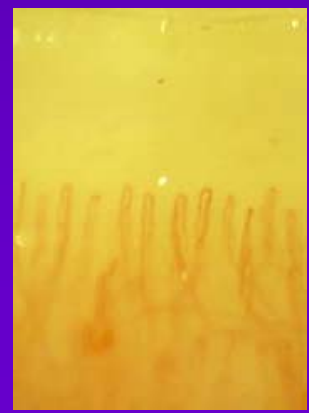
* HR = hazard ratio; 95% CI = 95% confidence interval.





Conclusion. **Our prognostic capillaroscopic index identifies RP patients in whom the risk of developing SSDs is high. This model is a weighted combination of different capillaroscopy parameters that allows physicians to stratify RP patients easily, using a relatively simple diagram to deduce the prognosis. Our results suggest that this index could be used in clinical practice, and its further inclusion in prospective studies will undoubtedly help in exploring its potential in predicting treatment response.**



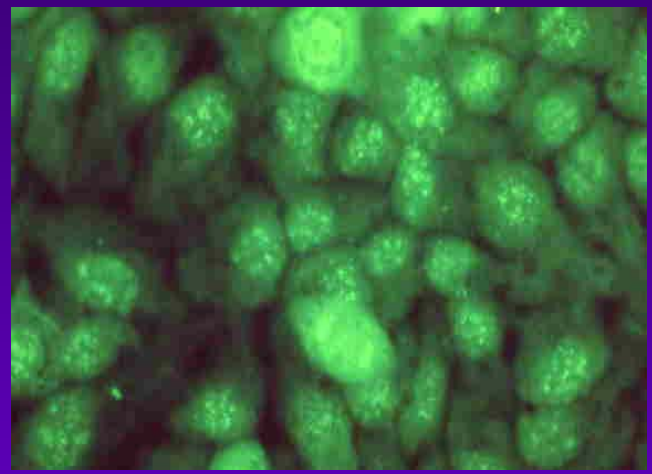


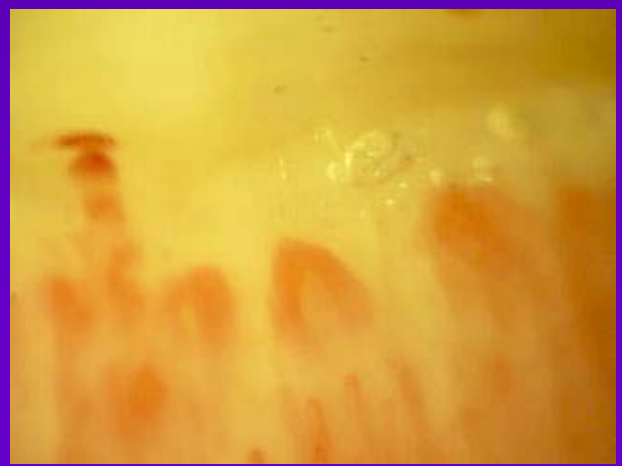
Autoantibodies and Microvascular Damage Are Independent Predictive Factors for the Progression of Raynaud's Phenomenon to Systemic Sclerosis

A Twenty-Year Prospective Study of 586 Patients, With Validation of Proposed Criteria for Early Systemic Sclerosis

Koenig M et al. *Arthritis and Rheumatism*. 2008;58:3.902-12

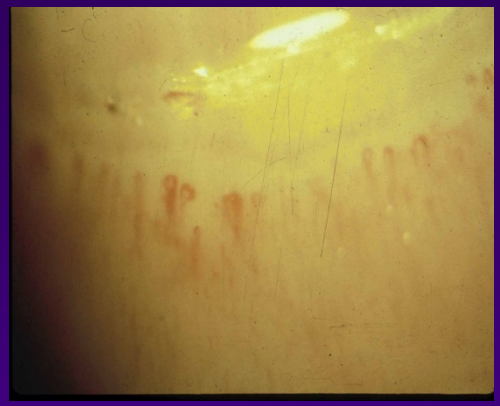
Last, this study is the first to validate the criteria for early SSc that were proposed by LeRoy and Medsger, but were not validated (21). According to these criteria, when the presence of RP is subjective only (i.e., by patient report only), as in the present study, early SSc may be diagnosed when *both* an SSc pattern on NCM and SSc-specific autoantibodies are observed (21). In our cohort, patients in whom both predictors were present at baseline were 60 times more likely to develop definite SSc than were patients without these predictors.



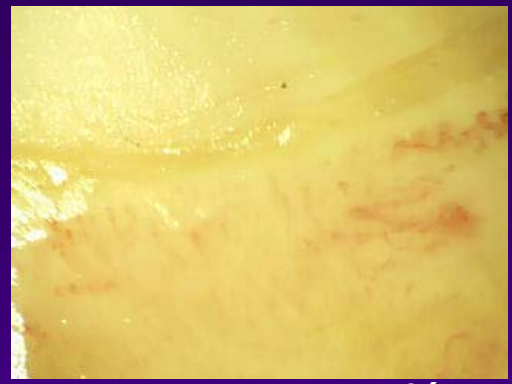


Conclusion. In RP evolving to definite SSc, microvascular damage is dynamic and sequential, while SSc-specific autoantibodies are associated with the course and type of capillary abnormalities. Abnormal findings oping definite SSc, whereas their absence rules out this outcome.

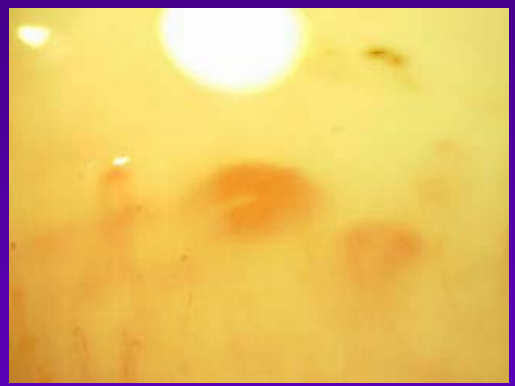
Capilaroscopia



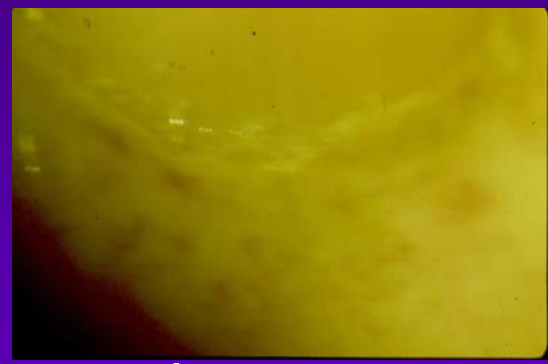
Dilataciones



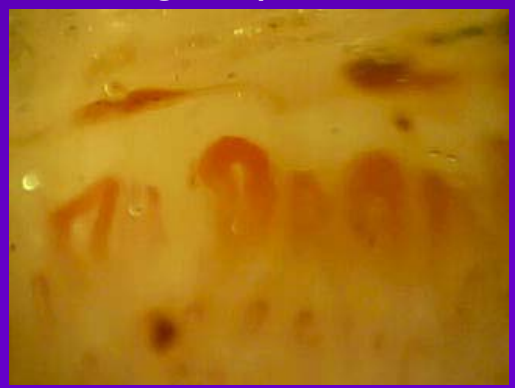
Desestructuración vascular



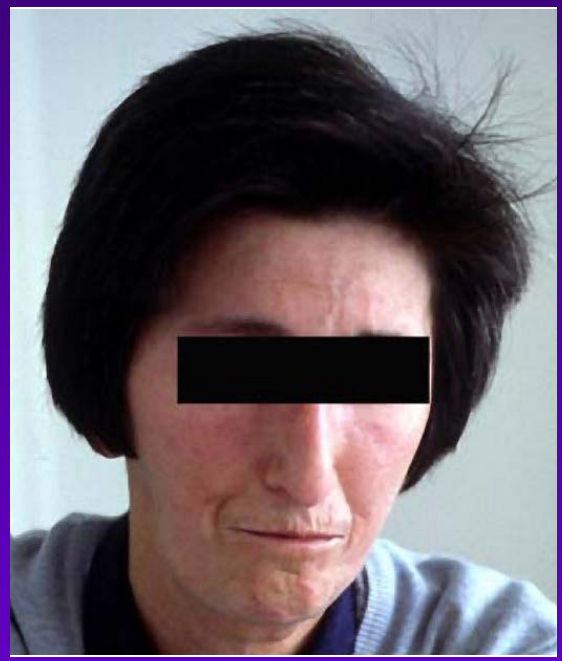
Megacapilares



Pérdida capilar



Megacapilares



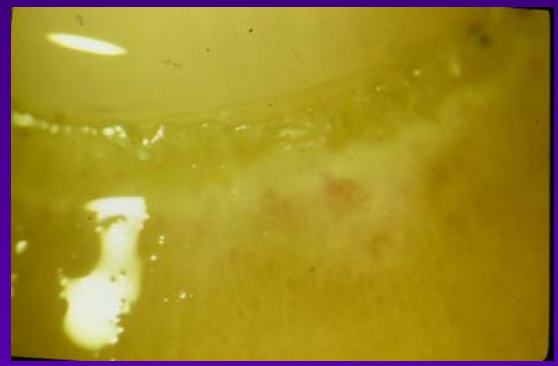
Esclerodermia

Hemorragias

CAPILAROSCOPIA. Esclerodermia

Patrones capilaroscópicos*

Patrón activo
- pérdida capilar intensa
- desestructuración vascular
- dilataciones escasas



Patrón lento
- dilataciones-megacapilares
- pérdida discreta

*HR.Mariqc

CAPILAROSCOPIA. Esclerodermia

TABLA 2

Subtipos de esclerodermia y alteraciones capilaroscópicas

Subtipo (n.º de casos)	Dilatación		Pérdida	
	Moderada	Extrema	Escasa	Extensa
Difusa (11)	5 (46)	4 (36)	3 (27)	7 (63)*
Limitada (52)	14 (27)	33 (63)	22 (42)	9 (17)*

* p = 0,003. Resultados expresados en n.º de casos (tanto por ciento).

TABLA 3

Número de órganos afectos y alteraciones capilaroscópicas

N.º de órganos (n.º de casos)	Dilatación		Pérdida	
	Moderada	Extrema	Escasa	Extensa
Uno (8)	1 (12)	7 (87)	4 (50)	0
Dos (30)	8 (26)	18 (60)	13 (43)	6 (20)
Tres (21)	9 (43)	10 (47)	6 (29)	8 (26)
Cuatro (4)	1 (25)	2 (50)	2 (50)	2 (50)

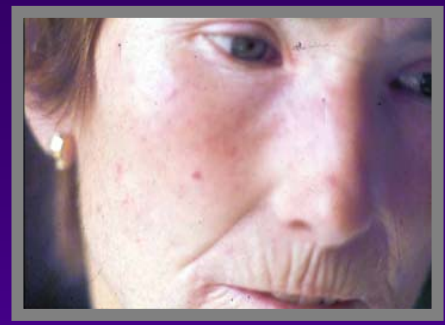
Resultados expresados en n.º de casos (tanto por ciento).
Valores de p > 0,05.

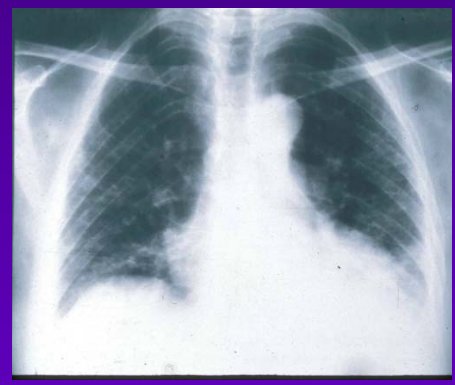
TABLA 4

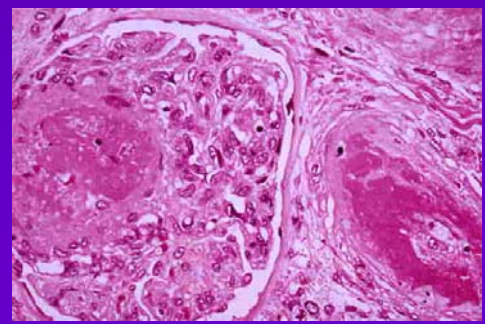
Tipo de afección visceral y alteraciones capilaroscópicas

Tipo de afección	N.º de casos (tanto por ciento)	Capilaroscopia patológica	Dilatación		Pérdida	
			Moderada	Extrema	Escasa	Extensa
Digestiva	54 (85)	51 (84)	15 (28)	31 (57)	20 (37)	14 (26)
Respiratoria	44 (69)	43 (97)	14 (32)	24 (54)	16 (36)	13 (29)
Cardíaca	48 (76)	48 (76)	14 (28)	28 (56)	17 (34)	15 (30)
Renal	4 (6)	4 (100)	1 (25)	2 (50)	2 (50)	2 (50)

Resultados expresados en n.º de casos (tanto por ciento).
Valores de p > 0,05.







Simeón et al. *Med Clin (Barc).* 1991;97:561-564

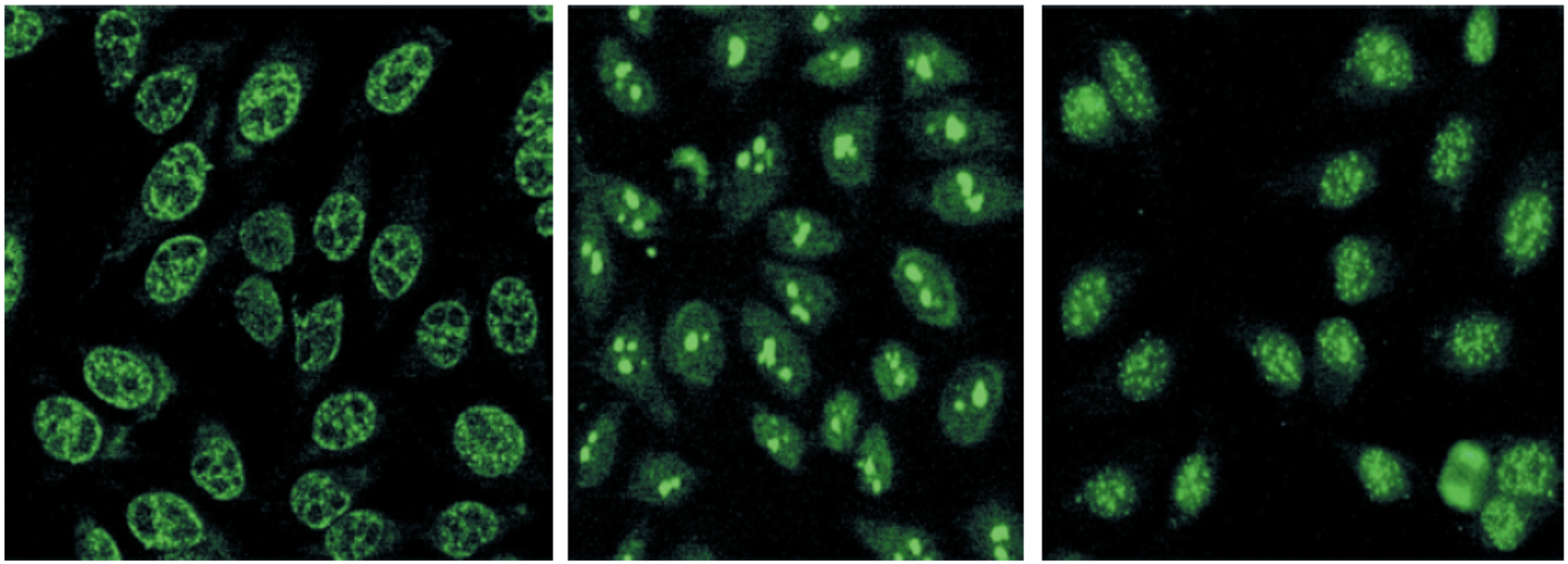
	a LcSSc (%)	b DcSSc (%)	c ssSSc (%)	pre-SSc	p value a *vs* b	p value a *vs* c	p value b *vs* c
Capillaroscopy	383 (68)	131 (54)	54 (78)	32(86,5)			
Slow pattern	231 (61.6)	50 (39)	37 (68.9)	21 (66)	<0.0001	<0.0001	<0.0001
Active pattern	114 (30.4)	78 (59.5)	4 (7.4)	3 (9,4)	<0.0001	<0.0001	<0.0001

	ACA (808) (%) 356 (44)	Scl70 (796) (%) 173 (21,7)	RNP (762) (%) 41 (5,3)	PM-Scl (311) (%) 14 (4,5)
Capilaroscopy	255 (71.6)	99 (57.2)	32 (78)	10 (71.4)
Slow pattern	162 (65.1)*	45 (49.5)*	12 (40)	5 (90)
Active pattern	66 (26.9)*	47 (47.9)*	16 (53.3)	4 (40)

Línea Esclerodermia (GEAS)

Esclerodermia: Anticuerpos antinucleares específicos

A



B

Classic Autoantibodies	Clinical Features	New Autoantibodies	Role
Anti–topoisomerase I	Diffuse cutaneous scleroderma	Anti–endothelial cell	Induce apoptosis of endothelial cells
Anticentromere proteins	Limited cutaneous scleroderma, pulmonary hypertension	Anti–FBN 1	Activate normal human fibroblasts
Anti–RNA polymerase I/II	Diffuse cutaneous scleroderma, renal involvement	Anti–MMP 1 and 3	Prevent degradation of ECM proteins
Antipolymyositis, sclerosis	Polymyositis, calcinosis	Anti-PDGFR	Stimulate normal human fibroblasts through Ha-Ras-ERK1/2-ROS
Antifibrillarin (U3RNP)	Diffuse cutaneous scleroderma, internal-organ involvement	Anti–Nag-2	Induce endothelial-cell apoptosis
Anti-Th/To	Limited cutaneous scleroderma, pulmonary fibrosis		

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Rheum Dis Clin N Am
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RHEUMATIC
DISEASE CLINICS
OF NORTH AMERICA

The Many Faces of Scleroderma

Virginia D. Steen, MD

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Clinical studies have shown that the use of limited cutaneous and diffuse cutaneous scleroderma does not adequately predict the prognosis in many patients. Perhaps systemic sclerosis should be used as a generic term such as "cancer" or "heart disease" and then use the autoantibody subset as a distinct form of the disease. Treatment is still focused on individual organ systems and different antibody subsets have different frequency and severity of organ involvement. Thus, the antibody subsets still need to be lumped under the umbrella of systemic sclerosis. At this point, it seems prudent to put

Table 1
Features of patients with limited scleroderma-specific autoantibodies

Antibody	ACA	Th/To	Pm/Scl	U1-RNP
No. of patients	291	72	36	71
Male sex, %*	**8**	19	19	21
African African, %*	3	4	3	**13**
Age of onset*	42	40	38	**33**
Diffuse SSc, %*	5	7	22	20
Disease duration				
At diagnosis*	**8.7**	**7.9**	3.2	3.2
Joints, %*	60	60	75	**94**
Digital ulcers, %*	**61**	29	**47**	49
Gangrene, %*	**18**	5	5	11
Digital tuft	**27**	7	**32**	17
Resorption* (x-ray numbers actually performed)	(41/151)	(2/28)	(7/22)	(5/29)
Calcinosis, %*	**46**	**22**	**39**	14
Muscle inflammation, %*	1	6	**58**	**27**
Any GI, %	57	33	39	39
Severe GI, %*	8	**13**	0	14
Any lung, %	45	62	58	53
Number with PFTs	(184)	(49)	(22)	(49)
Severe fibrosis, %*	6	**16**	**27**	**22**
Lowest FVC,* % predicted	87	**70**	**74**	75
Isolated PAH*	**19**	**32**	3	**14**
Severe heart, %*	4	7	6	11
Renal crisis, %*	1	4	4	7
Survival, % cumulative survival from diagnosis				
5 y, 10 y	85,75	**78,65**	**95,72**	**78,65**

Major differences in bold.

Abbreviations: ACA, anticentromere antibody; FVC, forced vital capacity; GI, gastrointestinal; PFT, pulmonary function test; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

* $P < .001$ by analysis of variance.

Steen, 2008

Table 2

Features of patients with diffuse scleroderma specific autoantibodies present

Antibody	TOPO	POL 3	U3 RNP
No. of patients	318	120	55
Male sex, %*	27	**19**	29
African African, %*	**17**	3	**29**
Age of onset*	43	44	**35**
Diffuse SSc, %*	**71**	**85**	64
Disease duration			
At diagnosis	2.2	1.5	2.9
Joints, %	**86**	**88**	**89**
Carpal tunnel, %*	28	**43**	27
Tendon rubs, %	**50**	**61**	**42**
Digital ulcers, %*	**63**	42	**58**
Gangrene, %*	**13**	3	9
Digital tuft	**28**	5	9
Resorption* (x-ray numbers actually performed)	49/173	3/54	2/22
Calcinosis, %*	17	14	**22**
Muscle inflammation, %*	9	4	**18**
Any GI, %	56	37	59
Severe GI, %*	8	5	**25**
Any lung %	73	49	67
Number with PFTs	(235)	(74)	(37)
Severe fibrosis, %*	**23**	7	**24**
Lowest FVC,* % predicted	**67**	81	**68**
Isolated PAH	2	6	24
Severe heart, %*	**16**	7	**18**
Renal crisis, %*	**10**	**28**	7
Survival, % cumulative survival from diagnosis			
5 y, 10 y	78,65	**90,75**	80,61

Major differences in bold.

Abbreviations: FVC, forced vital capacity; GI, gastrointestinal; PFT, pulmonary function test; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

* $P < .001$ by analysis of variance.

Steen, 2008

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The Many Faces of Scleroderma

Virginia D. Steen, MD

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In summary, scleroderma-specific autoantibodies are strongly associated with meaningful clinical manifestations. These antibodies can be helpful in determining prognosis, and monitoring and treating patients. They should be used in performing clinical trials and in doing genetic and basic research. Hopefully, these scleroderma antibodies will lead to a better understanding of the pathogenesis of scleroderma.

	ACA (808) (%)	Scl70 (796) (%)	p (ACA *vs* Scl70)
Number of patients	356 (44)	173 (21.7)	
LcSSc	293 (82.3)	45 (2.6)	< 0.001
DcSSc	17 (4.7)	116 (67)	< 0.001
ssSSc	27 (7.5)	6 (3.4)	< 0.001
Women	328 (92.1)	147 (85)	0.011
Age at onset	45.64 ± 14.45	44.73 ± 15.34	ns
Age at diagnosis	53.47 ± 13.75	49.01 ± 14.33	< 0.001
Time onset-diagnosis	7.84 ± 9.95	4.31 ± 7.09	< 0.0001
First Manifestation			
RP	299 (92.6)	130 (84.4)	0.013
Puffy hands	1 (0.3)	2 (1.3)	ns
Arthralgia	15 (4.6)	12 (17.8)	ns
Skin sclerosis	3 (0.9)	8 (5.2)	ns
ACR criteria fullfilled	202 (56.7)	151 (87.3)	<0.001
RP	345 (96.9)	158 (91.3)	0.005
Digital Ulcers	133 (37.4)	90 (52)	0.002
Telangiectasias	226 (63.9)	100 (57.8)	ns
Calcinosis	75 (21.1)	23 (13.3)	0.021

	ACA (808) (%)	Scl70 (796) (%)	p (ACA *vs* Scl70)
Osteomuscular	189 (53.1)	103 (59.5)	ns
Arthritis	42 (11.8)	40 (23.1)	< 0.001
Myositis	5 (1.4)	12 (6.9)	< 0.001
Tendon Friction Fubs	11 (3.1)	14 (8.1)	0.010
Acrosteolysis	26 (7.3)	22 (12.7)	0.045
Digestive involvement			
Oesophagus	188 (79)	113 (89)	ns
Gastric	39 (16.4)	58 (17)	ns
Malabsortion	7 (2.9)	14 (4.1)	ns
Lung involvement			
ILD	110 (30.9)	123 (71.1)	< 0.001
FVC (%) (mean ± SD)	94.22 ± 22	74 ± 20.76	< 0.001
DLCO/VA (%) (mean ± SD)	74.77 ± 21.9	74.85 ± 22.32	ns
FVC ≤ 70 (%)	28 (10.7)	64 (43.5)	< 0.001
Ground-glass	24 (14)	60 (56.1)	< 0.001
Reticular pattern	31 (8.7)	76 (43.9)	< 0.001

Línea Esclerodermia (GEAS)

	ACA (808) (%)	Scl70 (796) (%)	p (ACA *vs* Scl70)
PAH	55 (15.4)	37 (21.4)	ns
PAH isolated PAPs (mmHg) (mean ± SD)	19 (7.8) 39.14 ± 20	8 (4.3) 40.28 ± 16	ns ns
PAPm (mean ± SD)	40 ± 15.2	36.8 ± 14.1	ns
VTR (mean ± SD)	2.7 ± 0.75	2.6 ± 0.58	ns
Hearth involvement	115 (32.3)	62 (35.8)	ns
Pericarditis	11 (3.1)	17 (10.1)	0.002
Ischemia	39 (11)	12 (6.9)	ns
Conduction Alteration	43 (12)	22 (12.7)	ns
SRC	4 (1.1)	6 (3.5)	ns
Sicca Syndrome	143 (40.2)	53 (30.6)	0.034
Capilaroscopy	255 (71.6)	99 (57.2)	
Slow pattern	162 (65.1)	45 (49.5)	< 0.001
Active pattern	66 (26.9)	47 (47.9)	< 0.001
Death	38 (10.7)	30 (17.3)	0.027

Línea Esclerodermia (GEAS)

INDEPENDENT PREDICTORS OF DISEASE MANIFESTATIONS

	1	2	3
Age diagnostic (<65 / >=65)	DcSSc LcSSc	-	-
Time onset_diag (<65 / >=65)	DcSSc LcSSc	-	-
Arthritis	DcSSc	-	-
Myositis	DcSSc	ACA -	Scl70 -
Digital ulcers	DcSSc	Scl70 -	
Raynaud Phenomenon	DcSSc LcSSc	-	-
Digestive involvement	DcSSc	-	-
Oesophagus	DcSSc	ACA -	-
Gastric	DcSSc	-	-
Malabsortion	DcSSc	-	-
Lung involvement	DcSSc	ACA -	-
EPID	DcSSc	ACA -	Scl70 - Scl70 +
Ground-glass	DcSSc	ACA -	
Reticular pattern	DcSSc	ACA -	Scl70 - Scl70 +
HTAP	DcSSc	-	-
HTAP whitout EPID	-	-	-

	1	2	3
Hearth involvement	Scl70 - Scl70 +	-	-
Pericarditis	Scl70 - Scl70 +	-	-
Ischemia	-	-	-
Conduction alteration	ACA – ACA +	Scl70 – Scl70 +	-
CRE	DcSSc	-	-
Sicca Syndrome	ACA – ACA +	-	-
CVF ≤ 70%	ACA -	-	-
Capillaroscopy Active/Slow	DsSSc	-	-

Difusa / limitada: 17
ANAs : 3

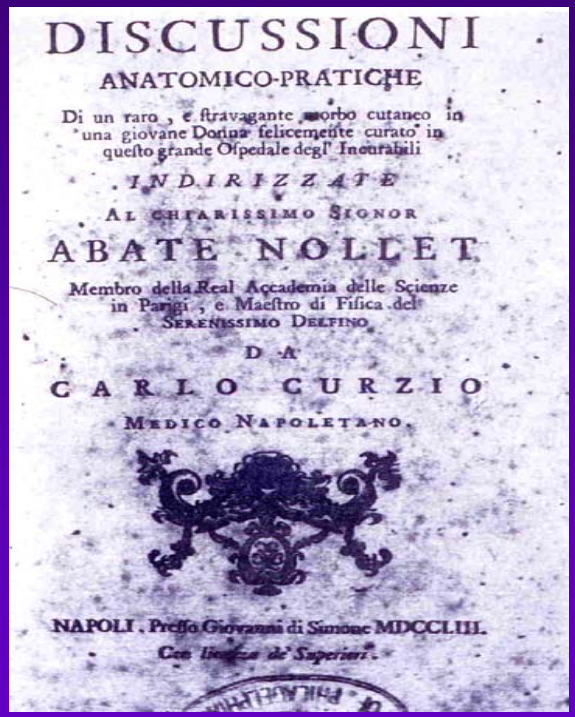
Línea Esclerodermia (GEAS)

ESCLERODERMIA

DISCUSSIONI ANATOMICO-PRATICHE

Di un raro, e stravagante morbo cutaneo in una giovane Donna felicemente curato in questo grande Ospedale degl'Incurabili

Esclerodermia. Tratamiento


DISCUSSIONI
ANATOMICO-PRATICHE
Di un raro, e stravagante morbo cutaneo in una giovane Donna felicemente curato in questo grande Ospedale degl' Incurabili
INDIRIZZATE
AL CHIARISSIMO SIGNOR
ABATE NOLLET
Membro della Real Accademia delle Scienze in Parigi, e Maestro di Fisica del SERENISSIMO DELFINO
DA
CARLO CURZIO
MEDICO NAPOLETANO
NAPOLI, Presso Giovanni di Simone MDCCLIII.
Con licenza de' Superiori.

Carlo Curzio, 1753

"Después de un periodo de 11 meses, la piel de la enferma estaba perfectamente blanda y flexible, podía moverse, levantarse y realizar todas sus funciones naturales"

Baños de vapor y leche caliente
Sangrías (en el pie)
Pequeñas dosis de mercurio