SEAP-IAP
[Sociedad Española de Anatomía Patológica]
[International Academy of Pathology]

La Fe
Hospital Universitari i Politècnic

REUNIÓN ONLINE DE LAS TERRRITORIALES VALENCIANA Y CANARIA DE LA SEAP

PRIMERA PARTE
AVANCES EN LA ENFERMEDAD DE CASTLEMAN

Dayana Pita, Laura Galeano, Liliana Castillo, Gema Moreno, Mónica Bauza, Nuria Rausell, Francisco Vera-Sempere

Jueves 26 de Noviembre, 2020

ORL

Bultos dolorosos en ambas parótidas

E. FISICO

G. Parótidas y submaxilar derecha dolorosas

E. FISICO

Adenopatías cervicales grandes e induradas

CONCLUSIÓN

Sospecha de s. linfoproliferativo con afectación parotídea bilateral

TAC

G. cervicales, supraclavicular, axilares, mediastínicos y paratraqueales

TAC

Aumento de tamaño bilateral, difuso y homogéneo de g. parótidas

Correlacionar con PET-TAC

PAAF y biopsia de adenopatía cervical

PAAF: hiperplasia linfoide

BQX G. CERVICAL: muestra escasa, valoración limitada

EXERESIS DE GANGLIO CERVICAL

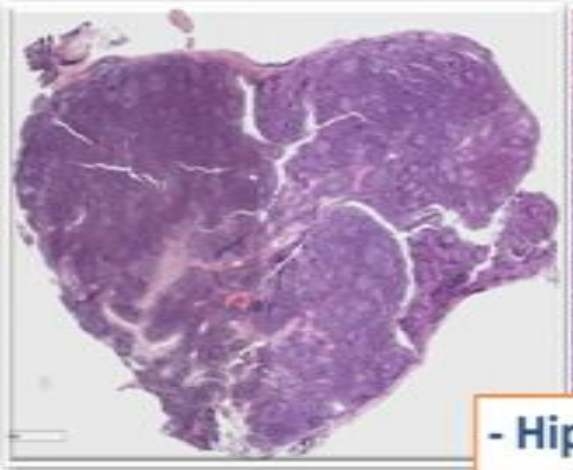
Mujer

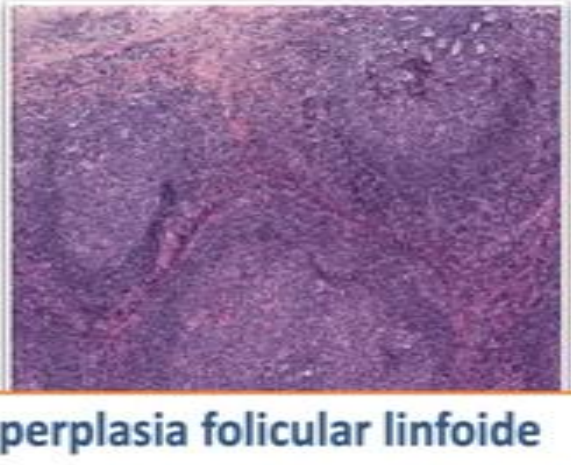
77 años

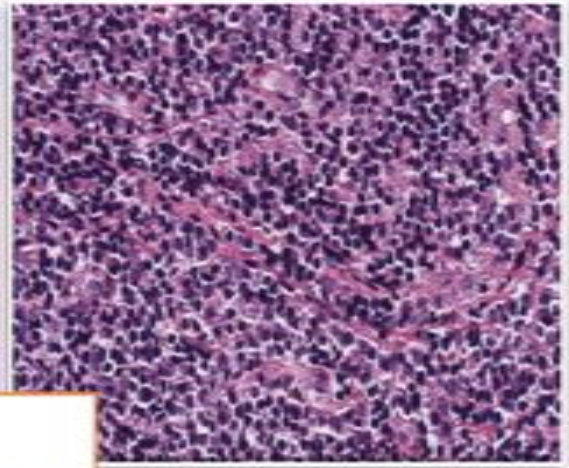
Originaria de Bolivia

HTA

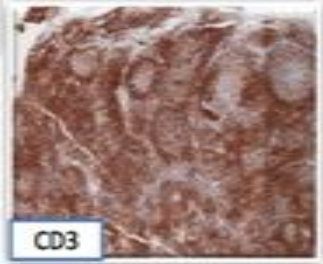
Ex fumadora

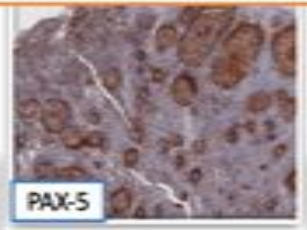


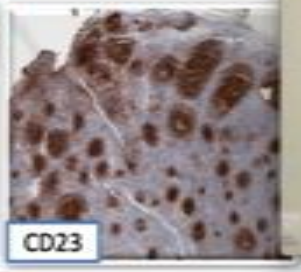




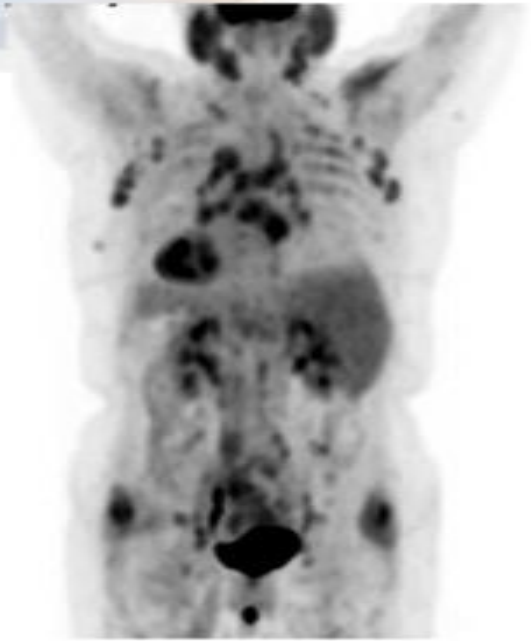
- Hiperplasia folicular linfoide
- Ausencia de s. linfoproliferativo







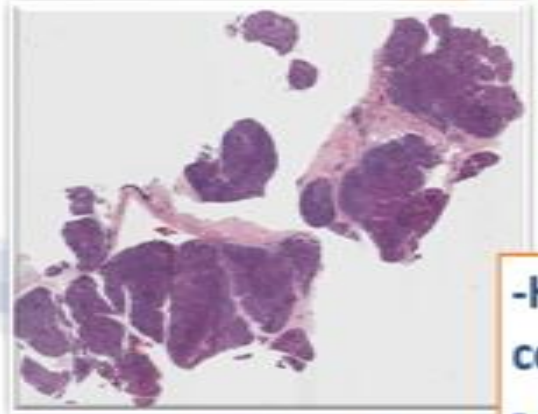
PET-TAC

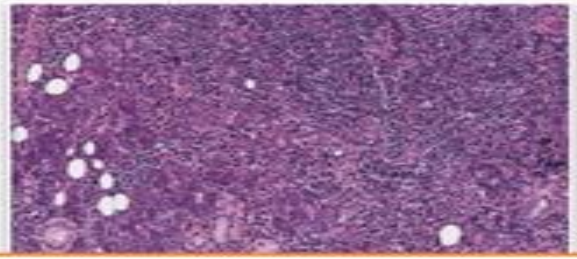


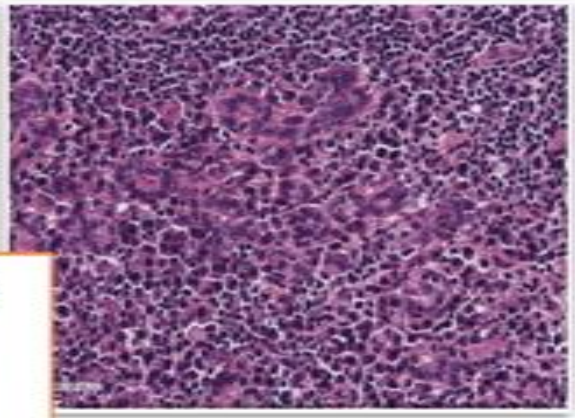
Hipercaptación en:
- Adenopatías supra e infra diafragmáticas.
- Glándulas salivales mayores (carácter infiltrativo vs inflamatorio).
- Tejido de partes blandas lumbar y presacro (sugiere fibrosis retroperitoneal inflamatoria).

Primera sospecha diagnóstica: síndrome linfoproliferativo vs proceso inflamatorio.

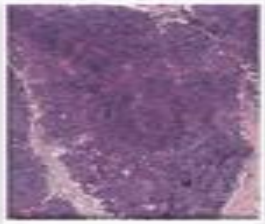
BIOPSIA DE GLÁNDULA PARÓTIDA

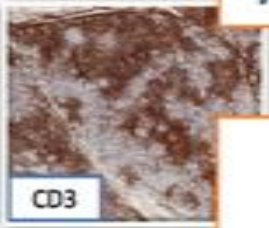




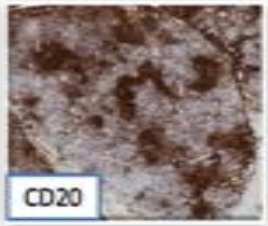


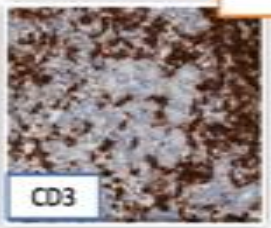
-Hiperplasia folicular linfoide con plasmocitosis policlonal
- Ausencia de linfoma





Reordenamiento de IgH
NEGATIVO





Revaloración por medicina interna

Infecciosos

Autoinmunes

INMUNOGLOBULINAS			
# Ig A		134 mg/dL	70 - 400
# Ig M		41 mg/dL	40-230
# Ig G	↑	4.670 mg/dL	700 - 1.600
INMUNOFIJACION			
INMUNOFIJACIÓN DE SUERO/C.MONOCLONAL		Ausencia de banda monoclonal.	
AUTOINMUNIDAD			
Ac. Anti-Nucleares (ANA/ENAS) (Screening ElIA)		NEGATIVO Incluye los autoanticuerpos: DNAdc, Sm, Rib-P, PCNA, U1-RNP, SS-A/Ro, SS-B/La, Scl-70, CENP-B, Fibrilarina, RNA Pol III, Jo-1, Mi-2 y PM-Scl.	

INMUNOGLOBULINAS			
# Ig A		93 mg/dL	70 - 400
# Ig M	↓	32 mg/dL	40-230
# Ig G	↑	4.758 mg/dL	700 - 1.600
SUBCLASE Ig G1	↑	1.320 mg/dL	490 - 1.140
SUBCLASE Ig G2		356 mg/dL	150 - 640
SUBCLASE Ig G3		42 mg/dL	20 - 110
SUBCLASE Ig G4	↑	5.140,0 mg/dL	8 - 140
# INMUNOGLOBULINA E	↑	876,0 kU/L	0,0 - 100,0

Revaloración por medicina interna

Infecciosos

Autoinmunes

INMUNOGLOBULINAS			
# Ig A		134 mg/dL	70 - 400
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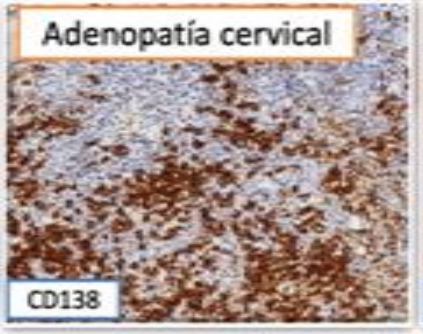
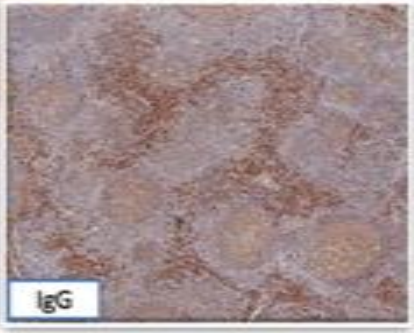
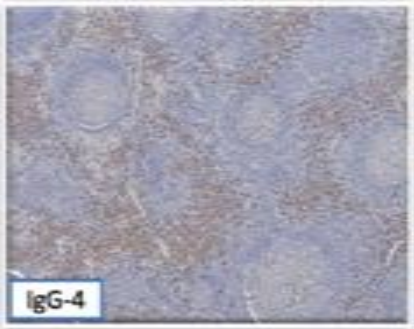
# Ig G	↑	4.670 mg/dL	700 - 1.600
INMUNOFIJACION			
INMUNOFIJACIÓN DE SUERO/C.MONOCL			
AUTOINMUNIDAD			
Ac. Anti-Nucleares (Screening ElIA)			

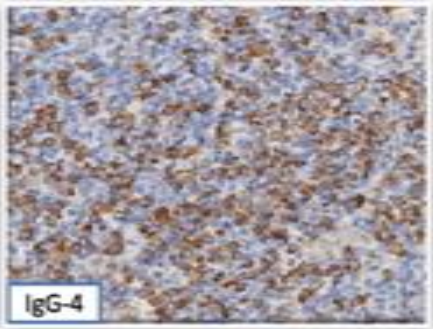
Sospecha de enfermedad relacionada con IgG4

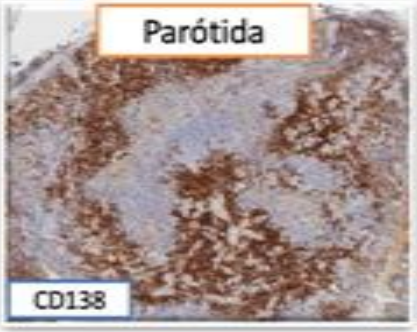
INMUNOGLOBULINAS			
# Ig A		93 mg/dL	70 - 400
# Ig M	↓	32 mg/dL	40-230
# Ig G	↑	4.758 mg/dL	700 - 1.600
SUBCLASE Ig G1	↑	1.320 mg/dL	490 - 1.140
SUBCLASE Ig G2		336 mg/dL	150 - 640
SUBCLASE Ig G3		42 mg/dL	20 - 110
SUBCLASE Ig G4	↑	5.140,0 mg/dL	8 - 140
# INMUNOGLOBULINA E	↑	876,0 KUA/l	0,0 - 100,0

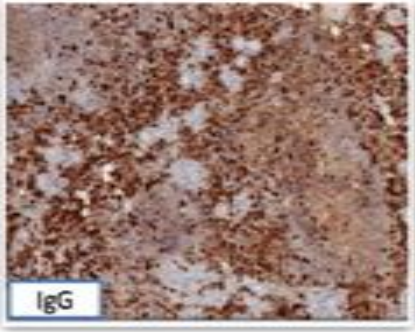


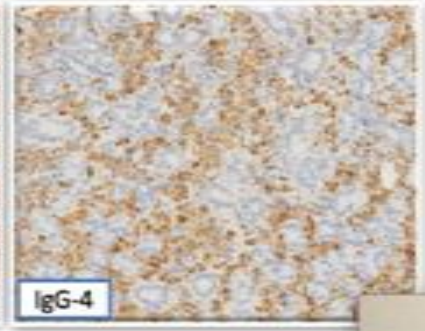






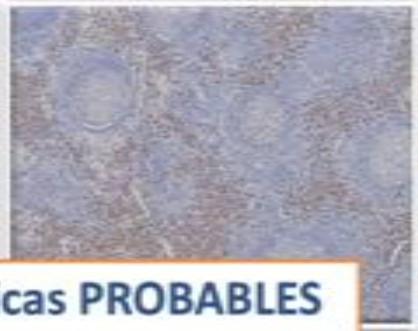


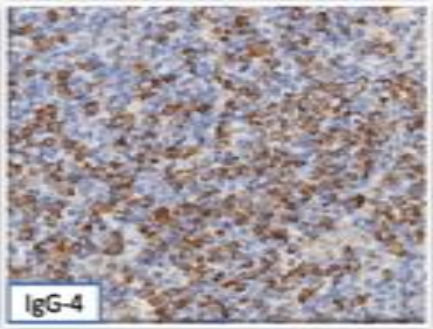




Hiperplasia folicular linfoplasmocitoide, ratio IgG4+/IgG+ >40% y >100 células IgG4+ por campo de gran aumento.

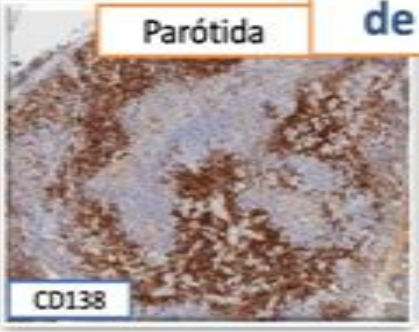
Adenopatía cervical

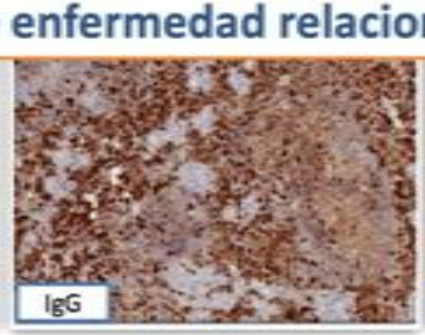




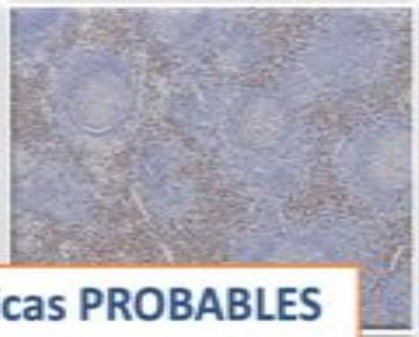
Características histológicas PROBABLES de enfermedad relacionada con IgG4.

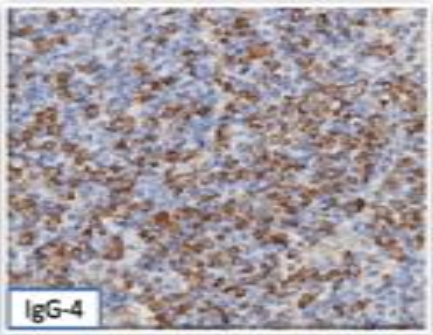
Parótida





Hiperplasia folicular linfoplasmocitoide, ratio IgG4+/IgG+ >40% y >100 células IgG4+ por campo de gran aumento.





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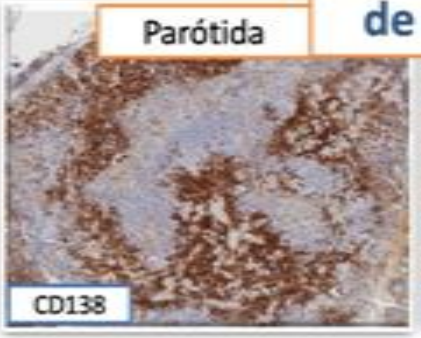

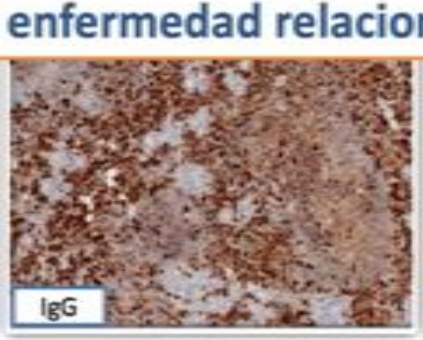

Hiperplasia folicular linfoplasmocitoide, ratio IgG4+/IgG+ >40% y >100 células IgG4+ por campo de gran aumento.

ENFERMEDAD RELACIONADA CON IgG4

Enfermedad sistémica poco común.

Lesiones esclerosantes tipo masa en casi cualquier lugar anatómico

Apariencia histopatológica característica según el órgano + c. plasmáticas IgG4+, con o sin niveles séricos de IgG4 elevados

1. Infiltrado linfoplasmocitario denso
2. Fibrosis dispuesta así sea focalmente en patrón estoriforme
3. Flebitis obliterativa

Consensus statement on the pathology of IgG4-related disease

Vikram Deshpande[1,25], Yoh Zen[2,25], John KC Chan[3], Eunhee E Yi[4], Yasuharu Sato[5], Tadashi Yoshino[6], Günter Klöppel[7], J Godfrey Heathcote[8], Arezou Khosroshahi[9], Judith A Ferry[1], Rob C Aalberse[10], Donald B Bloch[11], William R Brugge[12], Adrian C Bateman[13], Mollie N Carruthers[14], Suresh T Chari[15], Wah Cheuk[3], Lynn D'Cruz[16], Carlos Fernandez-Del Castillo[17], David G Forcione[18], Daniel L Hamilos[19], Terumi Kamisawa[20], Satomi Kasashima[21], Shigeyuki Kawa[22], Mitsuhiro Kawano[23], Gregory Y Lauwers[1], Yasufumi Masaki[24], Yasuni Nakanuma[25], Kenji Notohara[26], Kazuichi Okazaki[27], Ji Kon Ryu[28], Takako Saeki[29], Dushyant V Sahani[30], Thomas C Smyrk[31], James R Stone[1], Masayuki Takahira[32], George J Webster[33], Motohisa Yamamoto[34], Giuseppe Zamboni[35], Hisanori Umehara[36] and John H Stone[4].

Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012 Sep;25(9):1181-92. doi: 10.1038/modpathol.2012.72. Epub 2012 May 18. PMID: 22596100.

Table 1 Histopathology of IgG4-related disease: variability of findings in certain organs

	Inflammation	*Fibrosis*	*Phlebitis*	*Others*
Lacrimal gland	No unique features	Typical storiform fibrosis is relatively uncommon. More often collagenous fibrosis	Sometimes lacks obliterative phlebitis	
Salivary gland	Often associated with conspicuous lymphoid follicle formation	Storiform fibrosis is rare in parotid and minor salivary glands	Sometimes lacks obliterative phlebitis	
Lymph node	No unique features	Fibrosis is only seen in inflammatory pseudotumor-like lesions	Most often lacks obliterative phlebitis	Five histological patterns are recognized: (1) multicentric Castleman's disease-like, (2) follicular hyperplasia, (3) interfollicular expansion, (4) progressive transformation of germinal center, and (5) nodal inflammatory pseudotumor-like. The specificity of these histologic changes in the absence of other evidence of IgG4-RD remains controversial
Lung	Small aggregates of neutrophils may be present in alveolar spaces or within the inflammatory infiltrates	Sometimes lacks storiform fibrosis, particularly in non-solid lesions (eg, interstitial pneumonia)	No unique features	Obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions
Kidney	No unique features	No unique features	Obliterative phlebitis is less common particularly in needle biopsies	

Table 1 Histopathology of IgG4-related disease: variability of findings in certain organs

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			No unique features	Obliterative arteritis is often seen in pulmonary manifestations, particularly solid lesions
			Obliterative phlebitis is less common particularly in needle biopsies	

1. Tipo enf. Castleman multicéntrica

2. Hiperplasia folicular

3. Expansión interfolicular

4. Tipo transformación progresiva de centros germinales

5. Tipo seudotumor inflamatorio

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

TÉRMINOS DIAGNÓSTICOS

Histología altamente sugestiva	Por lo menos 2/3 características histológicas + contaje IgG4 (según el órgano)
Histología probable	Parcial espectro histológico o el perfil IHQ. (Típicamente infiltrado linfoplasmocitario con contaje IgG4+)
Histología insuficiente	No cumple criterios

Table 1. Pathologic differential diagnosis of IgG4-RD

Infections
Bacterial
Mycobacterial
Viral
Spirochetal – e.g., syphilis
Infections involving specific sites:
Aortitis
Otitis media/mastoiditis
Tumors
Inflammatory myofibroblastic tumor
Inflammatory infiltrate in background of tumors
Lymphoproliferative disorders
MALT lymphoma with plasmacytic differentiation
Plasma cell neoplasia
Eosinophilic disorders
Eosinophilic angiocentric fibrosis
Kimura disease
Angiolymphoid hyperplasia with eosinophilia
Inflammatory/Autoimmune disorders
Inflammatory pseudotumor
Systemic disease
Multicentric Castleman disease
Rosai–Dorfman disease
Sarcoidosis
ANCA-associated vasculitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Pancreatobiliary tract
Primary sclerosing cholangitis
Type 2 AIP
Follicular cholangitis
Orbit/Salivary glands
Sjogren syndrome
Chronic sialadenitis, not otherwise specified

APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

REVIEW ARTICLE

IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach

JACOB R. BLEDSOE,[1] EMANUEL DELLA-TORRE,[2,3] LUCREZIA ROVATI[2,3] and VIKRAM DESHPANDE[4]

[1]Department of Pathology, UMass Memorial Medical Center, University of Massachusetts, Worcester, MA, USA; [2]Unit of Immunology, Rheumatology, Allergy, and Rare Diseases (UniRAR), Università Vita-Salute San Raffaele – San Raffaele Scientific Institute, Milan, Italy; [3]Ragon Institute of MGH, MIT, and Harvard University, Cambridge, MA; and [4]The James Homer Wright Pathology Laboratories of the Massachusetts General Hospital, Boston, MA, USA

Bledsoe JR, Della-Torre E, Rovati L, Deshpande V. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. APMIS. 2018 Jun;126(6):459-476. doi: 10.1111/apm.12845. PMID: 29924455.

Clínico	Serológico	Histopatología	Calidad del Dx
Compromiso de órgano: Disfunción, edema localizado o difuso	IgG4 sérica > 135 mg/dl	IgG4/IgG > 0,4 y > 10 cels IgG4 + x CAP	Definitivo
Criterios específicos de órgano para IgG4 (pancreatitis autoinmune, Mikulicz)			Definitivo
Compromiso de órgano: Disfunción, edema localizado o difuso	IgG4 sérica < 135 mg/dl	IgG4/IgG > 0,4 y > 10 cels IgG4 + x CAP	Probable
Compromiso de órgano: Disfunción, edema localizado o difuso	IgG4 sérica > 135 mg/dl	No disponible o no diagnóstica	Posible
Compromiso de órgano: Disfunción, edema localizado o difuso	IgG4 sérica < 135 mg/dl	No disponible o no diagnóstica	No considerar

Reumatol Clin. 2017;13:160–6

Ardila-Suarez O, Abril A, Gómez J. Enfermedad relacionada con IgG4: revisión concisa de la literatura. Reumatol Clin. 2017;13:125-6. DOI: 10.1016/j.reuma.2016.05.009.

Conclusiones

- Enfermedad sistémica de difícil diagnóstico.
- Aunque la histología e IHQ son pruebas sólidas para el diagnóstico, se requiere una cuidadosa correlación clínica, analítica y radiológica para un diagnóstico definitivo.
- La presencia **AISLADA** de c. plasmáticas IgG4+ o un aumento del ratio IgG4/IgG, constituyen hallazgos **NO** específicos.
- Los niveles séricos de IgG4 **NO** siempre se encuentran aumentados.
- El diálogo con el médico clínico es crucial para descartar otras entidades que puedan presentarse con niveles séricos y tisulares de IgG4.

No debemos utilizar términos categóricos para evitar un diagnóstico basado únicamente en los hallazgos histológicos.


Muchas gracias