REGISTRO ESPAÑOL DE LA ENFERMEDAD RELACIONADA CON IgG4

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Fernando Martínez Valle
Andreu Fernández Codina
SERVICIO DE MEDICINA INTERNA
UNIDAD DE ENFERMEDADES AUTOINMUNES
Hospital Valle d´Hebrón
BARCELONA
ESPAÑA

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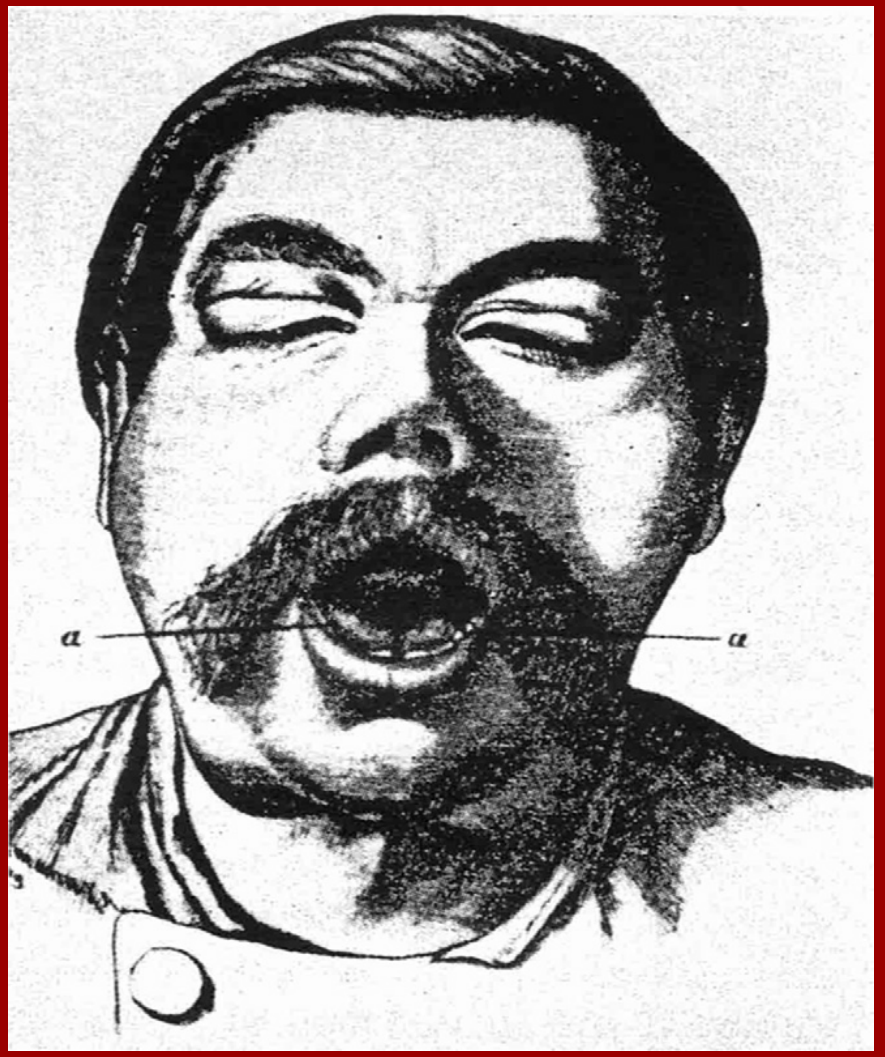
Consensus statement on the pathology of IgG4-related disease

IgG4-related disease is a newly recognized fibro-inflammatory condition characterized by several features: a tendency to form tumefactive lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4$^+$ plasma cells; storiform fibrosis; and—often but not always—elevated serum IgG4 concentrations.[1,2] The disease was initially recognized in the pancreas, disease now known as autoimmune pancreatitis. Autoimmune pancreatitis was linked with the presence of elevated levels of serum IgG4 in 2001.[1]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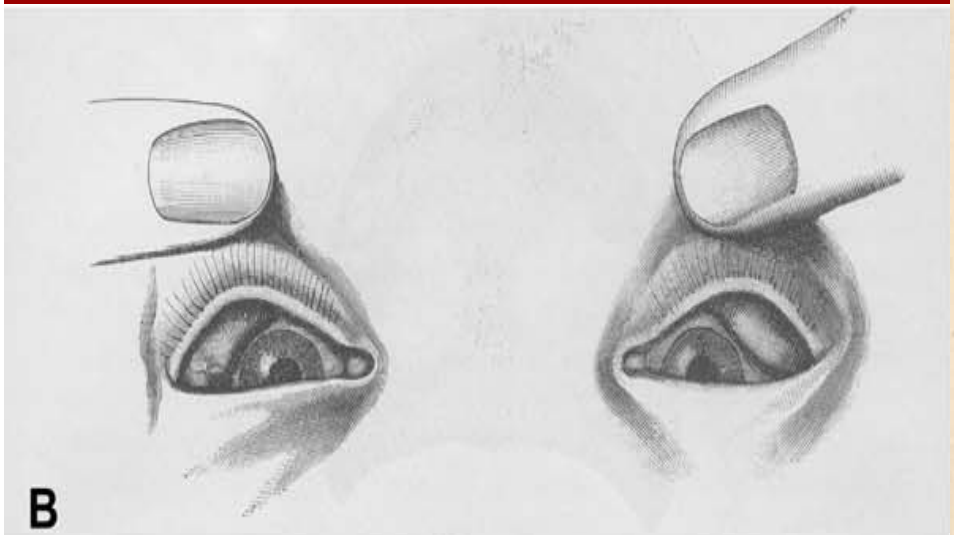

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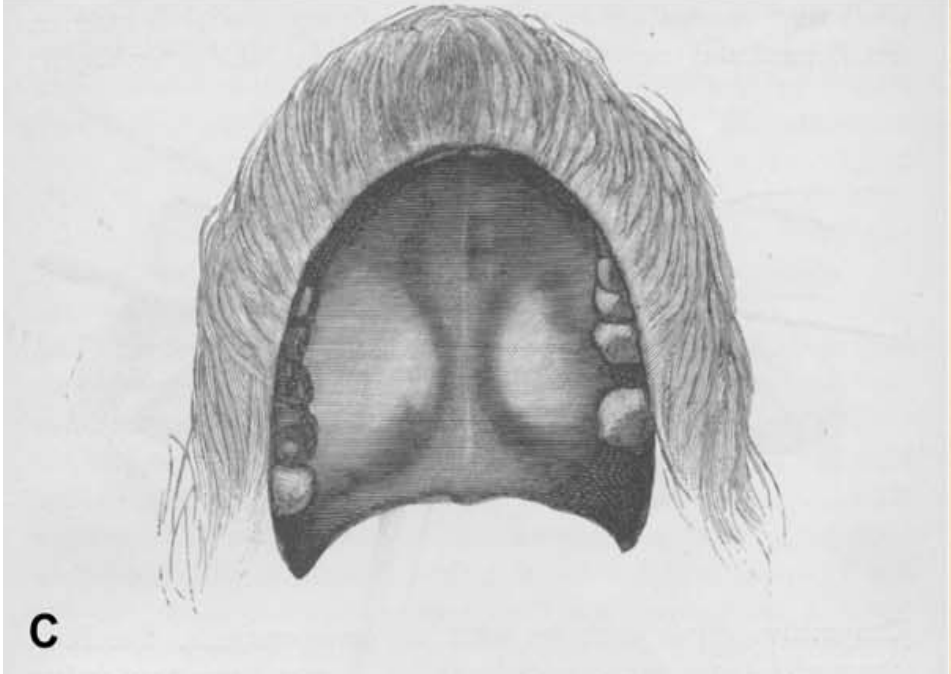

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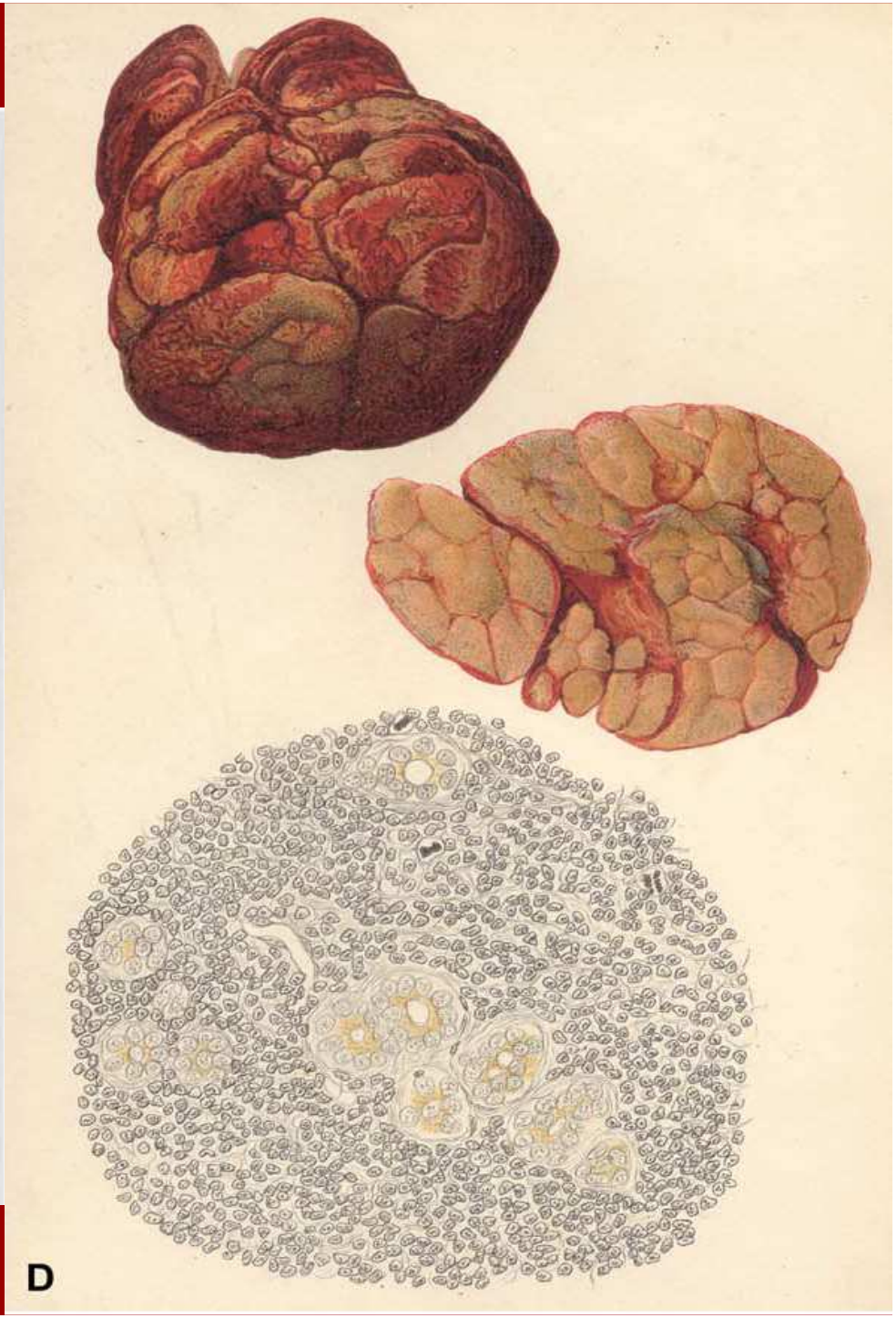


D

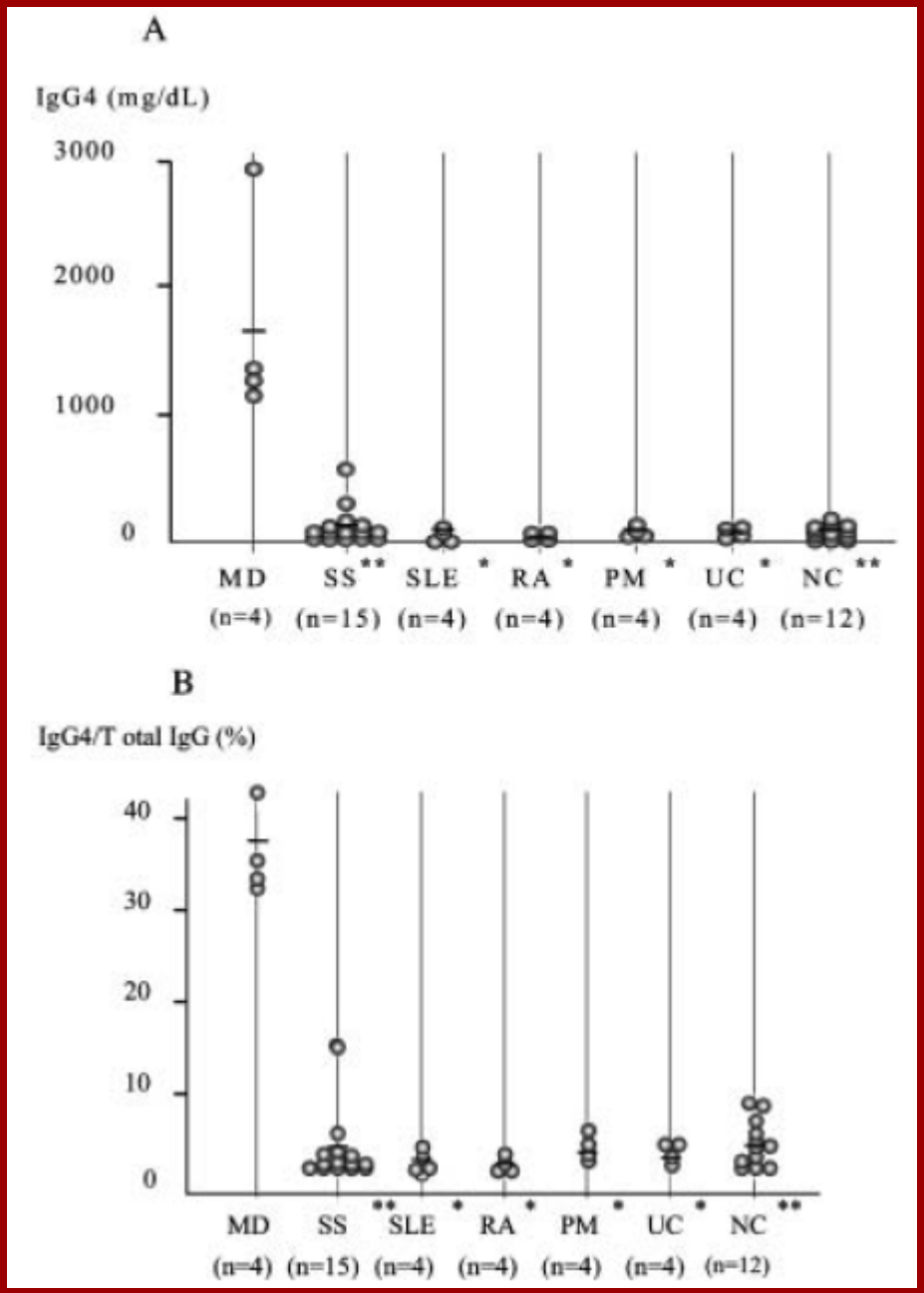
Scand J Rheumatol 2004;33:432–433

Elevated IgG4 concentrations in serum of patients with Mikulicz's disease

M Yamamoto, M Ohara, C Suzuki, Y Naishiro, H Yamamoto, H Takahashi, K Imai

First Department of Internal Medicine, Sapporo Medical University, School of Medicine, Sapporo, Hokkaido, Japan

Between 1997 and 2002, we diagnosed four patients (two men, two women) with Mikulicz's disease according to the following criteria: 1) more than two symmetrical swellings of lacrimal and major salivary glands; 2) prominent mononuclear infiltration of the lacrimal and salivary glands; 3) exclusion of sarcoidosis and lymphoproliferative disease; and 4) no detection of anti SS-A and SS-B antibody by the double immunodiffusion method. Serum samples


A
IgG4 (mg/dL)
3000
2000
1000
0
MD
(n=4)
SS
(n=15)
SLE
(n=4)
RA
(n=4)
PM
(n=4)
UC
(n=4)
NC
(n=12)
B
IgG4/T otal IgG (%)
40
30
20
10
0

Extended report

Proposal for a new clinical entity, IgG_4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG_4-related disorders

Y Masaki,[1] L Dong,[1,2] N Kurose,[3] K Kitagawa,[4] Y Morikawa,[5] M Yamamoto,[7] H Takahashi,[7] Y Shinomura,[7] K Imai,[8] T Saeki,[9] A Azumi,[10] S Nakada,[11] E Sugiyama,[12] S Matsui,[12] T Origuchi,[13] S Nishiyama,[14] I Nishimori,[15] T Nojima,[3] K Yamada,[16] M Kawano,[16] Y Zen,[17] M Kaneko,[18] K Miyazaki,[19] K Tsubota,[20] K Eguchi,[21] K Tomoda,[6] T Sawaki,[1] T Kawanami,[1] M Tanaka,[1] T Fukushima,[1] S Sugai,[1] H Umehara[1]

Ann Rheum Dis 2009;**68**:1310–1315. doi:10.1136/ard.2008.089169

Conclusion: Despite similarities in the involved organs, there are considerable clinical and pathological differences between IgG_4+MOLPS and SS. Based on the clinical features and good response to glucocorticoids, we propose a new clinical entity: IgG_4+MOLPS.

VS

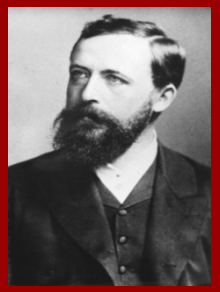


Table 1 Comparison of frequencies of symptoms and complications in patients with IgG_4-positive multiorgan lymphoproliferative syndrome (IgG_4+MOLPS) and those with typical Sjögren's syndrome (SS)

	IgG_4+MOLPS			Typical SS					
	All (n = 64)	Women (n = 33)	Men (n = 31)	All (n = 31)	Women (n = 29)	Japanese*	p Value†	p Value‡	p Value§
Xerophthalmia	32.8% (21)	42.4% (14)	22.6% (7)	93.5% (29)	93.1% (27)		<0.001	<0.001	0.114
Xerostomia	37.5% (24)	45.5% (15)	29.0% (9)	87.1% (27)	86.2% (25)		<0.001	0.001	0.205
Arthralgia	15.6% (10)	15.2% (5)	16.1% (5)	48.4% (15)	51.7% (15)		0.001	0.002	1.000
Allergic rhinitis	40.6% (26)	54.5% (18)	25.8% (8)	6.5% (2)	6.9% (2)	5–10%	0.001	<0.001	0.024
Bronchial asthma	14.1% (9)	18.2% (6)	9.7% (3)	3.2% (1)	3.4% (1)	3–5%	0.158	0.109	0.476
Autoimmune pancreatitis	17.2% (11)	3.0% (1)	32.3% (10)	0.0% (0)	0.0% (0)	<0.001%	0.014	0.532	0.002
Interstitial nephritis	17.2% (11)	9.1% (3)	25.8% (8)	6.5% (2)	6.9% (2)	<0.005%	0.210	1.000	0.074
Interstitial pneumonitis	9.4% (6)	9.1% (3)	9.7% (3)	32.3% (10)	31.0% (9)	<0.005%	0.008	0.051	1.000

Differences between Mikulicz's disease and Sjögren's syndrome (modified from reference [60]).

	Mikulicz's disease	Sjögren's syndrome
Age distribution	From 50s to 60s	From 40s to 50s
Sex ration	3:1 in favor of females	20:1 in favor of females
Gland swelling	Persistent	Recurrent
Dysfunction of salivary secretion	None – slight	Mild – severe
Keratoconjunctivitis sicca	None – slight	Mild – severe
Response to steroid	Very good	No change, or sometimes good
Serum IgG	Normal – very high	Normal – high
Antinuclear body	Dominance of negative cases	Dominance of positive cases
Anti-SS-A/SS-B antibodies	Negative	Positive (70%/30%)
Serum IgG4	Severely high	Normal
Glands biopsy	Infiltration of abundant IgG4-positive plasmacytes	No detection of IgG4-positive cells

IgG4-Related Disease (IgG4RD)

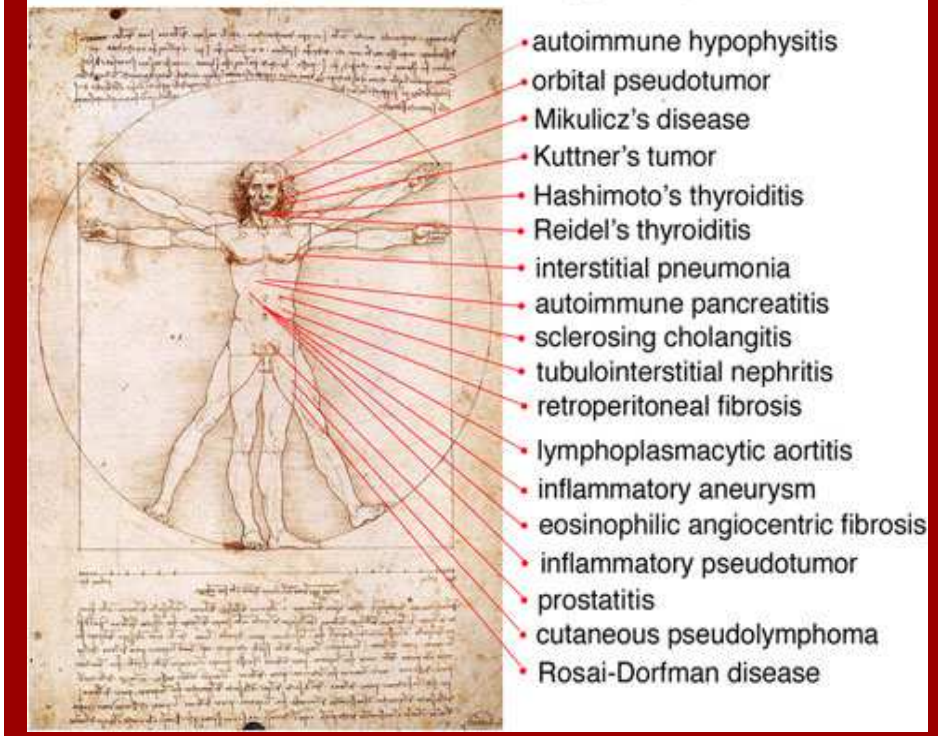
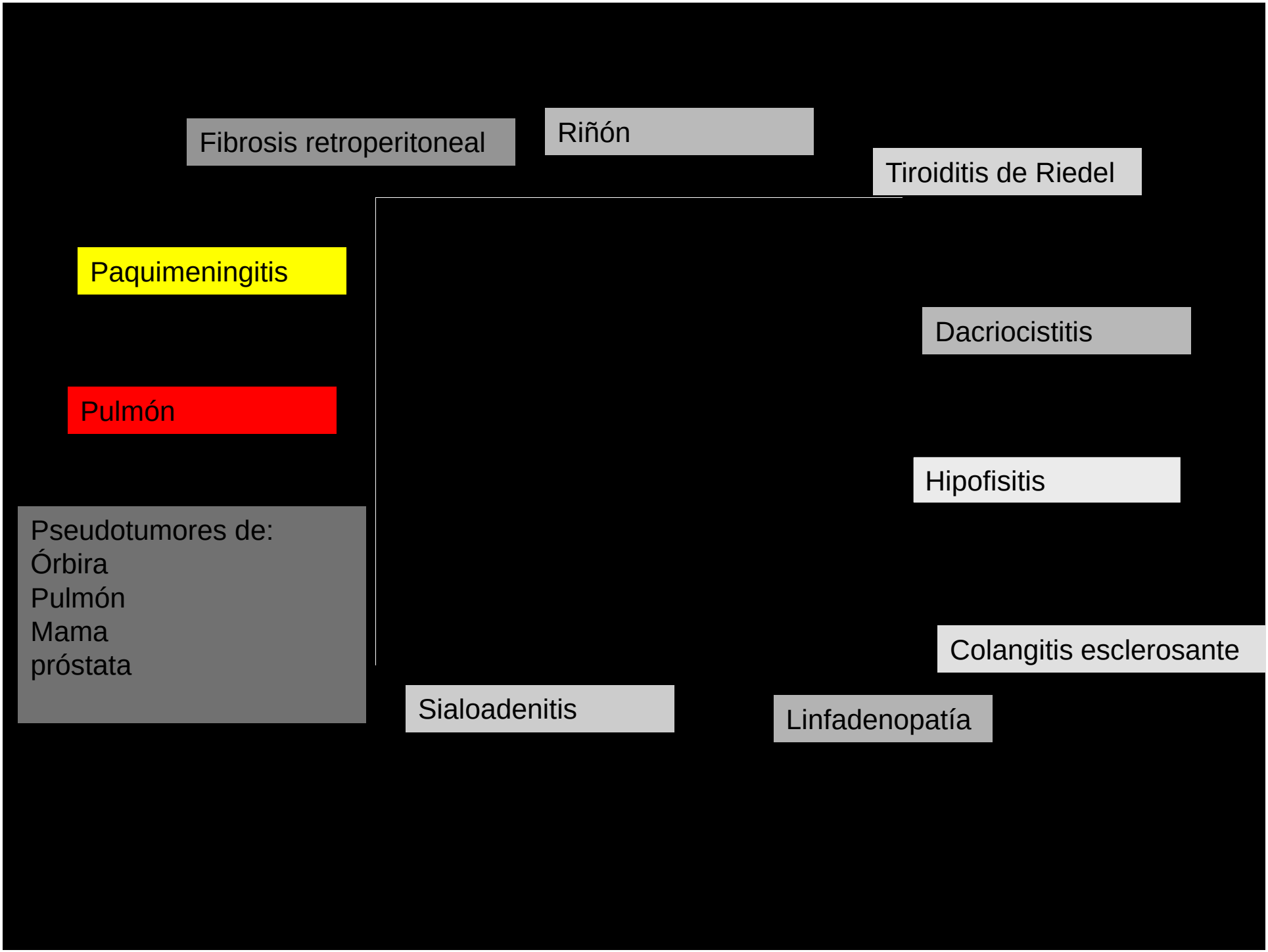


Table 2. Names of previously recognized conditions that comprise or may comprise parts of the IgG4-related disease spectrum

Mikulicz disease
Küttner tumor
Riedel thyroiditis
Eosinophilic angiocentric fibrosis
Multifocal fibrosclerosis
Lymphoplasmacytic sclerosing pancreatitis/ autoimmune pancreatitis
Inflammatory pseudotumor
Fibrosing mediastinitis
Sclerosing mesenteritis
Retroperitoneal fibrosis (Ormond disease)
Periaortitis/periarteritis
Inflammatory aortic aneurysm
Cutaneous pseudolymphoma
Idiopathic hypertrophic pachymeningitis
Idiopathic tubulointerstitial nephritis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Idiopathic cervical fibrosis


Fibrosis retroperitoneal
Riñón
Tiroiditis de Riedel
Paquimeningitis
Dacriocistitis
Pulmón
Hipofisitis
Pseudotumores de:
Órbira
Pulmón
Mama
próstata
Colangitis esclerosante
Sialoadenitis
Linfadenopatía

Riñón

Fibrosis retroperitoneal

Tiroiditis de Riedel

Paquimeningitis

Dacriocistitis

Pulmón

Hipofisitis

Pseudotumores de:
Órbira
Pulmón
Mama
próstata

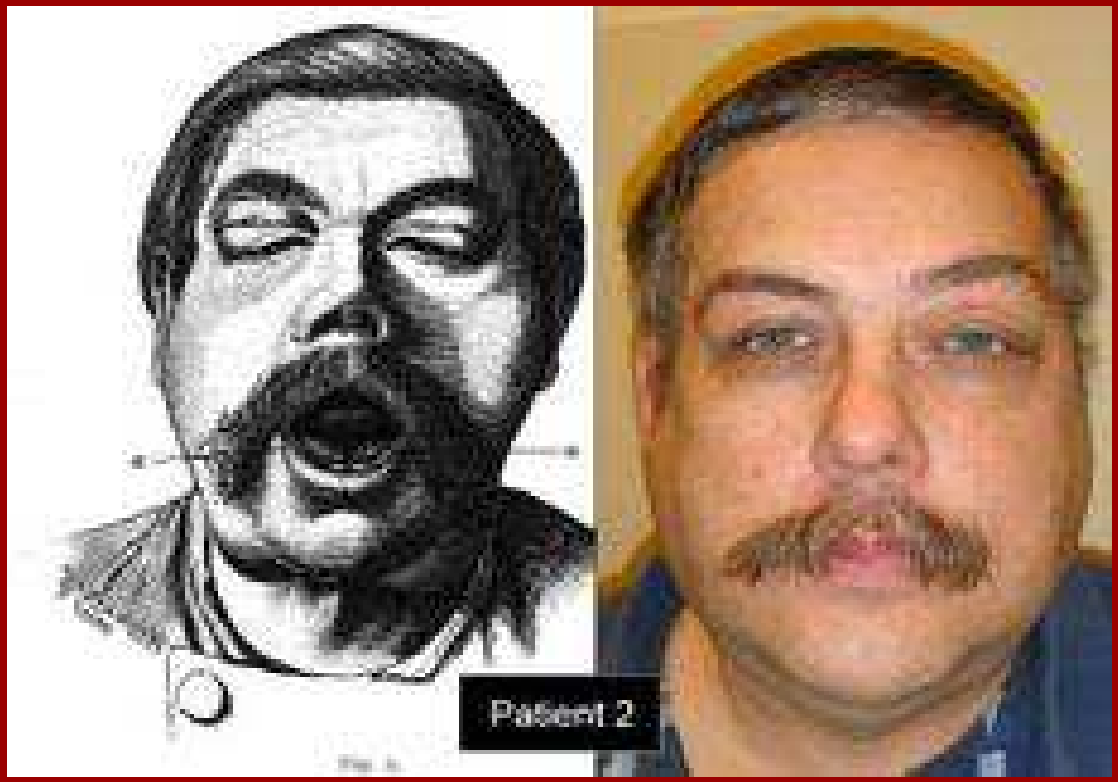
Colangitis esclerosante

Sialoadenitis

Linfadenopatía

Table 3. Preferred nomenclature for individual organ manifestations of IgG4-related disease

Organ system/tissue	Preferred name
Pancreas	Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
Eye	IgG4-related ophthalmic disease is the general term for the periocular manifestations of this disease. There are several subsets, outlined below.
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue (orbital inflammatory pseudotumor)	IgG4-related orbital inflammation (or IgG4-related orbital inflammatory pseudotumor)
Extraocular muscle disease	IgG4-related orbital myositis
Orbit with involvement of multiple anatomic structures	IgG4-related pan-orbital inflammation (includes lacrimal gland disease, extraocular muscle involvement, and other potential intraorbital complications)
Salivary glands (parotid and submandibular glands)	IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
Pachymeninges	IgG4-related pachymeningitis
Hypophysis	IgG4-related hypophysitis
Thyroid (Riedel thyroiditis)	IgG4-related thyroid disease
Aorta	IgG4-related aortitis/periaortitis
Arteries	IgG4-related periarteritis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis
Liver	IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
Lung	IgG4-related lung disease
Pleura	IgG4-related pleuritis
Pericardium	IgG4-related pericarditis
Kidney	IgG4-related kidney disease. The specific renal complications should be termed tubulointerstitial nephritis secondary to IgG4-related disease and membranous glomerulonephritis secondary to IgG4-related disease. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis.
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis



Stone, 2014

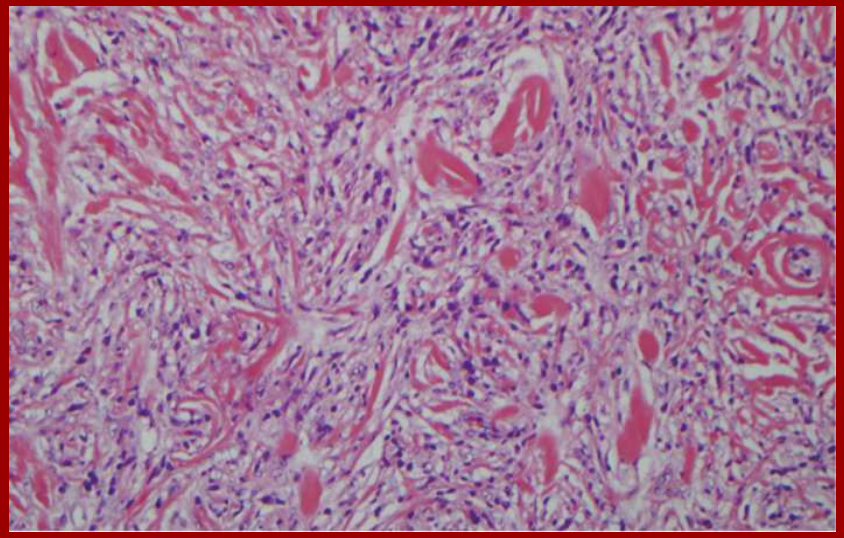
Proceso fibroinflamatorio que se caracteriza por:

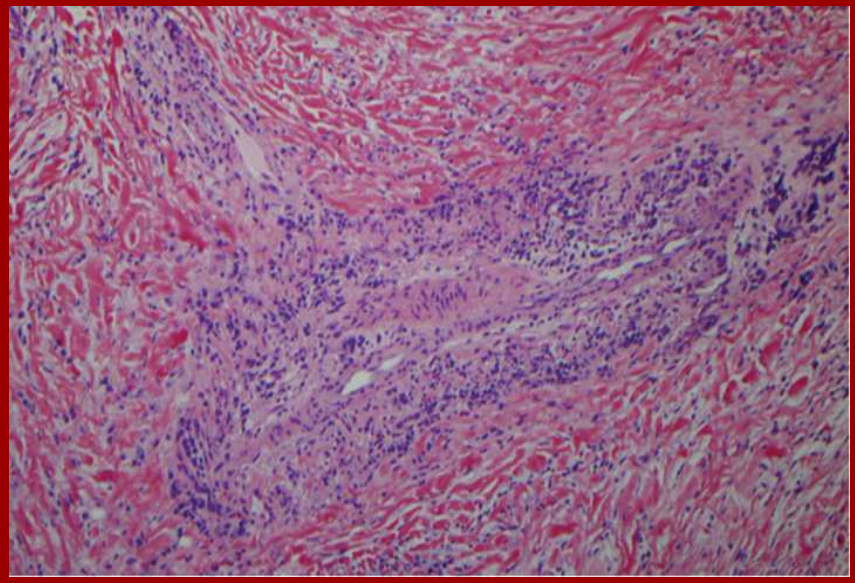
- *infiltrado linfoplasmocitario rico en células plasmáticas IgG4 +*
- *presencia de fibrosis estoriforme*
- *flebitis obliterativa*
- *eosinoflilia*

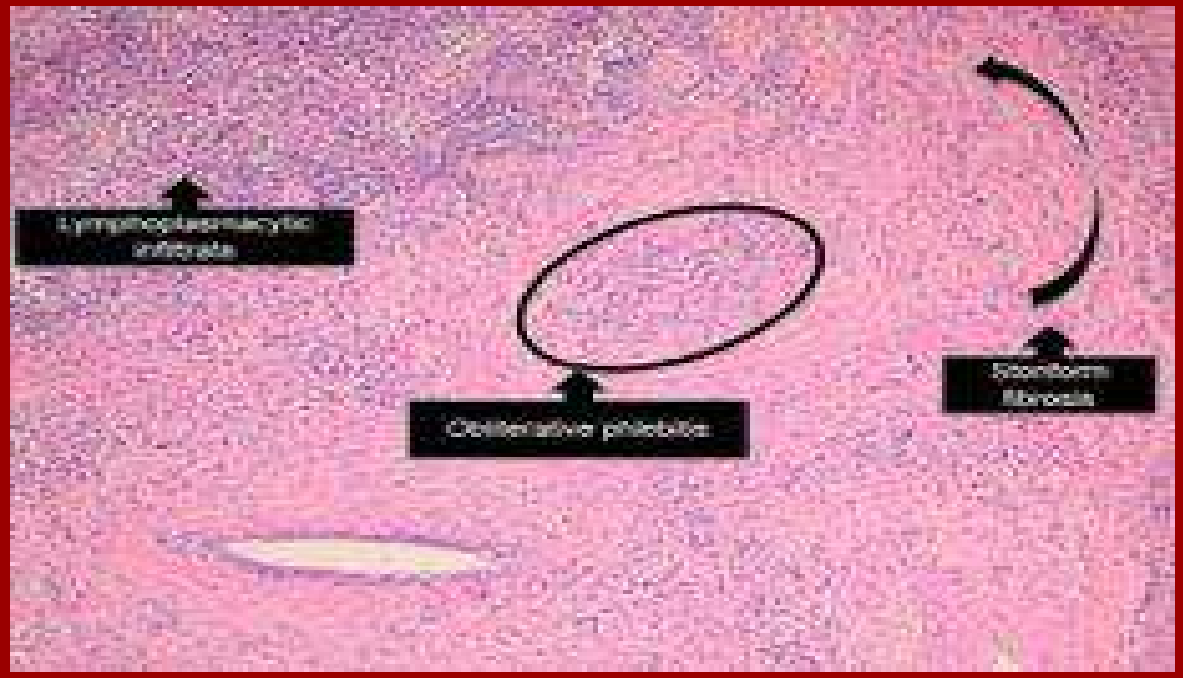
NO GRANULOMAS

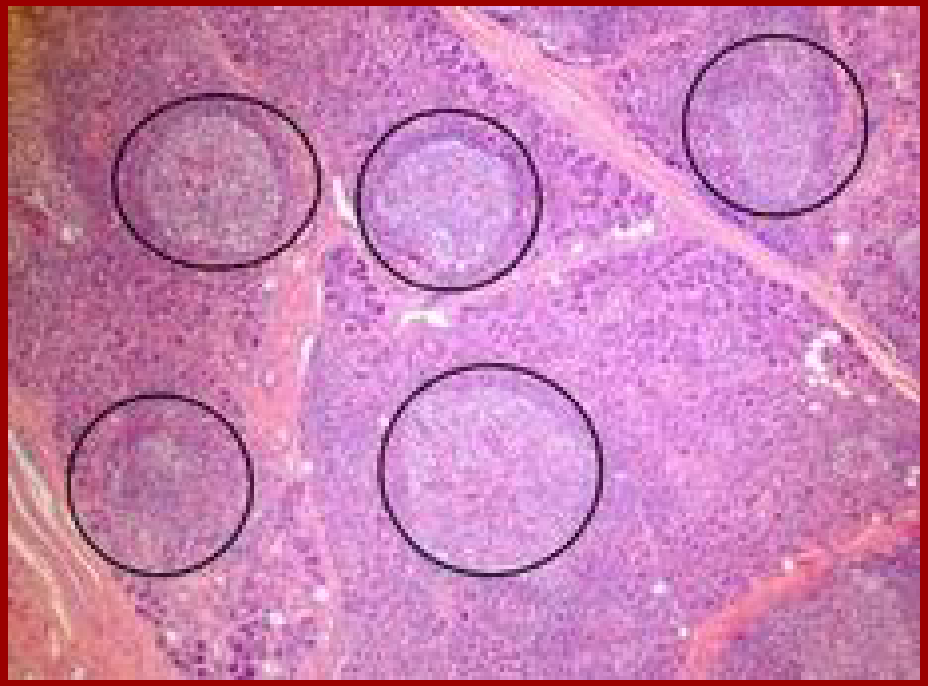
NO NECROSIS

- *pseudotumor inflamatorio*
- *buena respuesta a tratamiento con corticoides*






Lymphoplasmacytic infiltrate
Obliterative phlebitis
Storiform fibrosis



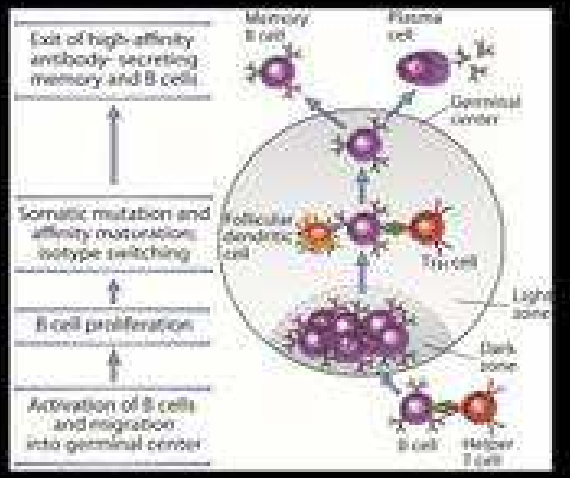
Stone, 2014

Interacción entre células B inmaduras y Thelper

Activación de células B ; migración a centros germinales

- Centro germinal

Típicamente en ganglios linfáticos



Interacción con células dendríticas foliculares y Células Tf

Mutaciones somáticas : switching isotype

Células B de memoria

Plasmablasto

Células plasmática

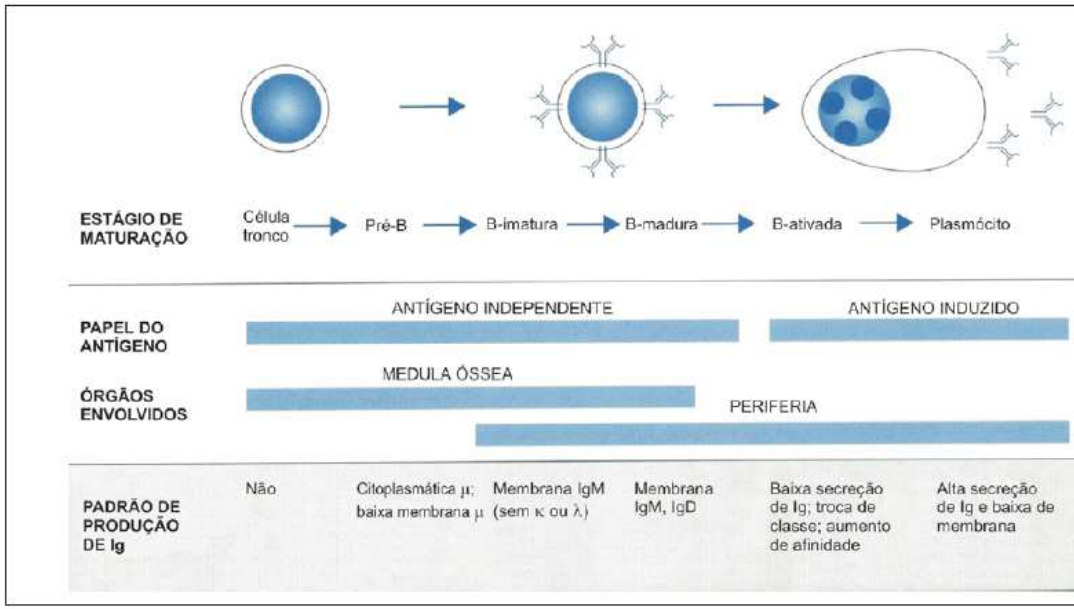
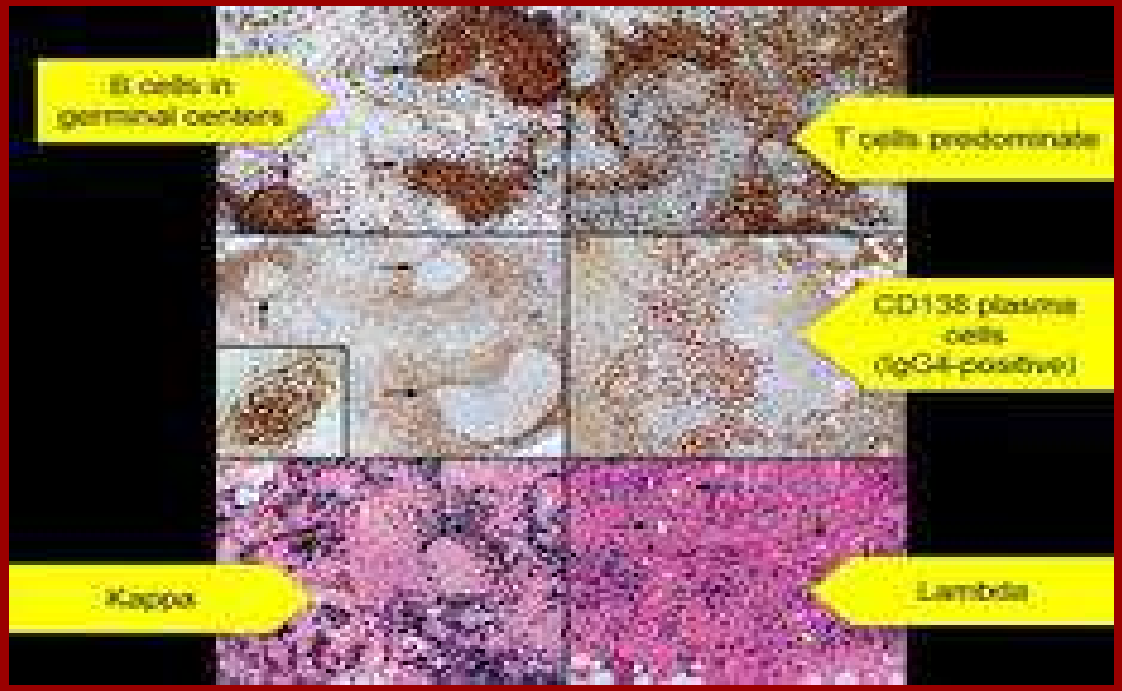
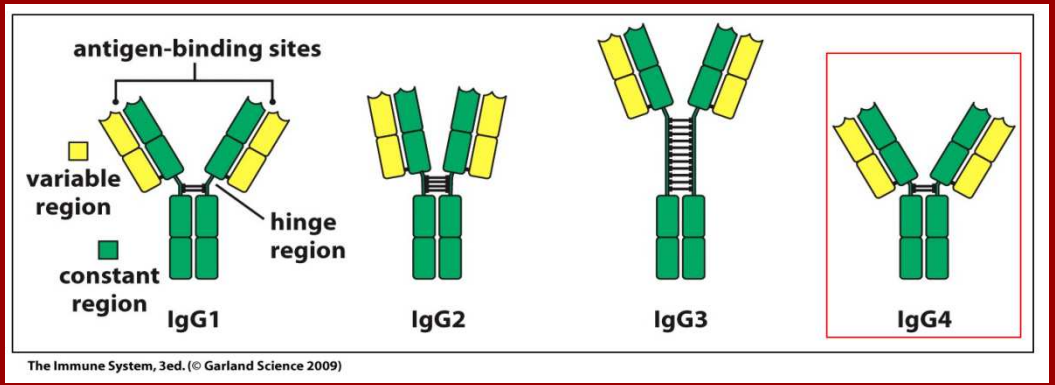


Figura 1. Ontogênese dos plasmócitos

AVANCES RECIENTES EN LA ENFERMEDAD RELACIONADA CON LA IgG4





"Fab arm exchange" o "Half-antibody exchange reaction"

Ac bivalentes monoespecíficos

↓

Puentes disulfuro intracatenarios (Cadenas pesadas unidas por enl. no covalentes*)

↓

Disociación de las cadenas pesadas del anticuerpo ("Half antibodies")

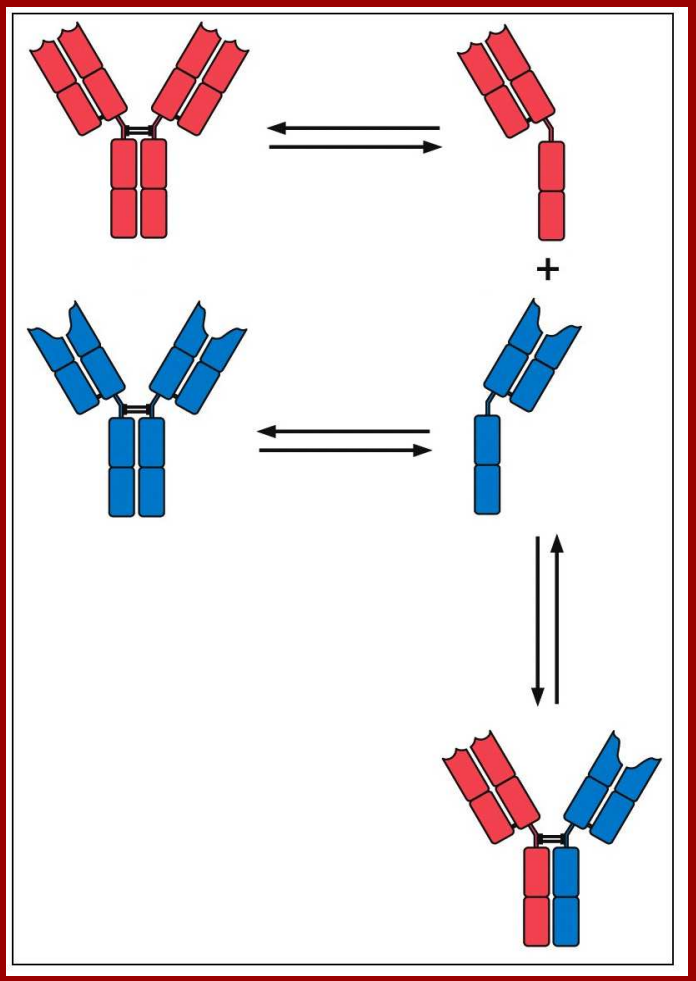
↓

Unión de cadenas pesadas de distintos Ac

↓

Ac monovalentes biespecíficos

Anticuerpos hibridos no pueden formar inmunocomplejos y por tanto no activan el complemento



- Es la subclase de IgG con menor concentración en suero
- Gran variabilidad interindividual: valores de referencia entre 1- 140mg/dL

Función

- Se piensa que interviene en las respuestas crónicas a alérgenos
- No une C1q → No activa la vía clásica del complemento
- Afinidad muy baja por los receptores gamma FcRγI, FcRγII y FcRγIII

Función efectora muy reducida:

- Puede competir por Ag con otras inmunoglobulinas: **posible contexto antiinflamatorio**
- Subclase de elección para algunos mAb terapéuticos en los que es preferible evitar estas funciones o no son necesarias

Ni los niveles séricos de IgG4 ni el recuento de células plasmáticas son suficientes para establecer el diagnóstico

Pacientes con IgG4-RD presentan concentraciones muy elevadas de plasmablastos

MEDULA OSEA

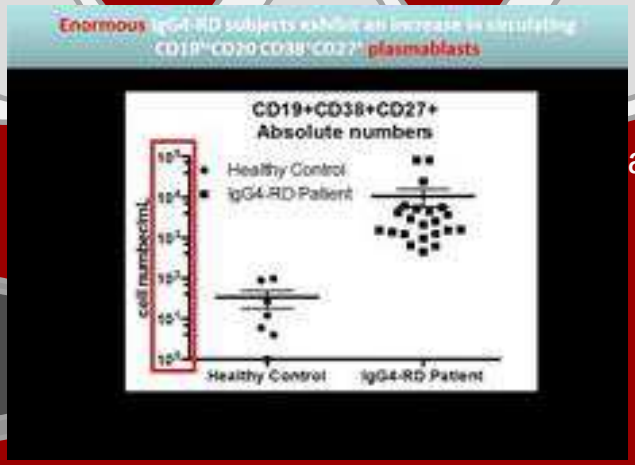
COMPARTIMENTO PERIFERICO

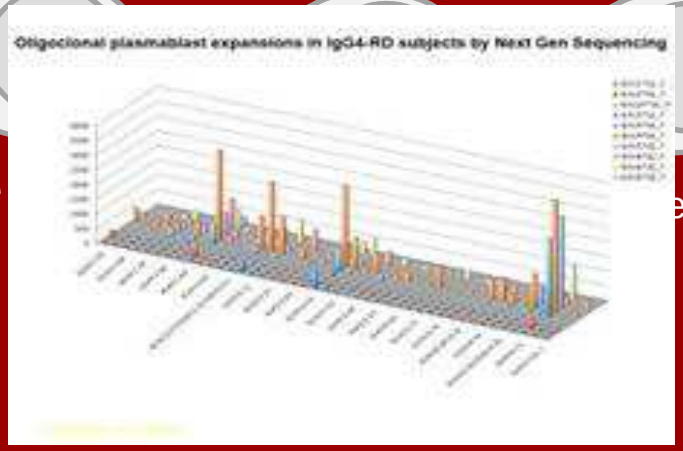
Pro B

adura

Naive

el B

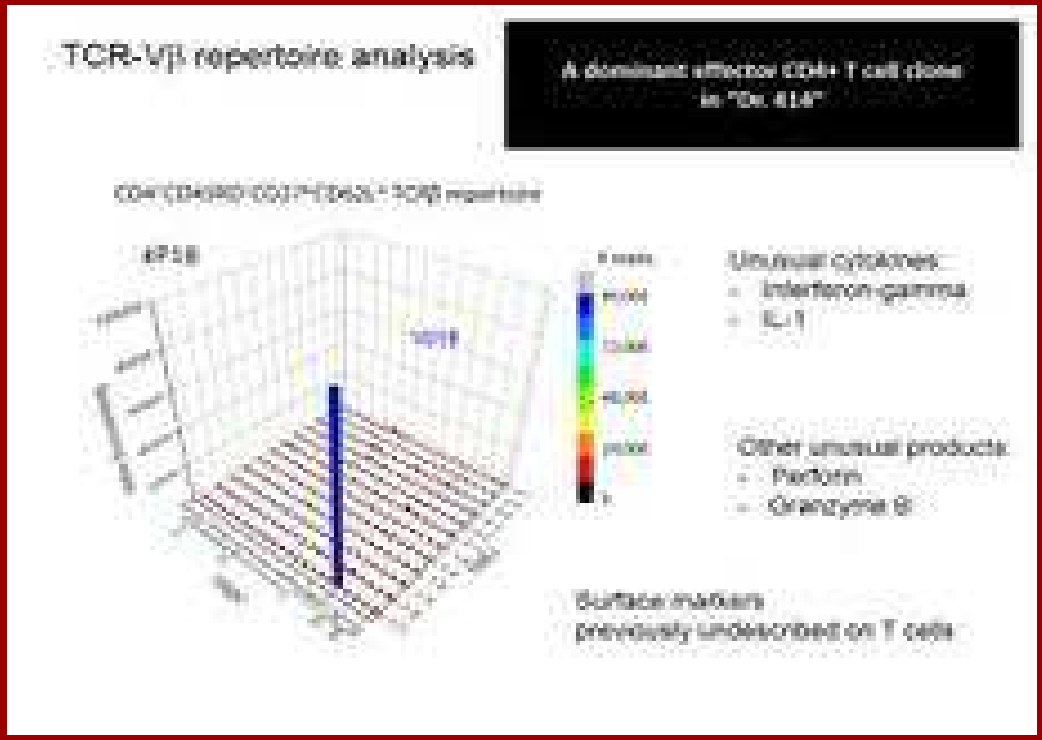




De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG_4-related disease

Hamid Mattoo, PhD,* Vinay S. Mahajan, MBBS, PhD,* Emanuel Della-Torre, MD, Yurie Sekigami, BS, Mollie Carruthers, MD, Zachary S. Wallace, MD, Vikram Deshpande, MD, John H. Stone, MD, MPH, and Shiv Pillai, MBBS, PhD *Boston, Mass*

Expansión clonal de células T TCR-VB



VB19

Marcadores de superficie no descritos previamente:
IFN gamma
IL-1
Perforina
Granzyme B

CD4 killer

¿papel de la IgG4 en esta entidad?

Plasmablastos circulantes han sufrido extensas mutaciones somáticas en:

CENTRO GERMINAL

Interrelación con células T

REGISTRO ESPAÑOL DE ENFERMEDAD RELACIONADA CON LA IgG4

GRUPO DE ENFERMEDADES AUTOINMUNES SISTEMICAS

Characteristic histological features
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform in character
3. Obliterative phlebitis

Cases with ≥ 2 pathology features

Cases with 1 pathology feature

	Numbers of IgG4+ plasma cells (/hpf)		Ref
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	6
Pancreas (surgical specimen)	>50	>50	30,32
Pancreas (biopsy)	>10	>10	56,57
Bile duct (surgical specimen)	>50	>50	49
Bile duct (biopsy)	>10	>10	58,59
Liver (surgical specimen)	>50	>50	49
Liver (biopsy)	>10	>10	12,60
Kidney (surgical specimen)	>30	>30	15
Kidney (biopsy)	>10	>10	61
Aorta	>50	>50	16,51,52
Retroperitoneum	>30	>30	8
Skin	>200	>200	62,63

IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD

Orange boxes = Probable histological features of IgG4-RD

(1) Histologically highly suggestive of IgG4-related disease.
(2) Probable histological features of IgG4-related disease.
(3) Insufficient histopathological evidence of IgG4-related disease.

-Muy sugestiva:

- al menos dos de las características histológicas
- contaje de células IgG4 +
- ratio IgG4/IgG > 40%

- Probable:

- sólo un hallazgo AP

ó

- no cumplen criterios IH

+

- IgG sérica >135 mgr/dl
- otra afectación orgánica (Rx ó AP)

Enfermedad meníngea o cutánea

To describe the clinical presentation and histopathological characteristics of a series of patients diagnosed with IgG4-RD in Spain

15 centros











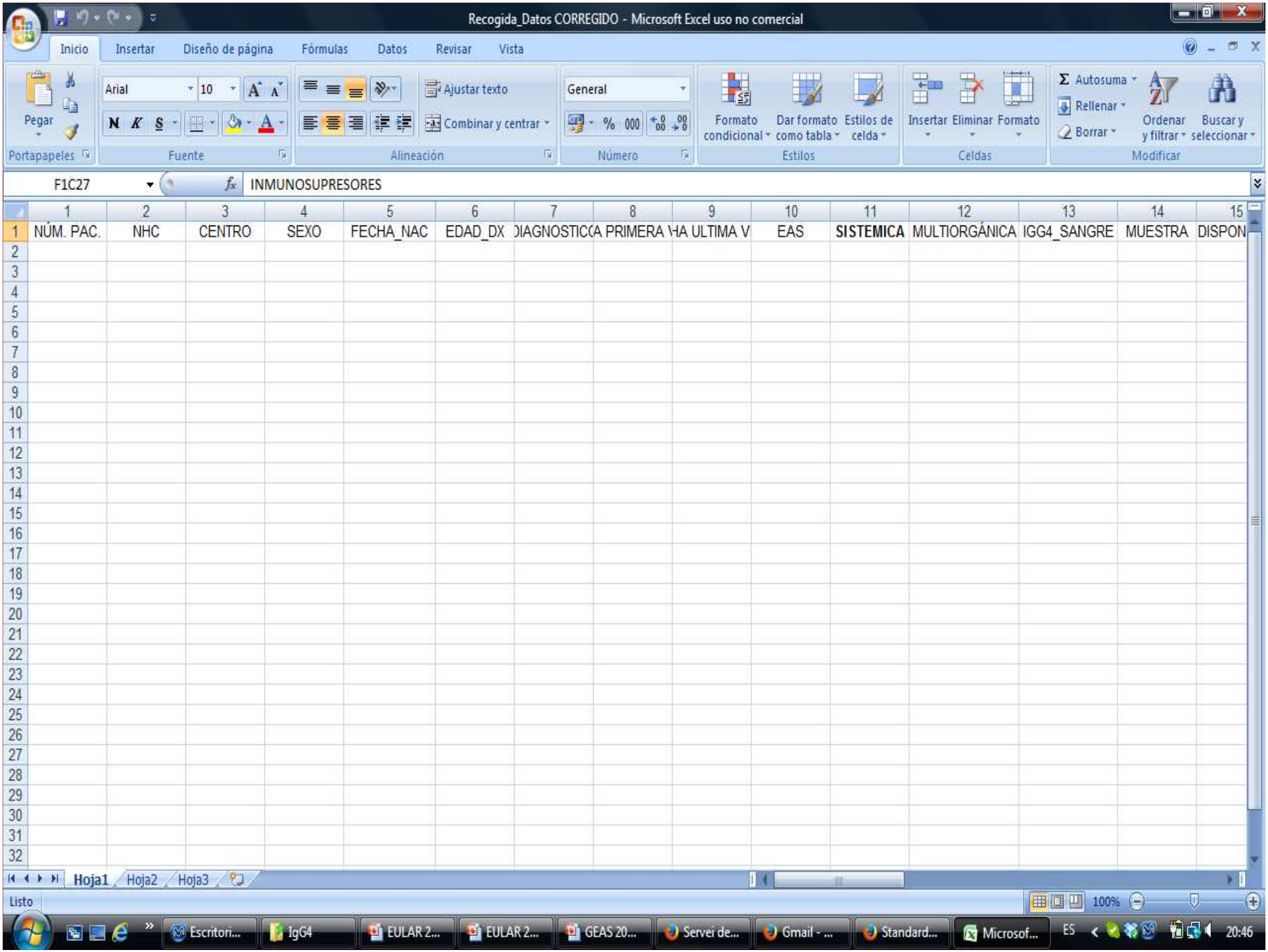



- Hospital La Paz (Madrid) 2 pacientes
- Hospital San Cecilio (Granada) 1 paciente
- Hospital de la Princesa (Madrid) 1 paciente
- Hospital de Manises 1 paciente
- Hospital Gregorio Marañón (Madrid) 9 pacientes
- Hospital Meixoeiro (Vigo) 1 paciente
- Hospital Valle del Nalón (Asturias) 1 paciente
- Hospital Ramón y Cajal (Madrid) 5 pacientes
- Hospital Joan XXIII (Tarragona) 2 pacientes
- Hospital Parc Taulí (Sabadell) 2 pacientes
- Hospital Clínic i Provincial (Barcelona) 2 pacientes
- Hospital Río Hortega (Valladolid) 1 paciente
- Hospital Vall d'Hebró (Barcelona) 19 pacientes

Total: 47 pacientes

Variables del Registro:

- Demográficas
- Clínicas
- Analíticas
- Anatomo-patológicas
- Radiológicas (PET-TAC)
- Tratamiento
- Evolutivas


Recogida_Datos CORREGIDO - Microsoft Excel uso no comercial
Inicio
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Modificar
F1C27
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1 NÚM. PAC. NHC CENTRO SEXO FECHA_NAC EDAD_DX DIAGNOSTICO A PRIMERA VHA ULTIMA V EAS SISTEMICA MULTIORGÁNICA IGG4_SANGRE MUESTRA DISPON
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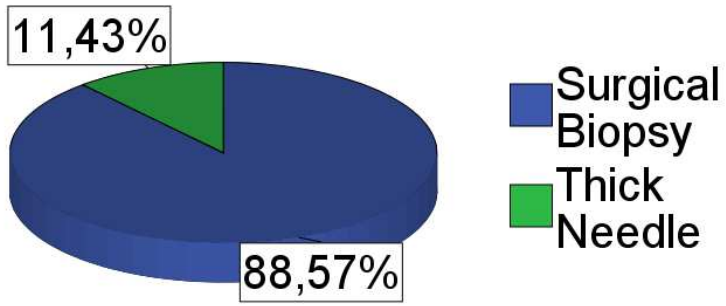
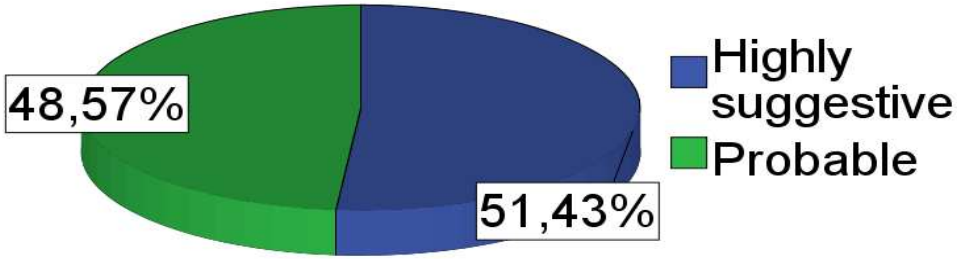
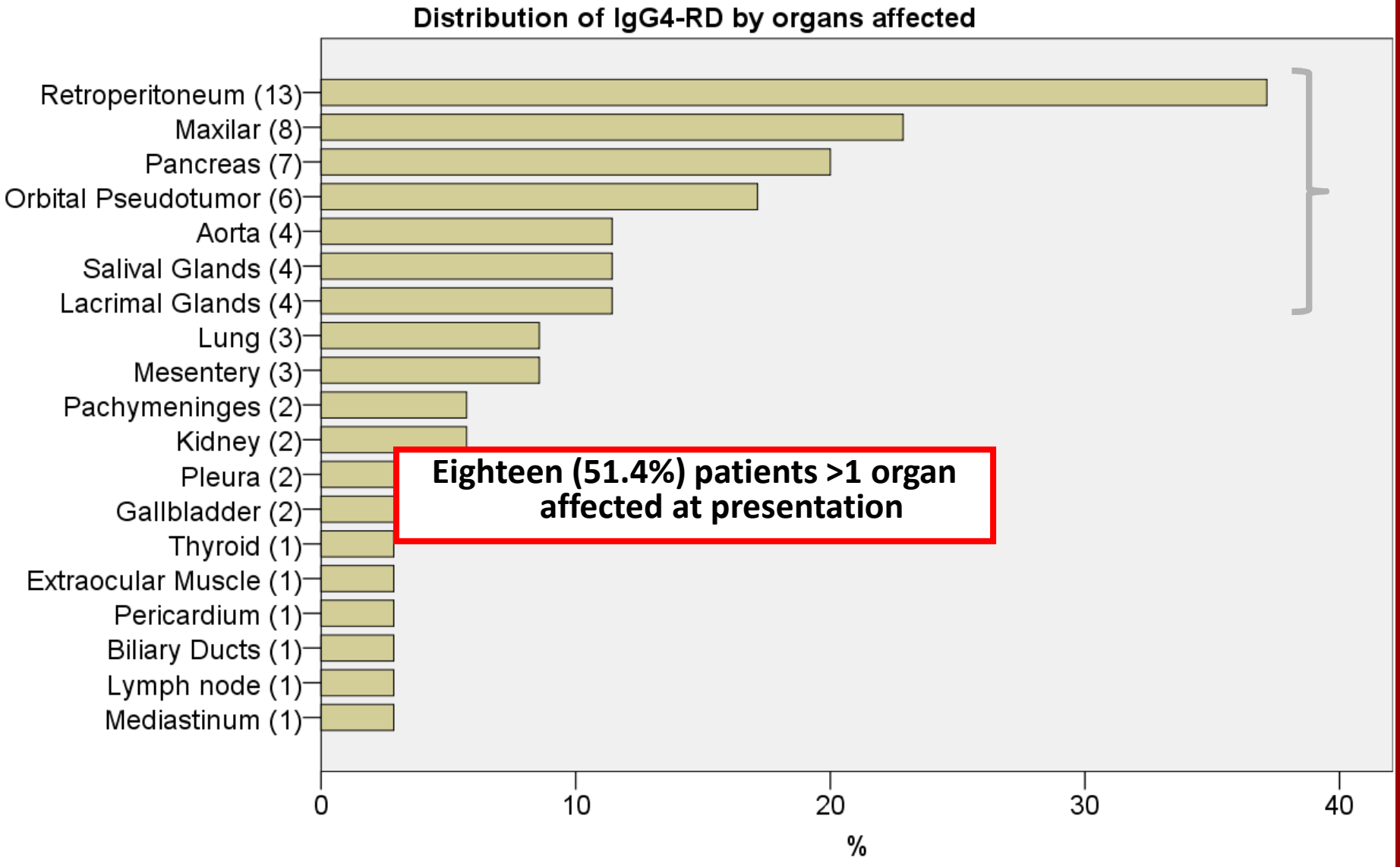
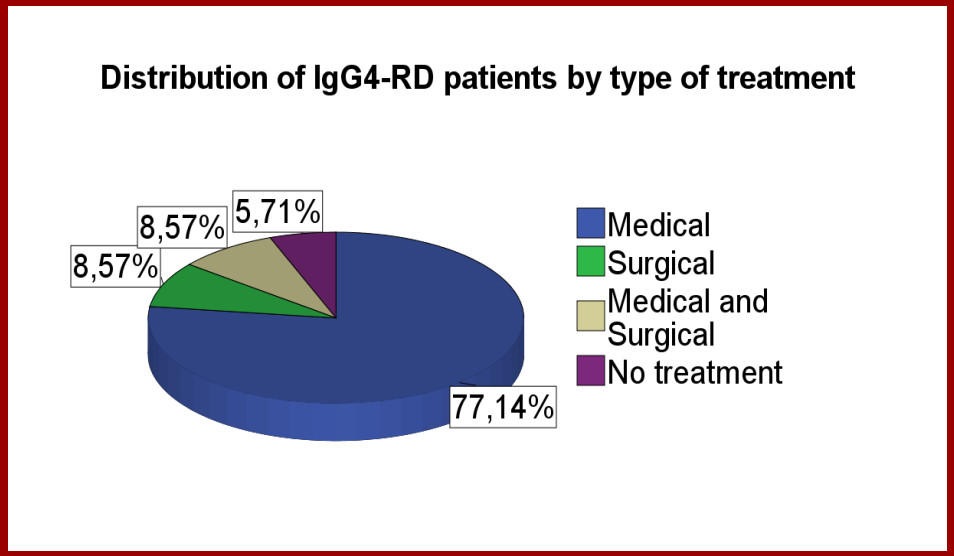
Pathology specimen source

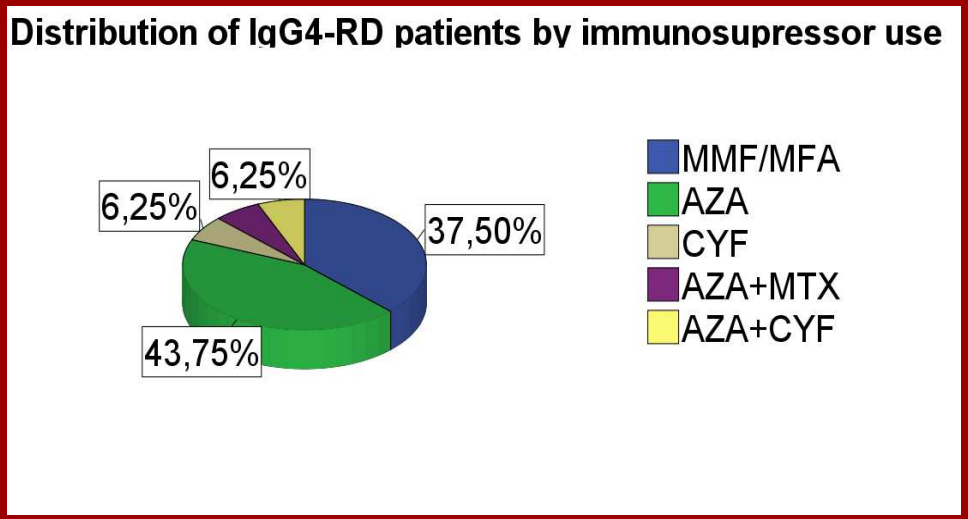


Pathological diagnostic cathegories




Distribution of IgG4-RD by organs affected
Retroperitoneum (13)
Maxilar (8)
Pancreas (7)
Orbital Pseudotumor (6)
Aorta (4)
Salival Glands (4)
Lacrimal Glands (4)
Lung (3)
Mesentery (3)
Pachymeninges (2)
Kidney (2)
Pleura (2)
Gallbladder (2)
Thyroid (1)
Extraocular Muscle (1)
Pericardium (1)
Biliary Ducts (1)
Lymph node (1)
Mediastinum (1)
0
10
20
30
40
%
Eighteen (51.4%) patients >1 organ affected at presentation





Corticoides:

- Administrados en 30 (85.7%) pacientes
- Dosis Media máxima: 60 mg/día (IQR 30 mg/day)
- Tiempo de dosis máxima media: 1 mes (IQR 0.25 months)
- Tiempo de descenso dosis: 7.5 meses (IQR 8.5 months)
- siete pacientes dosis de mantenimiento 5 mg/día (IQR 5mg/day)

Immunosupresores:

- En casos corticoideo-resistentes
- 16 (45.7%)

Biológicos:

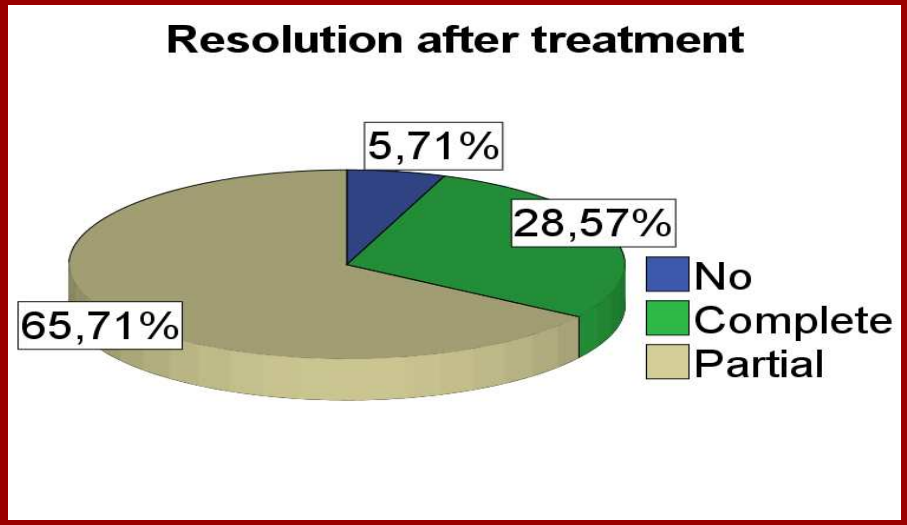
- En corticoides e inmunosupresores resistentes
- Rituximab: 2 (5.7%) patients

Cirugía:

- Cirugía radical con o sin tratamiento médico

No treatment:

- dos pacientes (afectación retroperitoneal mínima y dg reciente de afectación pancreática)



Evolution:

•No statistically significant differences were found between systemic and localized IgG4-RD regarding treatments

•Median follow up: 22.01 months (IQR 35.79 months)

•Corticosteroids alone were more frequently given in the complete response group

•No patients were refractory to all treatments

•Recurrences: 11 (33.3%)

Malignancies:

•Two (6.1%) patients presented a monoclonal gammopathy of unknown significance

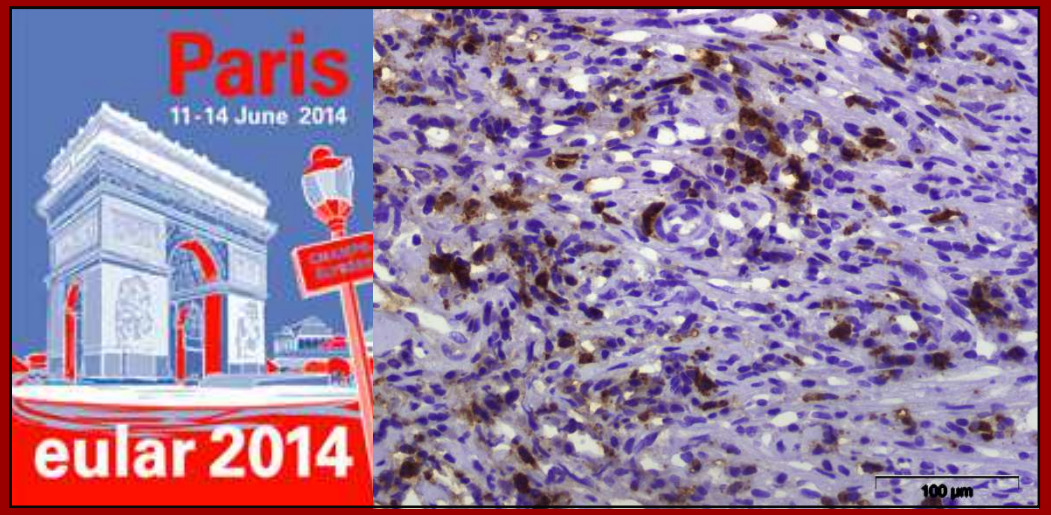
•One (3%) patient developed a prostate cancer

Survival:

•One subject died in a car accident

•No patient dead due to IgG4-RD

IGG4-RELATED DISEASE SPANISH REGISTER:



CLINICAL AND EPIDEMIOLOGICAL FEATURES

Andreu Fernández-Codina

Fernando Martínez-Valle

Autoimmune Systemic Diseases Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain

THU0365

IGG4-RELATED DISEASE SPANISH REGISTER: DESCRIPTION OF TREATMENT AND EVOLUTION

Andreu Fernández-Codina[1], Fernando Martínez-Valle[1] on behalf of Roser Solans, Cristina López, Blanca Pinilla, Mariona Cid, Tito Eduardo Junco, Ángel Robles, Juan José Sirvent, Xavier Ustrell, José Luis Calleja; IgG4-Reladed Disease Spanish Register (REIGG4-GEAS)

[1]Systemic Autoimmune Diseases Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain

OBJETIVES:

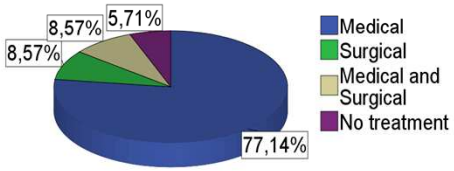
To describe the therapeutical experience and the evolution of a series of patients diagnosed with IgG4-related disease (IgG4-RD) in Spain.

METHODS:

- Retrospective multicentric study
- Patients were enrolled from 11 different centers in Spain
- Inclusion period ranged from October 2013 to January 2014
- Patients included met one of the following international agreement criteria by *Deshpande* et al.: histologically highly suggestive or probable IgG4-RD. Patients with insufficient histopathological evidence of IgG4-RD were excluded.

RESULTS (I):

Distribution of IgG4-RD patients by type of treatment



Brief epidemiological characterization:
- Patients included: 35
- Male: 27 (77.1%)
- Median age at diagnosis: 55 (IQR 29 years)
- Systemic disease (More than one organ affected): 18 (51.4%)

Corticosteroids:
- Administered in 30 (85.7%) patients
- Median maximum dose: 60 mg/day (IQR 30 mg/day)
- Median maximum dose time: 1 month (IQR 0.25 months)
- Dose tapering time: 7.5 months (IQR 8.5 months)
- Seven patients kept a maintenance dose of 5 mg/day (IQR 5mg/day)

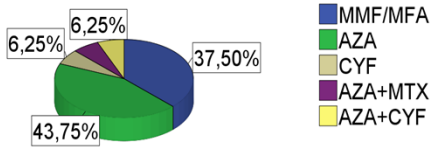
Immunosupressors:
- In corticosteroid resistant cases
- 16 (45.7%)

Biologics:
- In corticosteroid and immunosupressor resistant cases
- Rituximab: 2 (5.7%) patients

Surgery:
- Radical surgery with or without medical treatment

No treatment:
- One patient with minimal retroperitoneal involvement and another patient with pancreatic involvement and recent diagnosis did not receive any treatment

Distribution of IgG4-RD patients by immunosupressor use

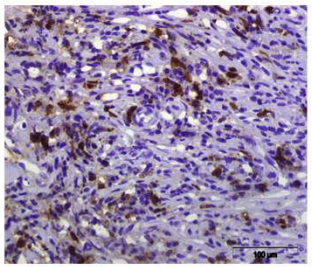


RESULTS (II):

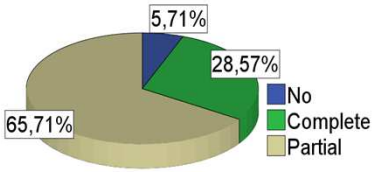
Evolution:
- No statistically significant differences were found between systemic and localized IgG4-RD regarding treatments
- Median follow up: 22.01 months (IQR 35.79 months)
- Resolution after treatment:
  - Complete (11): complete regression of the fibrotic mass/masses and systemic sympthoms
  - Partial (23): <50% of regression of the mass/masses and cease of the systemic sympthoms
  - None: This category includes both non treated patients.
- Corticosteroids alone were more frequently given in the complete response group
- No patients were refractory to all treatments
- Recurrences: 11 (33.3%)

Malignancies:
- Two (6.1%) patients presented a monoclonal gammopathy of unknown significance
- One (3%) patient developed a prostate cancer

Survival:
- One subject died in a car accident
- No patient dead due to IgG4-RD



Resolution after treatment



CONCLUSIONS:

- IgG4- RD is a rare entity in Spain
- Corticosteroids, initially at high doses, followed by a slow dose descent, with or without immunosupressors were the mainstay treatment
- Rituximab was the only biological drug used. Surgery was needed occasionally
- Partial disappearance of the fibrotic component with resolution of systemic symptoms was the most common outcome after treatment
- No deceases were directly attributed to IgG4-RD
- Standardized treatment guidelines could optimize healthcare in IgG4-RD patients
- More collaborative studies are required in order to assess the treatment response and the evolution of IgG4-RD

Correspondence to andreu.fernandez@vhebron.net

GEAS

Grupo de Enfermedades Autoinmunes Sistémicas

¿FUTURO?

-Incluir nuevos pacientes

- investigación

- Seroteca

- publicaciones

REGISTRO ESPAÑOL DE ENFERMEDAD RELACIONADA CON LA IgG4

ferranmartinezvalle@gmail.com
andreufernandez@hotmail.com