RIIP

RENCONTRES en IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Jeudi 5 et Vendredi 6 octobre 2023

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

IMAGE FREEPIK

Sous l'égide de :

Comment je diagnostique et je traite une Maladie associée aux IgG4

Nicolas Schleinitz

Département Médecine Interne

Hôpital Timone Marseille

RIIP Rencontres en Immunologie & Immunothérapie Pratiques

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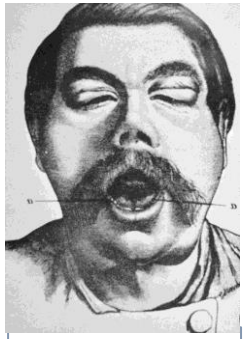
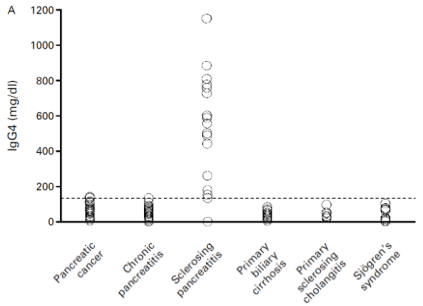


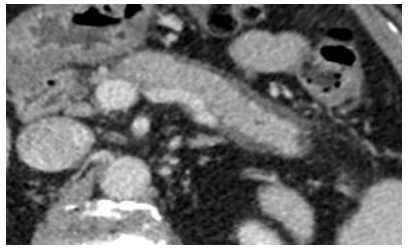
Mikulic'z

1888

Sarles H et al.
Chronic sclerosing and inflammatory pancreatitis



1961

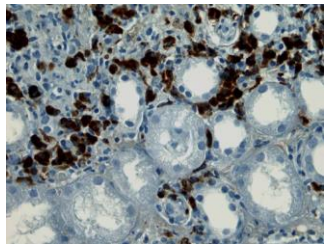


Yoshida et al. 1995

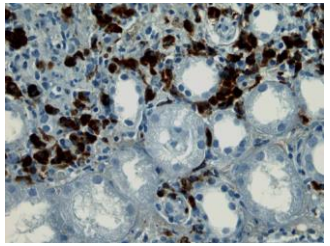
2001

Hamano H et al.
NEJM

Kamisawa T.
IgG4+plasmocytes pancréas and RPF



2004



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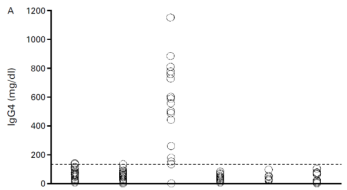


2011

ACR/EULAR Classification criteria

2019

International consensus: IgG4-RD

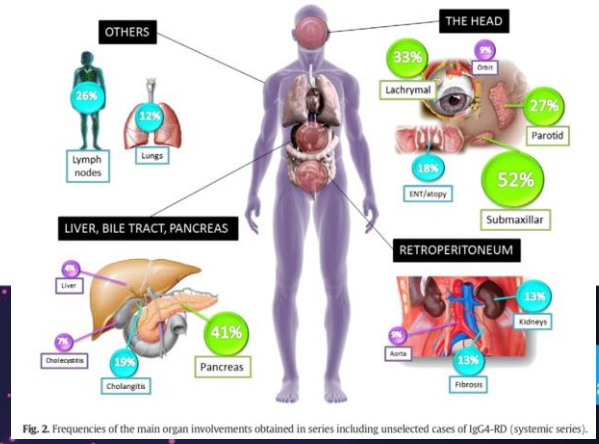
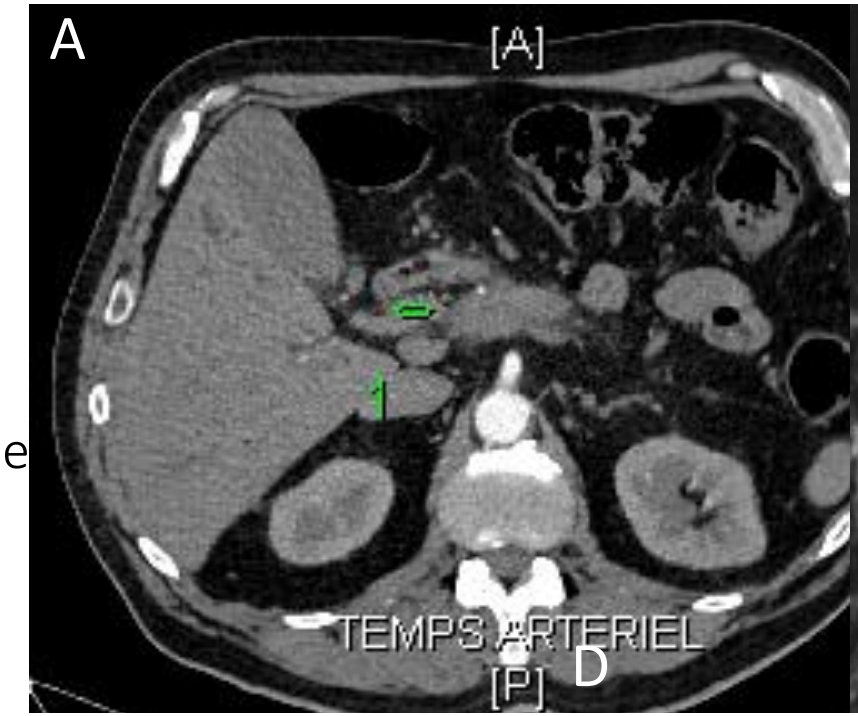


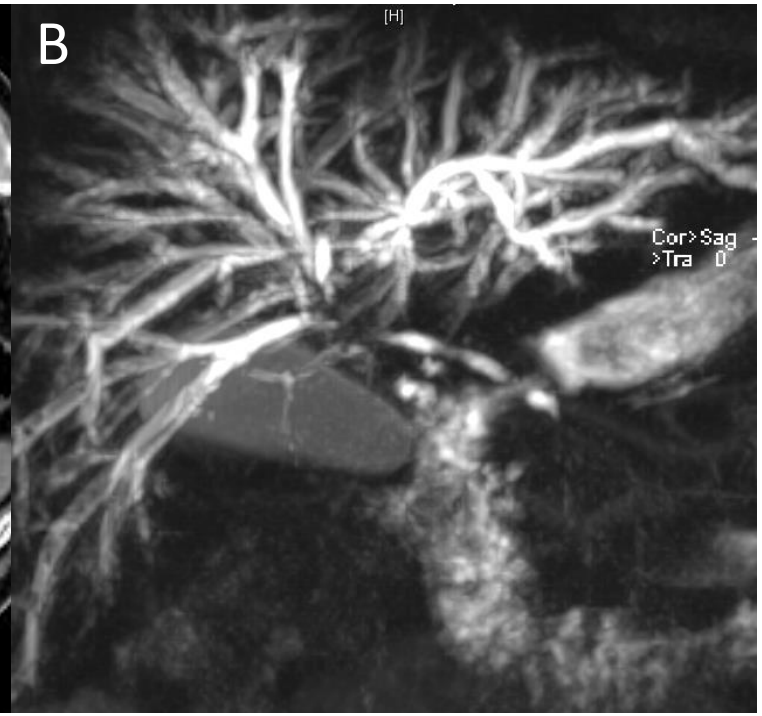
Fig. 2. Frequencies of the main organ involvements obtained in series including unselected cases of IgG4-RD (systemic series).

Homme 62ans

Amaigrissement
Ictère
Douleur hypochondre droit
(ADP réactionnelle -10ans, Atopie)

CT scan & MRI: Masse tumorale du hile hépatique avec dilatation des voies biliaires intrahépatiques : tumeur de Klastskin (cholangiocarcinome)





Histologie :polyclonal lymphoplasmocytic infiltrates, periductal fibrosis and obliterative phlebitis (figure C and D). Immunohistochemistry : 100 $IgG4^+$ plasmocytes/ HPF,
IgG4/IgG ratio of 80%
IgG4 sériques 3,24g/L

Diagnostic

Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts

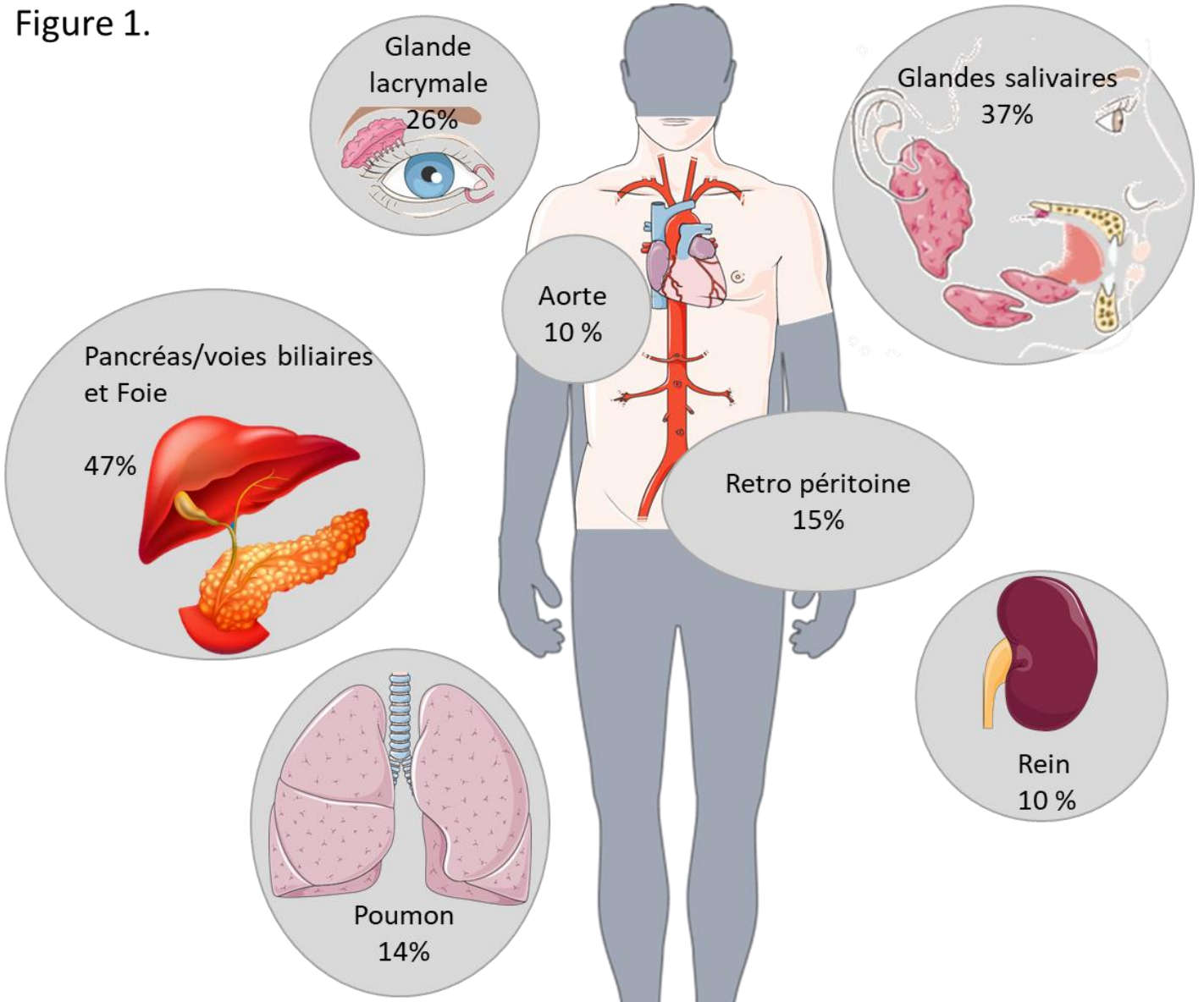
Zachary S Wallace,[1,2,3] Yuqing Zhang,[1,2,3] Cory A Perugino,[1,3] Ray Naden,[4] Hyon K Choi,[1,2,3] John H Stone,[1,3] for the ACR/EULAR IgG4-RD Classification Criteria Committee

Table 1 Demographic features overall and by sex and race (derivation cohort)

		Sex		Race	
	All (n=493)	Male (n=322)	Female (n=171)	Asian (n=208)	Non-Asian (n=285)
Age at symptom onset (years, mean, SD)	57.7 (14.5)	59.9 (14.3)	53.4 (14.0)	61.2 (13.2)	55.1 (14.9)
Age at diagnosis	59.5 (14.0)	61.7 (13.8)	55.4 (13.5)	62.6 (12.8)	57.2 (14.4)
Time to diagnosis	1.8 (3.4)	1.7 (3.6)	2.0 (2.9)	1.4 (2.7)	2.2 (3.7)
Male (n,%)	322 (65.3%)	–	–	126 (60.6%)	196 (68.7%)
Race					
Caucasian	198 (40.2%)	144 (44.7%)	54 (31.6%)	–	198 (69.5%)
Asian*	208 (42.2%)	126 (39.1%)	82 (47.9%)	208 (42%)	–
Asian, not otherwise specified	48 (9.7%)	34 (10.6%)	14 (8.2%)	48 (9.7%)	–
Japanese	105 (21.3%)	61 (18.9%)	44 (25.7%)	105 (21.3%)	–
Chinese	53 (10.8%)	29 (9.0%)	24 (14.0%)	53 (10.8%)	–
Latino/Hispanic	58 (11.8%)	32 (9.9%)	26 (15.2%)	–	58 (20.4%)
South Asian	14 (2.8%)	10 (1.1%)	4 (2.3%)	–	14 (4.9%)
Black	9 (1.8%)	8 (2.5%)	5 (2.9%)	–	9 (3.2%)
Other	6 (1.2%)	2 (0.6%)	0 (0%)	–	6 (2.1%)
IgG4 concentration (mg/dL, median, IQR)	342.5 (160–870)	382 (177–870)	302 (124–866)	666 (321–1230)	240.5 (100–505)
Not checked	15 (3.0%)	13 (4.0%)	2 (1.2%)	0 (0%)	15 (5.3%)
Normal	90 (18.3%)	49 (15.2%)	41 (24.0%)	17 (8.2%)	73 (25.6%)
>Normal < 2×ULN	83 (16.8%)	54 (16.8%)	29 (17.0%)	24 (11.5%)	59 (20.7%)
>2×Normal <5×ULN	149 (30.2%)	98 (30.4%)	51 (29.8%)	67 (32.2%)	82 (28.8%)
>5×ULN	156 (31.6%)	108 (33.5%)	48 (28.1%)	100 (48.1%)	56 (19.6%)
Biopsy performed	421 (85.4%)	267 (82.9%)	154 (90.1%)	188 (90.4%)	233 (81.8%)
Obliterative phlebitis	91 (18.5%)	55 (17.1%)	36 (21.1%)	19 (9.1%)	72 (25.3%)
Storiform fibrosis	195 (39.6%)	126 (39.1%)	69 (40.4%)	57 (27.4%)	138 (48.4%)
Number of organs affected (mean, SD)	2.9 (1.8)	2.9 (1.9)	2.8 (1.6)	2.9 (1.5)	2.9 (1.9)
Single organ	120 (24.3%)	75 (23.3%)	45 (26.3%)	33 (15.9%)	87 (30.5%)
Multiorgan (≥2 organs)	373 (75.6%)	247 (76.7%)	126 (73.7%)	175 (84.1%)	198 (69.5%)
Head and Neck	263 (53.3%)	151 (46.9%)	112 (65.5%)	141 (67.8%)	122 (42.8%)
Salivary gland	186 (37.7%)	110 (34.2%)	76 (44.4%)	109 (52%)	77 (27.0%)
Orbital	32 (6.5%)	15 (4.7%)	17 (9.9%)	8 (3.9%)	24 (8.4%)
Extraocular muscle	20 (4.1%)	6 (1.9%)	14 (8.2%)	5 (2.4%)	15 (5.3%)
Lacrimal gland	128 (26.0%)	61 (18.9%)	67 (39.2%)	80 (38.5%)	48 (16.8%)
Pancreato-hepatobiliary	235 (47.7%)	178 (55.3%)	57 (33.3%)	88 (42.3%)	147 (51.6%)
Pulmonary	70 (14.2%)	51 (15.8%)	19 (11.1%)	30 (14.4%)	40 (14.0%)
Aorta	51 (10.3%)	38 (11.8%)	13 (7.6%)	20 (9.6%)	31 (11.0%)
Retroperitoneum	78 (15.8%)	62 (19.3%)	16 (9.4%)	28 (13.5%)	50 (17.5%)
Renal	77 (15.6%)	58 (18.0%)	19 (11.1%)	34 (16.3%)	43 (15.1%)

*Two patients (0.4%) were Korean, both were male.
ULN, upper limit of normal.

Figure 1.



Diagnostic

Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts

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Table 2 Phenotypic groups of IgG4-RD (derivation cohort)*

Variables used to identify groups†	Group 1 'Pancreato-Hepato-Biliary' (%)	Group 2 'Retroperitoneum and Aorta' (%)	Group 3 'Head and Neck-Limited' (%)	Group 4 'Mikulicz and Systemic' (%)	P value
Pancreas	87	12	15	46	<0.001
Liver	13	1	2	5	<0.001
Biliary	55	<1	<1	27	<0.001
Orbital	<1	3	22	<1	<0.001
Extraocular muscle	<1	1	13	4	<0.001
Sinusitis	3	<1	17	16	<0.001
Parotid gland	2	1	22	49	<0.001
Submandibular gland	15	5	50	77	<0.001
Lacrimal gland	3	3	60	48	<0.001
Renal	11	13	5	36	<0.001
Lung	2	15	7	39	<0.001
Lymph node	15	25	29	67	<0.001
Prostate	1	<1	<1	14	<0.001
Thoracic aorta	1	10	1	3	<0.001
Abdominal aorta	3	22	<1	13	<0.001
Retroperitoneum	4	53	2	8	<0.001
Proportion of cohort	31	24	24	22	
Average probability (Mean)	93	92	90	90	

Table 3 Demographics and key covariates according to IgG4-RD phenotype groups (derivation cohort)

Covariate	Group 1 'Pancreato-Hepato-Biliary'	Group 2 'Retroperitoneum and Aorta'	Group 3 'Head and Neck-Limited'	Group 4 'Mikulicz and Systemic'
Female (%)	21%	25%	76%	72%
Asian (%)	37%	25%	67%	59%
Age at diagnosis (year, mean, SD)	63 (13)	58 (16)	55 (13)	63 (13)
Time to diagnosis (year, mean, SD)	0.9 (1.8)	1.8 (4.0)	2.3 (3.4)	2.0 (3.6)
Serum IgG4 concentration (mg/dL, median, IQR)	316 (147–622)	178 (63–322)	445 (183–888)	1170 (520–2178)

Diagnostic

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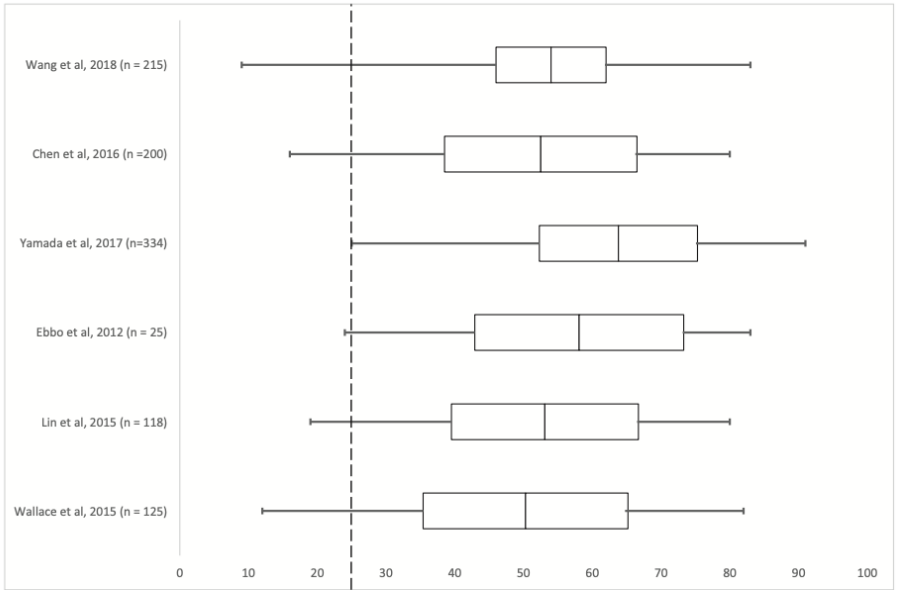
*Two patients (0.4%) were Korean, both were male.
ULN, upper limit of normal.

Ce qui est plus rare…

Formes pédiatriques et juvéniles

A descriptive study of IgG4-related disease in children and young adults

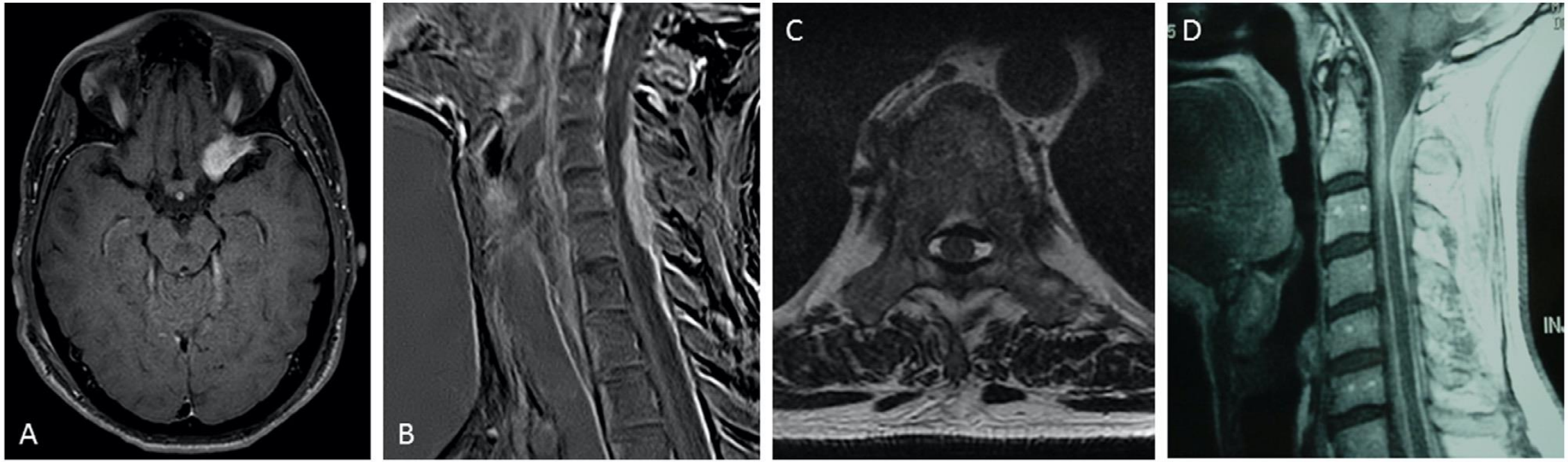


Age médian premier symptômes 15,3 ans (n=22)

Diagnostic Ce qui est plus rare…

Clinical presentation, treatment and outcome of IgG4-related pachymeningitis: From a national case registry and literature review

Cléa Melenotte[a], Julie Seguier[a], Mikael Ebbo[a], Elsa Kaphan[b], Emmanuelle Bernit[a], Laurent Saillier[c], Bertrand Audoin[b], Delphine Feyeux[d], Laurent Daniel[e], Pierre-Hugues Roche[f], Thomas Graillon[g], Henry Dufour[g], Clémence Boutière[b], Nadine Girard[h], Fabienne Closs-Prophette[i], Constance Guillaud[j], Nathalie Tieulié[k], Alexis Regent[l], Jean Robert Harlé[a], Mohamed Hamidou[m], Arsène Mekinian[n], Aurélie Grados[o], Nicolas Schleinitz[a,*] Seminar Arth Rheum 2017



sIgG4 normales dans 50% des cas

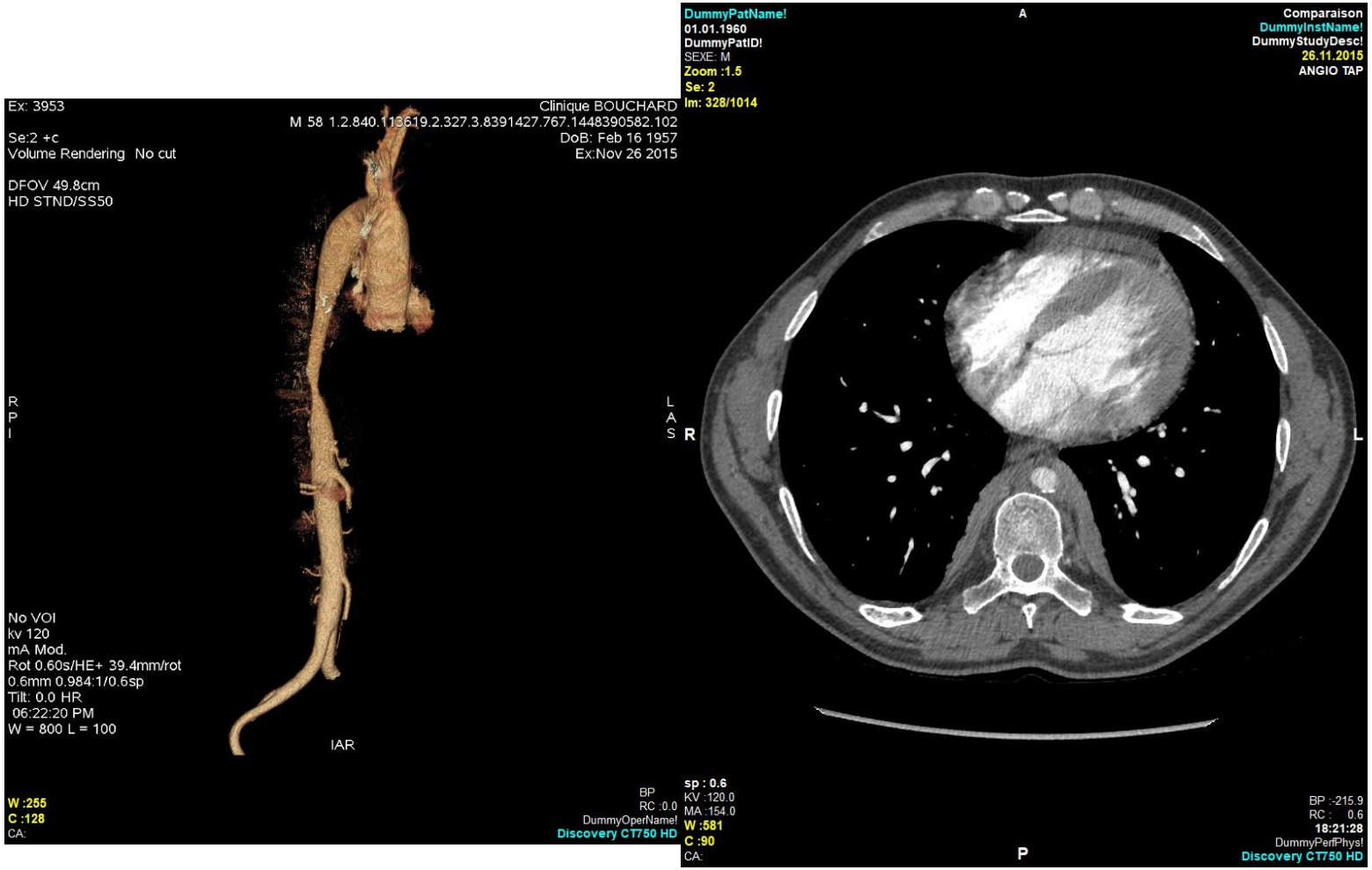
Atteintes extra méningées (seulement) ∽30% des formes spinales et ∽40% de formes cérébrales

Diagnostic Ce qui est plus rare…

Homme 52 ans

HTA
Rétinopathie hypertensive (stade 3 à OG et stade 2 à OD droit)

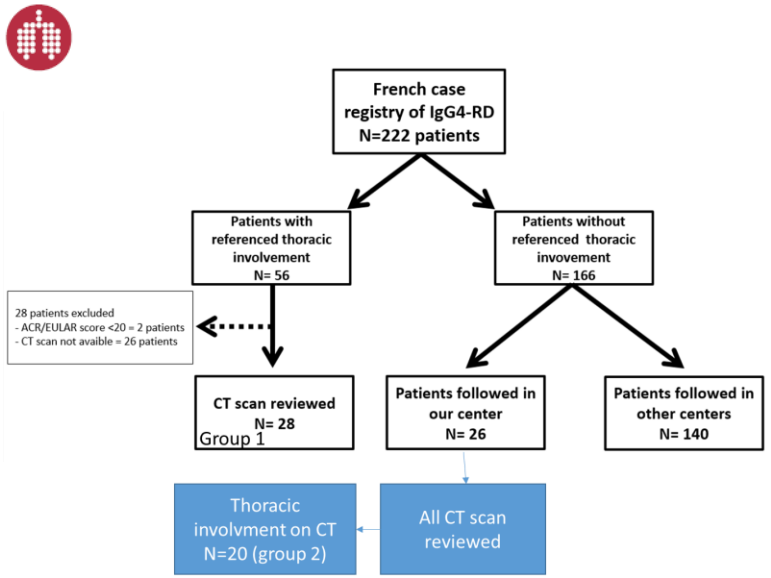
Aortite avec réduction de calibre de >75% responsable d'une hypertension artérielle
CRP : 36 mg/L.
ANCA –
IgG4 0,72g/L



Diagnostic Ce qui est plus rare…

Thoracic involvement and imaging patterns in IgG4-related disease

Romain Muller[1,13], Paul Habert[2,13], Mikael Ebbo[1], Julie Graveleau[3], Mathieu Groh[4], David Launay[5], Sylvain Audia[6], Gregory Pugnet[7], Fleur Cohen[8], Antoinette Perlat[9], Audrey Benyamine[10], Boris Bienvenu[11], Lea Gaigne[1], Pascal Chanez[12], Jean Yves Gaubert[2] and Nicolas Schleinitz[1]



Type of chest involvement	Global population n=48
Bronchovascular	27 (56%)
Lymph node enlargement	15 (31%)
Nodular	7 (25%)
Interstitial disease	7 (25%)
GGO	5 (10%)
Retromediastinal fibrosis	2 (4%)
Pleural	4 (8%)

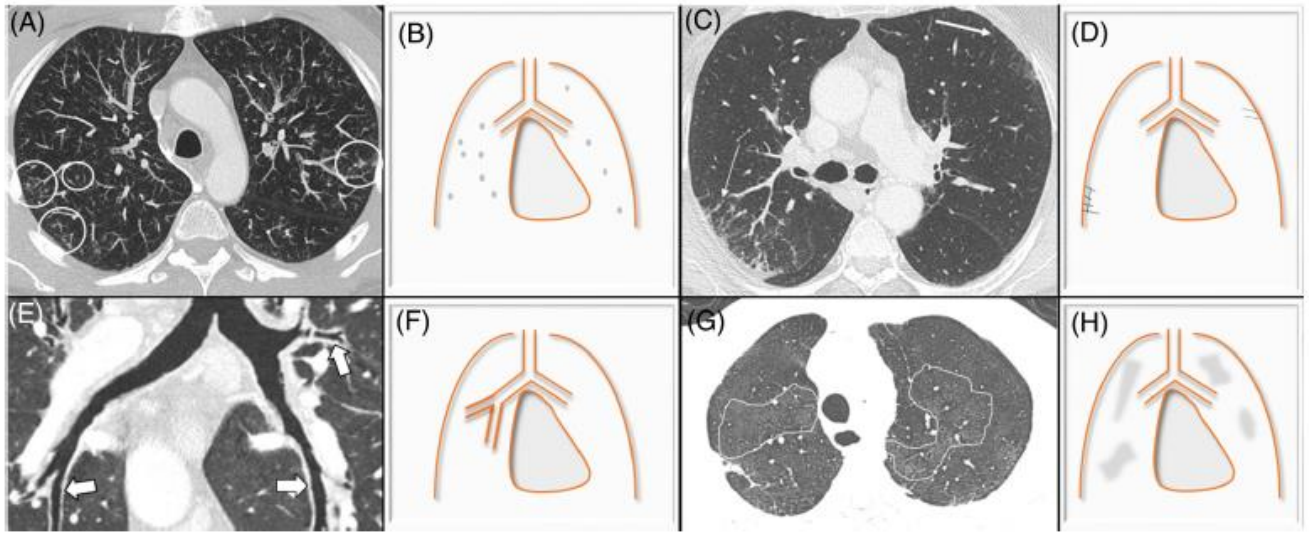
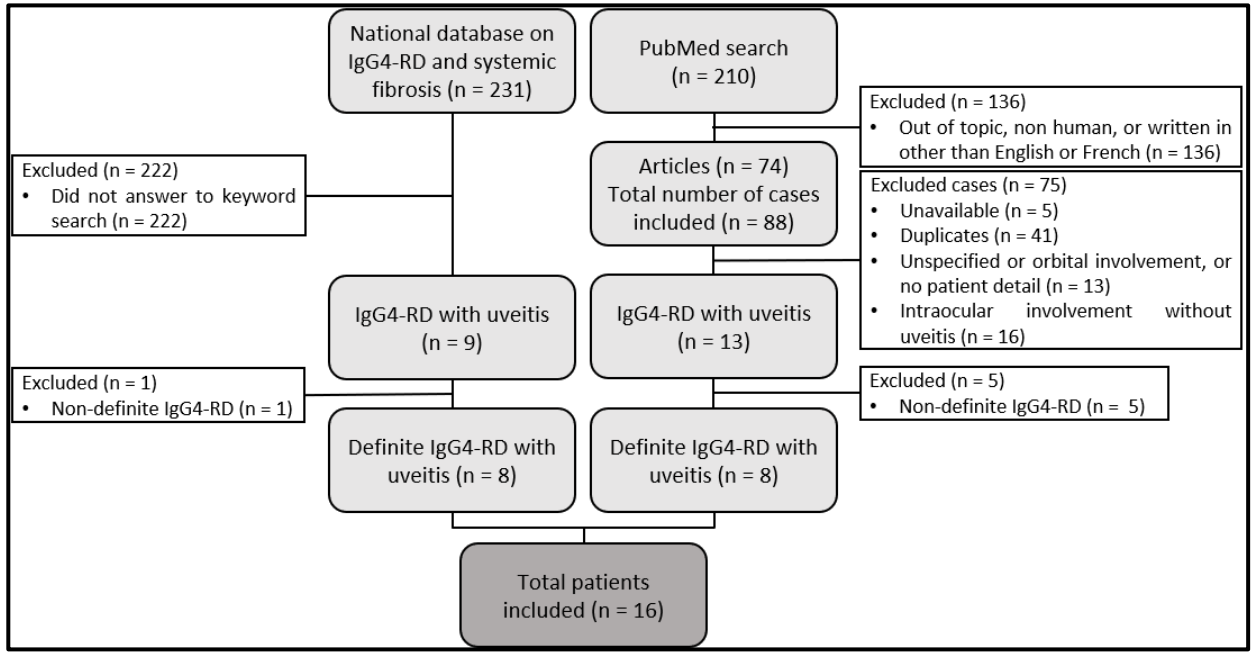
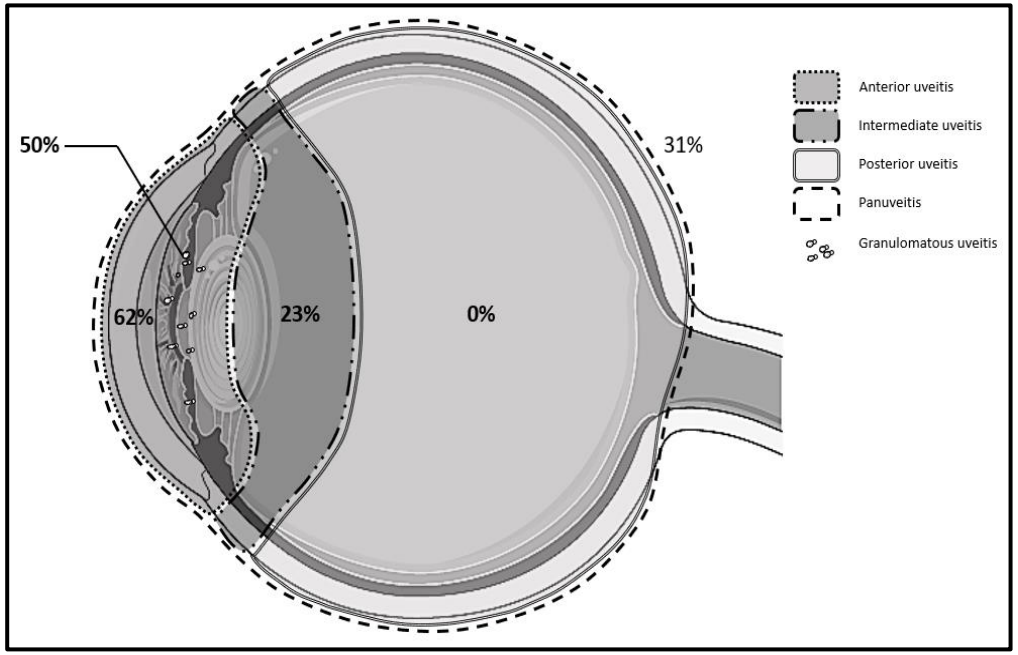


FIGURE 1 The four CT-scan lung patterns of IgG4-RD involvement. Axial chest CTs in parenchyma window associated with illustrations of the four lungs patterns. (1) *Nodular pattern*: small or pericentimers nodules randomly dispose (inside the circles). A 4 mm thickness with maximal intensity projection was performed to highlight the abnormalities (A,B). (2) *Interstitial disease pattern*: fine bilateral subpleural lines and not only in the posterior localization (thin arrows) (C,D). (3) *Peribronchovascular pattern*: diffuse bronchial wall thickening in curvilinear reconstruction (white arrows) (E,F). (4) *Ground-glass opacities (GGO) pattern*: area of GGO highlighted with 4 mm thickness minimal intensify projection reconstruction and circled (G,H).

Diagnostic Ce qui est plus rare…ou discutable

Uvéite

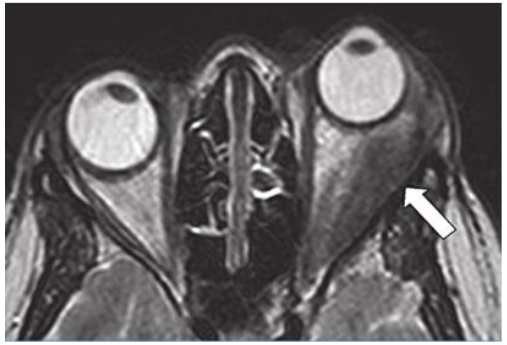
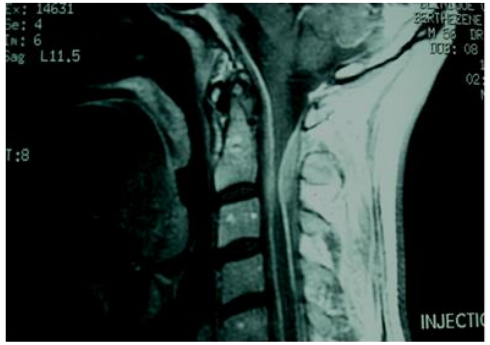
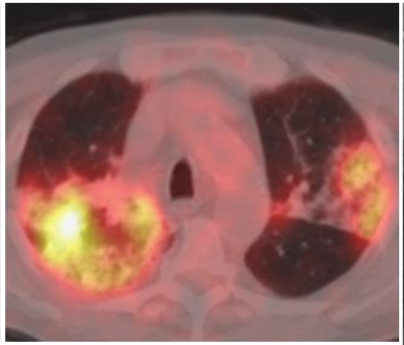
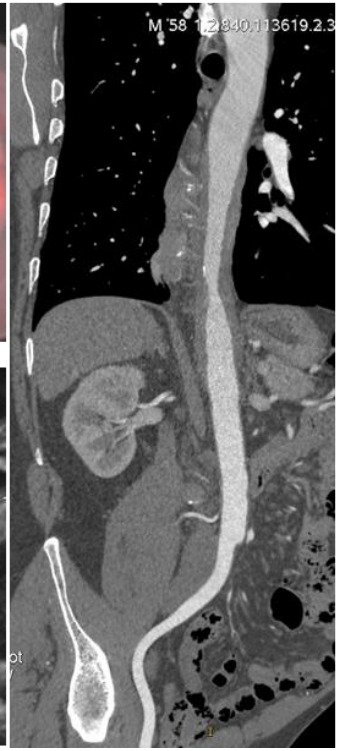


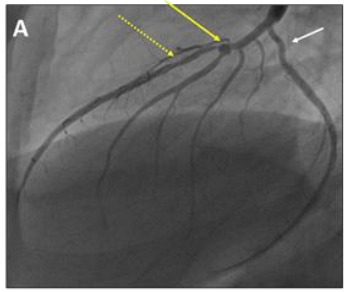


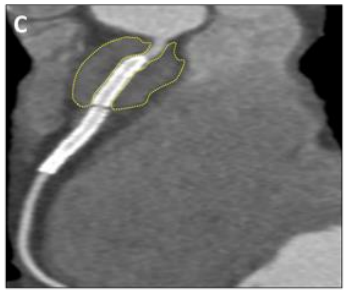
Uveitis occurred before the diagnosis of IgG4-RD in 10/12 cases (83%) with a median of 15 months (1 – 24).
Uveitis was the sole symptom for IgG4-RD in 4/16 cases (25%).

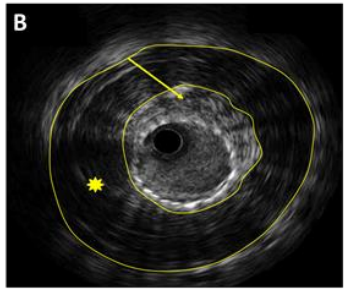
Diagnostic

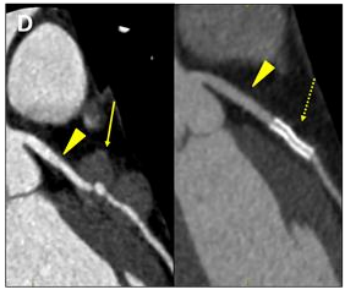
Y penser souvent mais diagnostiquer prudemment !

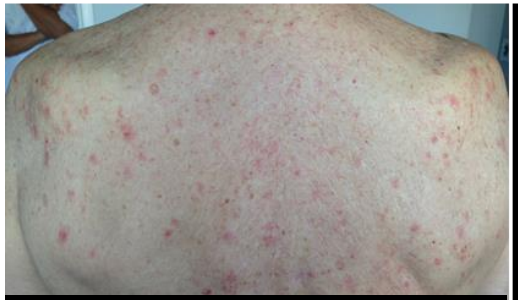
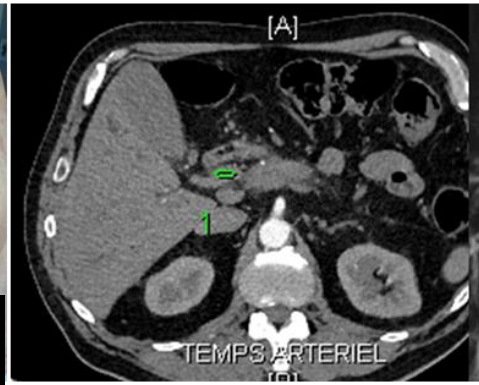





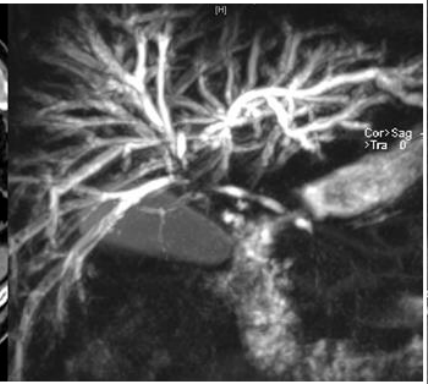
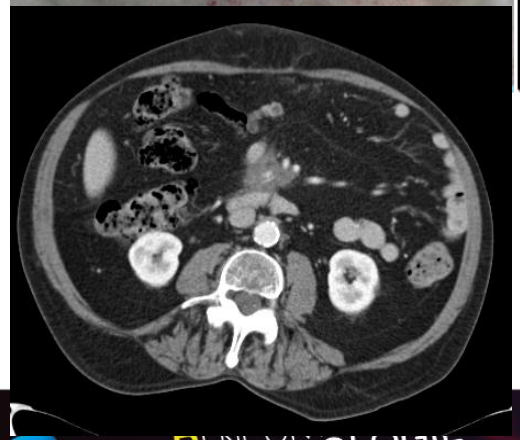
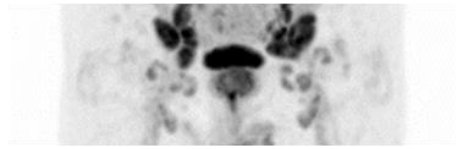








Diagnostic
Et la biologie peut elle nous aider ?

Elévation des IgG4 sériques +++
Normales 20 à 50% selon les séries
Effet prozone (faux négatifs)
Différents kits de dosage/normales

Spécificité 60 %
VPP 34 %
Carruthers M et al Ann Rheum Dis 2015

<u>Anomalies biologiques évocatrices</u>

IgG4 seriques, ratio IgG/IgG4

Eosinophilie

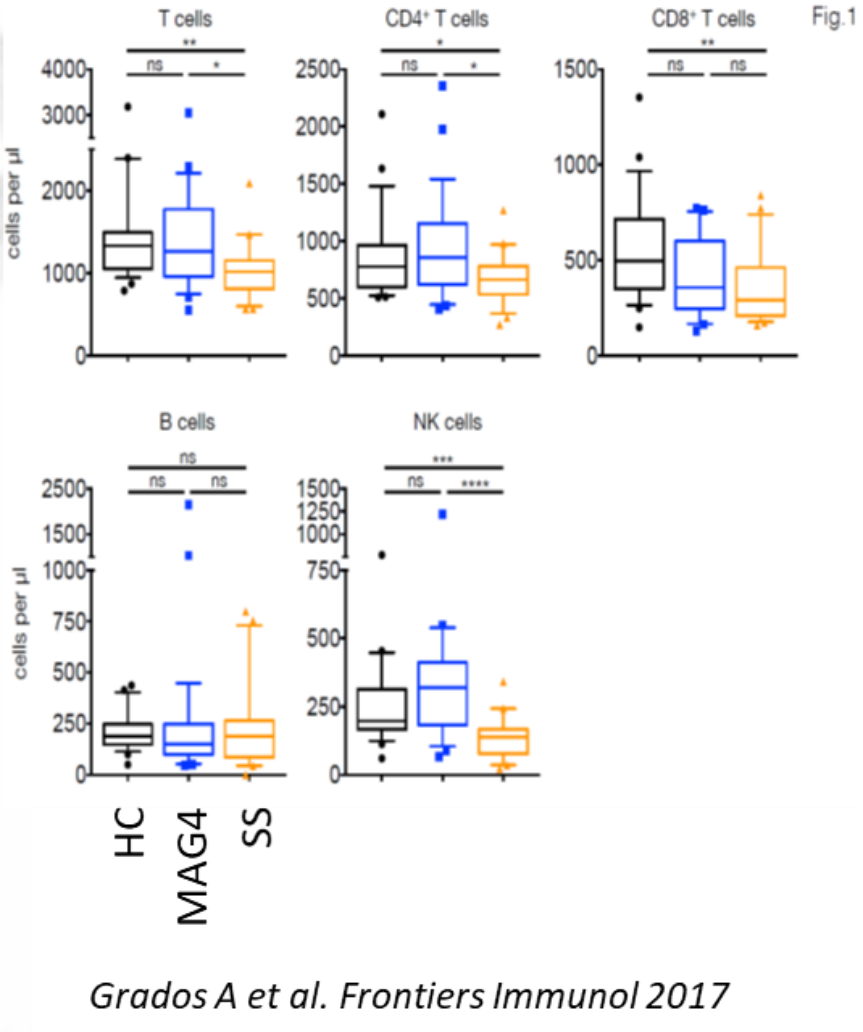
Electrophorèse des protéines sériques

Complément abaissé

IgE totales augmentées

La CRP est peu élevée

Apport du typage de sous populations lymphocytaires T et B ?



Grados A et al. Frontiers Immunol 2017

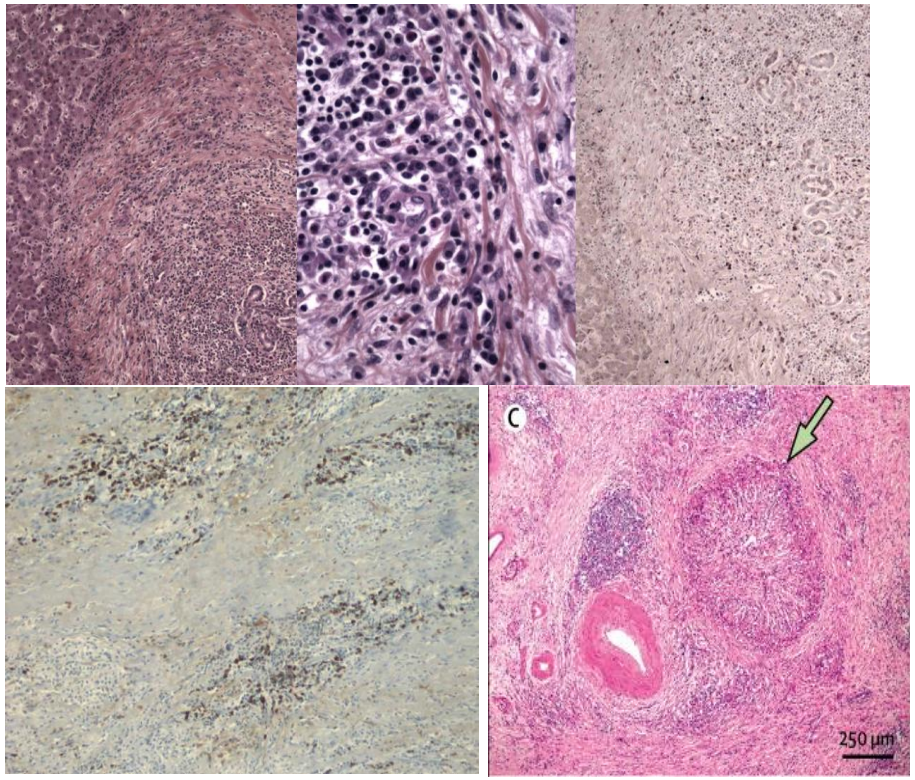
Diagnostic
Et les critères de CLASSIFICATION ACR/EULAR 2019

1. Entry Criteria Characteristic* clinical or radiologic involvement of a typical organ (e.g.,pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges, or thyroid gland [Riedel's thyroiditis])

OR

pathologic evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain etiology in one of these same organs.

Diagnostic
Et les critères de CLASSIFICATION ACR/EULAR 2019

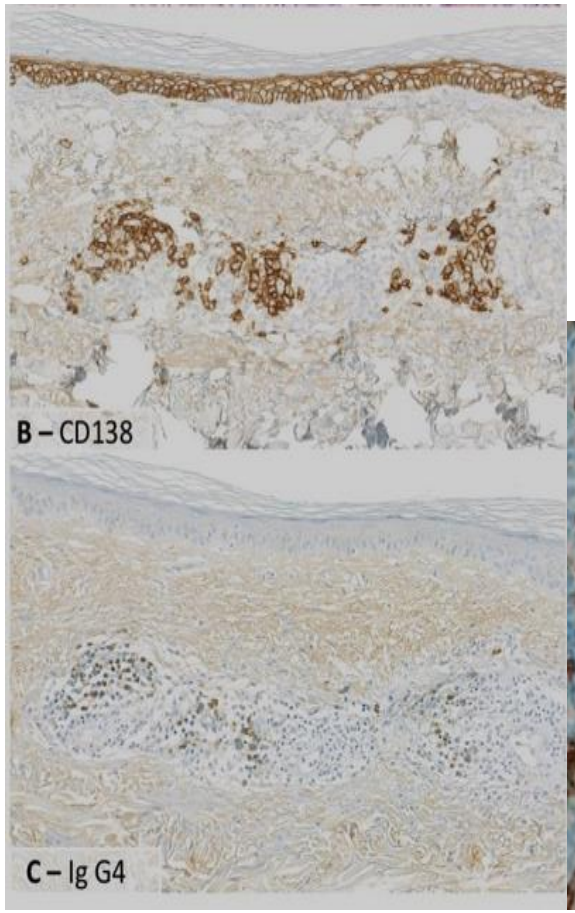


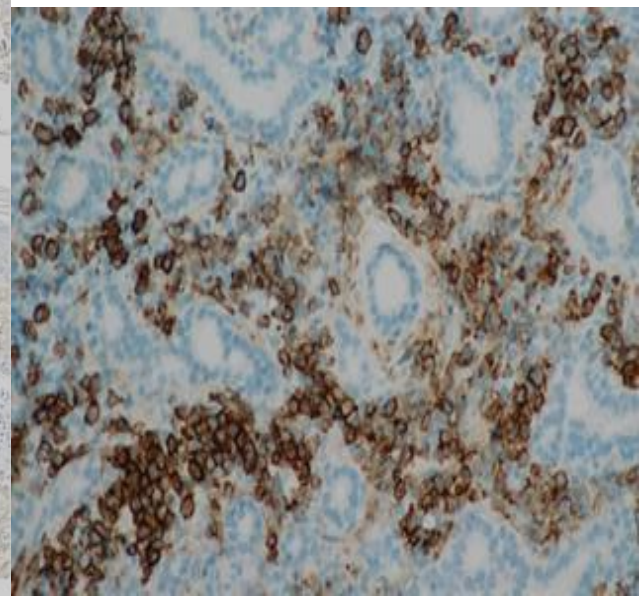
A.

3. Inclusion Criteria	Domains and Items	Weight‡
	Histopathology	
	Uninformative biopsy	+ 0
	Dense Lymphoplasmacytic Infiltrate	+ 4
	Dense Lymphoplasmacytic Infiltrate and Obliterative Phlebitis	+ 6
	Dense Lymphoplasmacytic Infiltrate and Storiform Fibrosis with or without Obliterative Phlebitis	+ 13
	Immunostaining† (Table 2b)	**+ 0-16**

Critères de classification ACR/EULAR 2019

Diagnostic
Et les critères de CLASSIFICATION ACR/EULAR 2019





B.

Table 4B: Weight Assigned for Each Combination of Immunostaining Items*

IgG4:IgG+ Ratio	IgG4+ Cells/HPF				
		0 to 9	Indeterminate‡	10 to 50	≥50
	0 to 40%	0	7	7	7
	Indeterminate‡	0	7	7	7
	41-70%	7	7	14	14
	≥70%	7	7	14	16

*Biopsies from the lymph node, GI tract, and skin are not acceptable for use in weighting the immunostaining domain

Diagnostic
Et les critères de ~~CLASSIFICATION ACR/EULAR 2019~~

Adénopathies 2 à 65% selon les séries

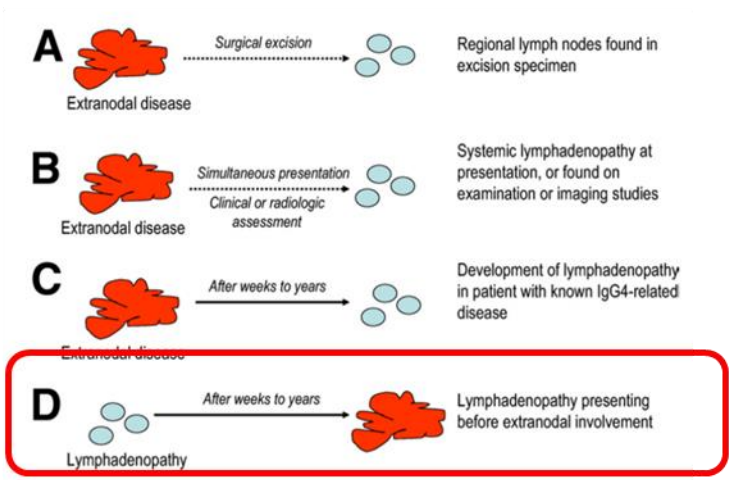
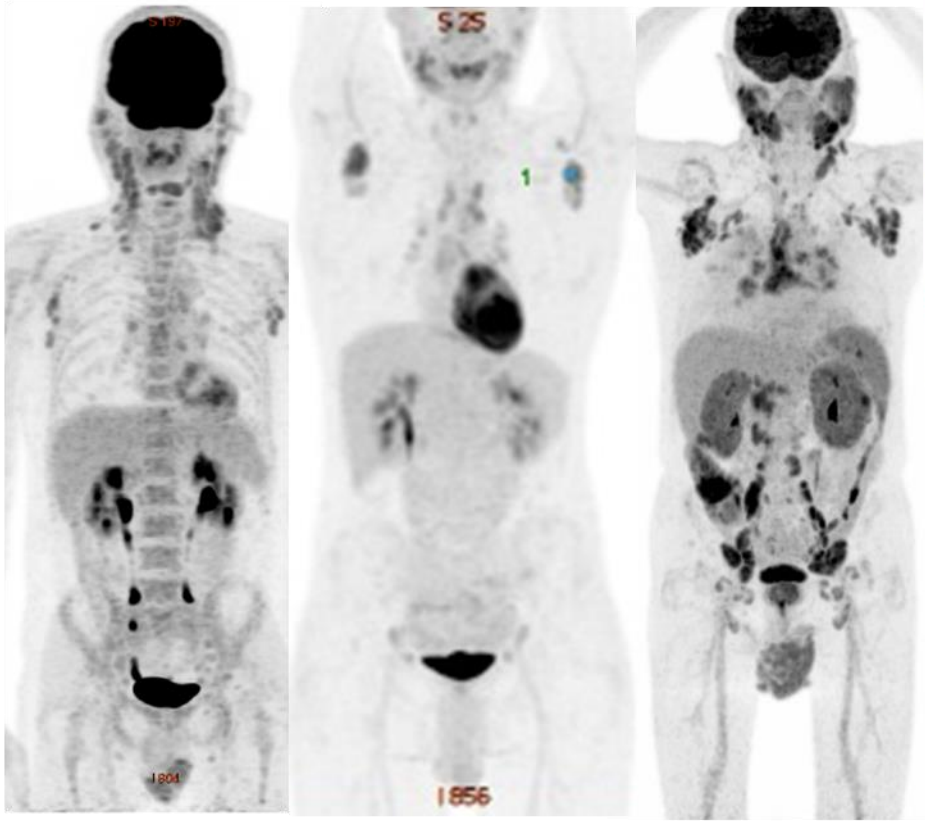


Figure 1 Different scenarios for the occurrence of lymphadenopathy in IgG4-related disease.

Cheuk and Chan IgG4-Related Lymphadenopathy Seminars in Diagnostic Pathology, Vol 29, No 4, November 2012



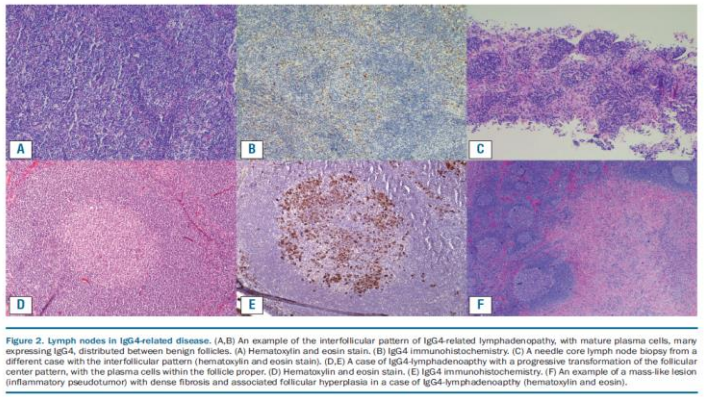
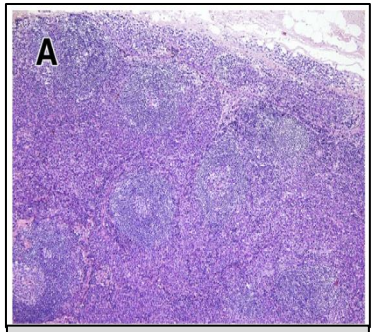


Figure 2. Lymph nodes in IgG4-related disease. (A,B) An example of the interfollicular pattern of IgG4-related lymphadenopathy, with mature plasma cells, many expressing IgG4, distributed between benign follicles. (A) Hematoxylin and eosin stain. (B) IgG4 immunohistochemistry. (C) A needle core lymph node biopsy from a different case with the interfollicular pattern (hematoxylin and eosin stain). (D,E) A case of IgG4-lymphadenoapthy with a progressive transformation of the follicular center pattern, with the plasma cells within the follicle proper. (D) Hematoxylin and eosin stain. (E) IgG4 immunohistochemistry. (F) An example of a mass-like lesion (inflammatory pseudotumor) with dense fibrosis and associated follicular hyperplasia in a case of IgG4-lymphadenoapthy (hematoxylin and eosin).



Type I
Castleman like

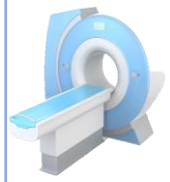
Diagnostic
Et les critères de CLASSIFICATION ACR/EULAR 2019

ACR/EULAR exclusion criteria

Clinical

Fever>38°
No response to GC
(minimum 40mg/d PDN-4w)

Imagery



Imagerie évoquant pathologie maligne
Progression radiologique rapide
Anomalie des os long évocatrice d'ECD
Splénomégalie

Biological

Leucopenia, thrombopenia
Eosinophilia > 3G/L
MPO ou PR3 +
PRo, La, dsDNA,RNP, Sm +
Cryoglobulinemia

Pathology

Cancer
Infiltration mostly by PNN
Necrotizing vasculitis
Necrosis
Granuloma
Histocytosis
Myofibroblastic tumor

Diseases

Castleman MC
IBD if pancreatitis
Hashimoto thyroiditis
if isolated

Critères de classification ACR/EULAR 2019

Diagnostic
Et les critères de CLASSIFICATION ACR/EULAR 2019

Clinical and imagery

Bilateral Lacrimal, Parotid, Sublingual, and Submandibular Glands	
No set of glands is involved	+ 0
One set of glands is involved	+ 6
Two or more sets of glands are involved	+ 14
Chest	
Not checked or neither of the items listed is present	+ 0
Peribronchovascular and septal thickening	+ 4
Paravertebral Band-Like Soft Tissue in the Thorax	+ 10
Pancreas and Biliary Tree	
Not checked or none of the items listed is present	+ 0
Diffuse pancreas enlargement (loss of lobulations)	+ 8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+ 11
Pancreas (either of above) and biliary tree involvement	+ 19
Kidney	
Not checked or none of the items listed is present	+ 0
Hypocomplementemia	+ 6
Renal pelvis thickening/soft tissue	+ 8
Bilateral renal cortex low density areas	+ 10
Retroperitoneum	
Not checked or neither of the items listed is present	+ 0
Diffuse thickening of the abdominal aortic wall	+ 4
Circumferential or antero-lateral soft tissue around the infra-renal aorta or iliac arteries	+ 8

Critères de classification ACR/EULAR 2019

Diagnostic

Mr C 79 ans

Episode 1: Douleurs abdominales **œdème pancréatique minime et une infiltration de la graisse de continuité**. NFS normale,, **créatinine 77 µmol/l**, Protides 87 g/l, **CRP 76 mg/l => lithiase vesiculaire cholecystectomie**

Episode 2 (M+6): **cholangite se prolongeant sur l'ensemble de la VBP**. **Pancréas discrètement aréolaire de manière diffuse** sans lésion visible ni anomalie canalaire.**PNE 1.22 (1.47 le 5/11)**, **créatinine 80 µmol/l**, protides 72 g/l, CRP 6.5 mg/l, **bilirubine T 85 µmol/l**, **GGT 291 U/l, PAL 310 U/l, ASAT 75, ALAT 127**
Cholangite => Ac ursodesoxycholique

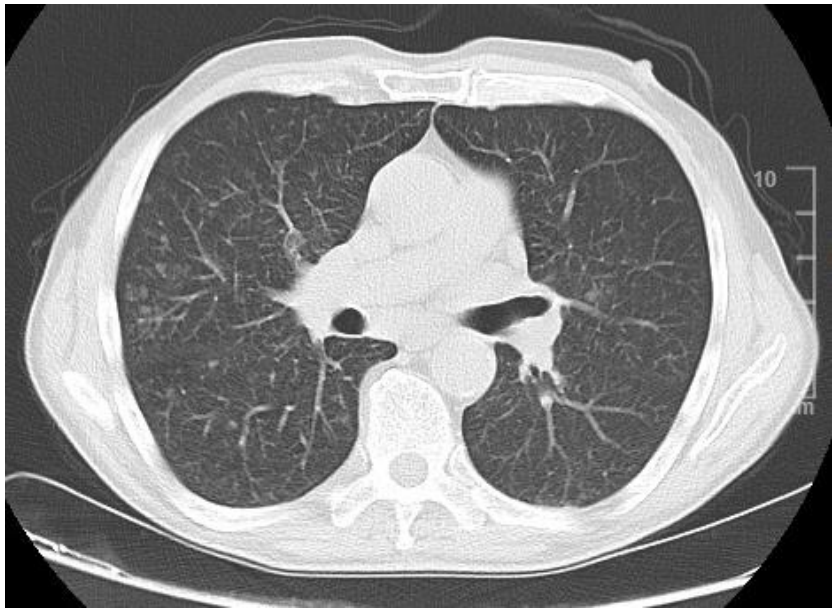
Episode 3(M+16): **Hypertrophie bilatérale symétrique des 2 glandes sous-mandibulaires** prédominant à droite. echographie de glandes salivaires faisant évoquer soit virus soit GS.
+ Urticaire traitée sans succès par anti Histaminiques+ Troubles urinaires+ Perte de poids

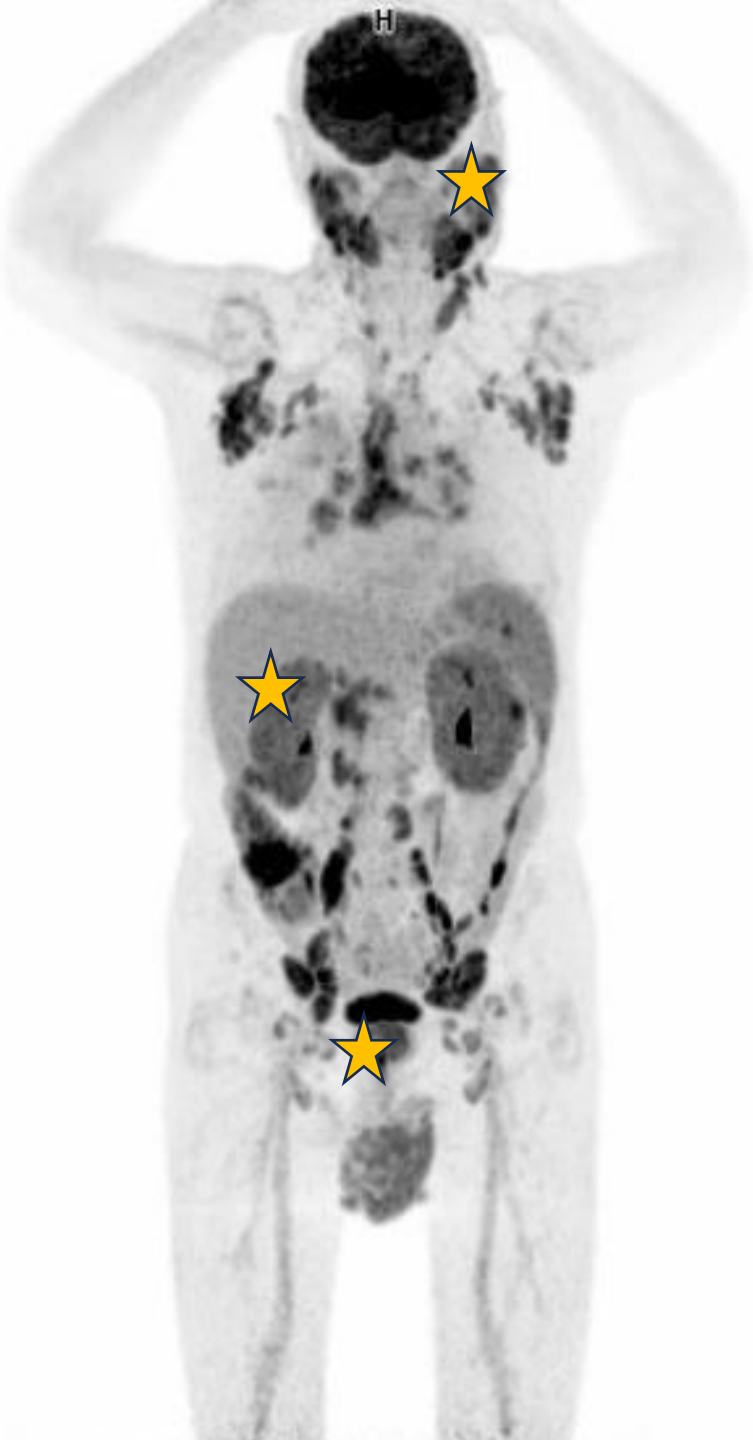
Episode 4 (M+20): AEG +++ Hb 10g/L, Plaquettes 237 G/L, PNEo 2G/L, CRP 10mg/L, Creatinine 198mcmol/L, protidemie 105g/L et albumine 29g/L
sérologies VIH et HHV8 négatives, PCR EBV 72000copies/ml, ACAN 1/1280eme sans ECT

Diagnostic

Mr C 79 ans

Episode 4 (M+20): AEG +++ Hb 10g/L, Plaquettes 237 G/L, PNEo 2G/L, CRP 10mg/L, Creatinine 198mcmol/L,
protidemie 105g/L et albumine 29g/L
sérologies VIH et HHV8 négatives, PCR EBV 72000copies/ml, ACAN 1/1280e
sans ECT





Diagnostic

Mr C 79 ans

Episode 4 (M+20): AEG +++ Hb 10g/L, Plaquettes 237 G/L, PNEo 2G/L, CRP 10mg/L, Creatinine 198mcmol/L, protidemie 105g/L et albumine 29g/L
sérologies VIH et HHV8 négatives, PCR EBV 72000copies/ml, ACAN 1/1280eme sans ECT

C3	▼ 0,16	g/l	(0,81 à 1,57)
C4	▼ <0,007	g/l	(0,129à 0,390)
CH50	▼ <20	%	(70 à 130)

DOSAGE PONDERAL DES IMMUNOGLOBULINES

technique de turbidimétrie OPTILITE (The Binding Site)
Nature du prélèvement : Sérum.

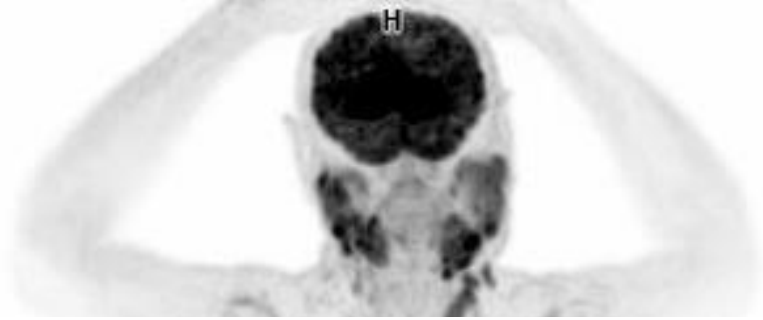
Test	Résultat	Unité	ValNor	Antérieur	Date
Immunoglobulines G	▲ 58,71	g/l	(6,90 à 14,00)		
Immunoglobulines A	1,07	g/l	(0,88 à 4,10)		
Immunoglobulines M	0,99	g/l	(0,34 à 2,10)		

CHAINES LEGERES LIBRES DES IMMUNOGLOBULINES

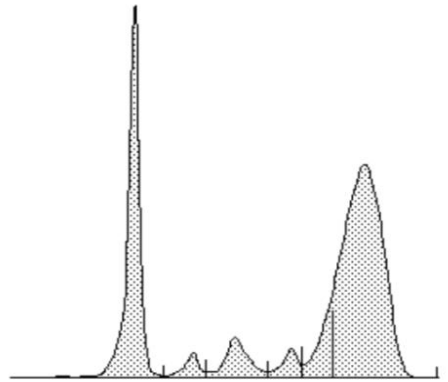
technique de turbidimétrie sur OPTILITE (The Binding Site)
Nature du prélèvement : Sérum.

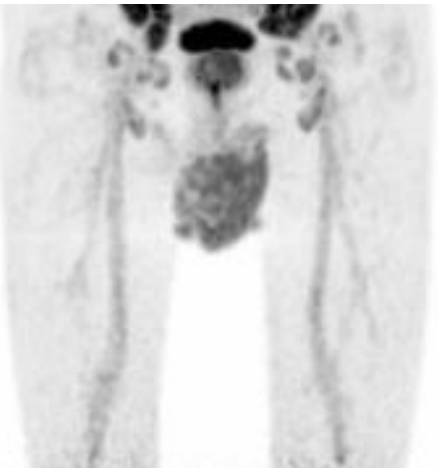
Test	Résultat	Unité	ValNor	Antérieur	Date
Kappa Libres	▲ 1019,00	mg/L	(3,30 à 19,40)		
Lambda Libres	▲ 281,90	mg/L	(5,71 à 26,30)		
Ratio K/L	▲ 3,61		(0,26 à 1,65)		

A noter qu'en cas d'insuffisance rénale, les normales sont (0,26 à 3,1).



	Résultat		Val Normales
Protéines sériques	▲ 105,3g/L		(58 à 76)
Albumine	▼ 28,4 %	soit ▼ 29,91g/l	40,20 - 47,60
Alpha 1	▼ 2,5 %	soit 2,63 g/l	2,10 - 3,50
Alpha 2	▼ 6,2 %	soit 6,53 g/l	5,10 - 8,50
Béta 1	▼ 3,1 %	soit ▼ 3,26 g/l	3,40 - 5,20
Béta 2	6,4 %	soit ▲ 6,74 g/l	2,30 - 4,70
Gamma	▲ 53,4 %	soit ▲ 56,23g/l	8,00 - 13,50





Diagnostic

Mr C 79 ans

Episode 4 (M+20): AEG +++ Hb 10g/L, Plaquettes 237 G/L, PNEo 2G/L, CRP 10mg/L, Creatinine 198mcmol/L, protidemie 105g/L et albumine 29g/L
sérologies VIH et HHV8 négatives, PCR EBV 72000copies/ml, ACAN 1/1280eme sans ECT

	Résultat			Val Normales
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Albumine	▼ 28,4	%	soit ▼ 29,91 g/l	40,20 - 47,60
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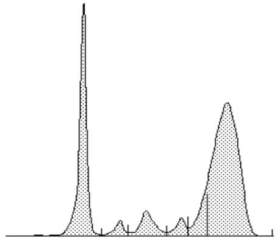
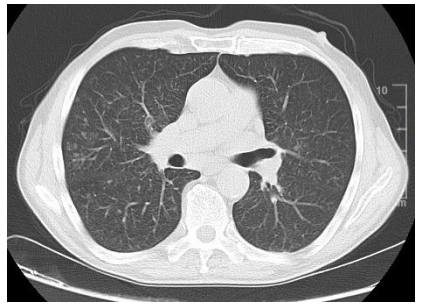
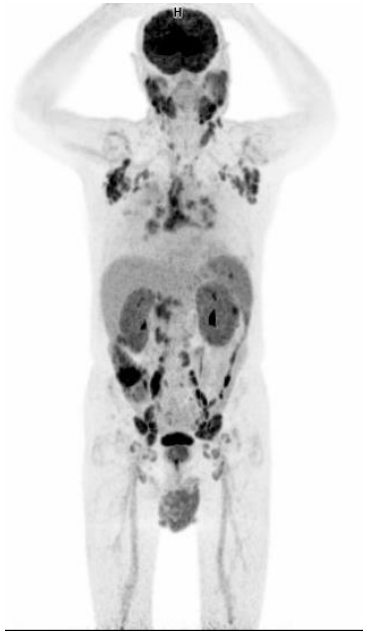
Gamma	▲ 53,4	%	soit ▲ 56,23 g/l	8,00 - 13,50







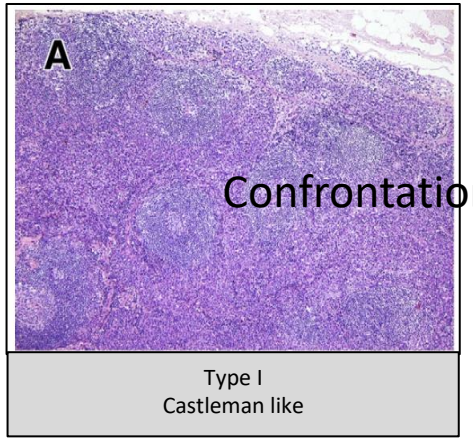
Critères internationaux de classification de la maladie de Castleman MI:

Deux criteres majeurs requis sont:

- Adenopahties ≥1 cm dans au moins deux territoires
- **Histologie ganglionnaire compatible avec une maladie de castleman**

Criteres mineurs (au moins 2 dont un biologique):

- Cliniques: altération de l'etat géneral, hepatosplenomegalie, oedemes/épanchements séreux, angiomes ou papules violacées, pneumonie lymphoide interstitielle (LIP)
- Biologiques: CRP élevée , anemie, thrombopenie ou thrombocytose, hypoalbuminemie, insuffisance renale, hypergammaglobulinemie polyclonale.



Type I
Castleman like

Confrontation clinique/anatomopathologiste ++++

Diagnostic

Table 3. Conditions that can mimic IgG4-related disease clinically and histopathologically

Antineutrophil cytoplasmic antibody–associated vasculitides
Granulomatosis with polyangiitis (Wegener's)
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Adenocarcinoma and squamous cell carcinoma, peritumoral infiltrate
Castleman's disease (multicentric or localized)
Cutaneous plasmacytosis
Erdheim-Chester disease
Inflammatory myofibroblastic tumor
Inflammatory bowel disease
Lymphoproliferative diseases
Extranodal marginal zone lymphomas
Lymphoplasmacytic lymphomas
Follicular lymphomas
Perforating collagenosis
Primary sclerosing cholangitis
Rhinosinusitis
Rosai-Dorfman disease
Sarcoidosis
Sjögren's syndrome
Splenic sclerosing angiomatoid nodular transformation
Xanthogranuloma

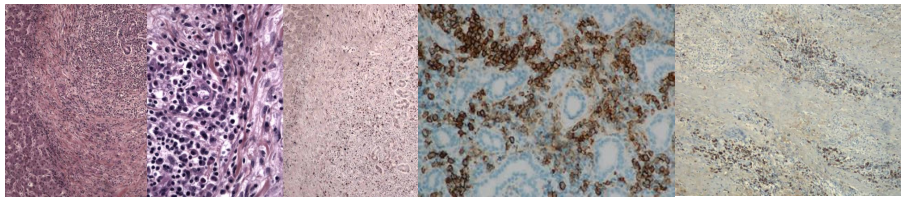
+ SHE

Koshrohahi A et al. ARheum 2015

IgG4-RD pathological lesions can be observed associated to :

- HES
- Castleman disease
- Destombes-Rosai-Dorfman (R-Histiocytosis)
- ANCA vasculitis
- Cancers
- Infectious diseases

Secondary IgG4-RD ?



Traitement

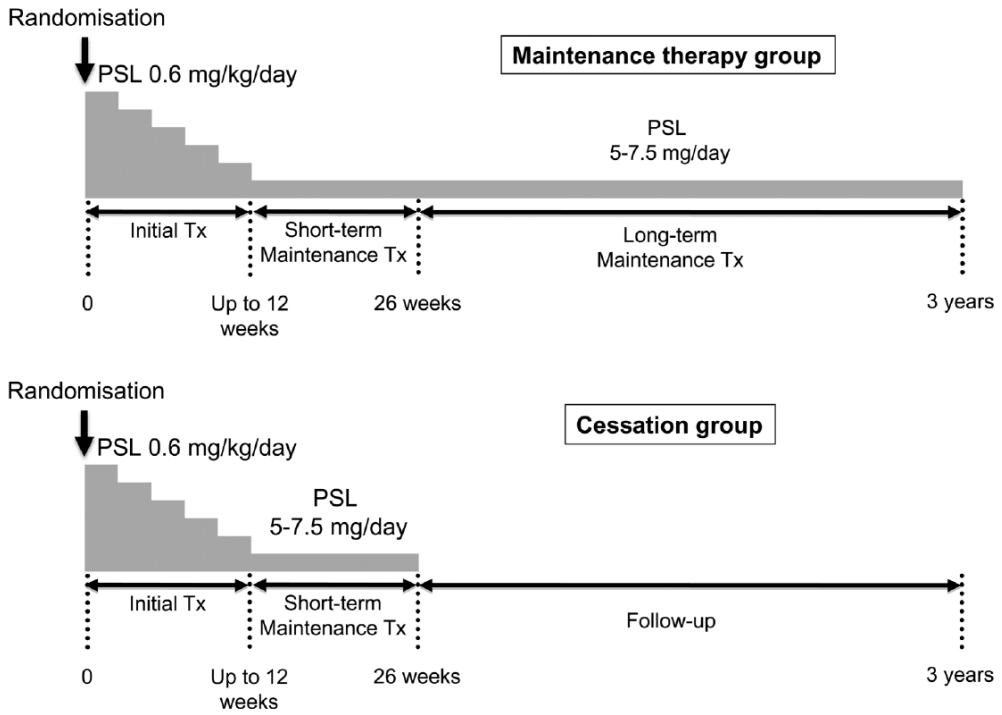
Traitement

Traitement- 1: Corticoides !

ORIGINAL ARTICLE

Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis

Masamune et al, Gut 2016



n=30

n=19

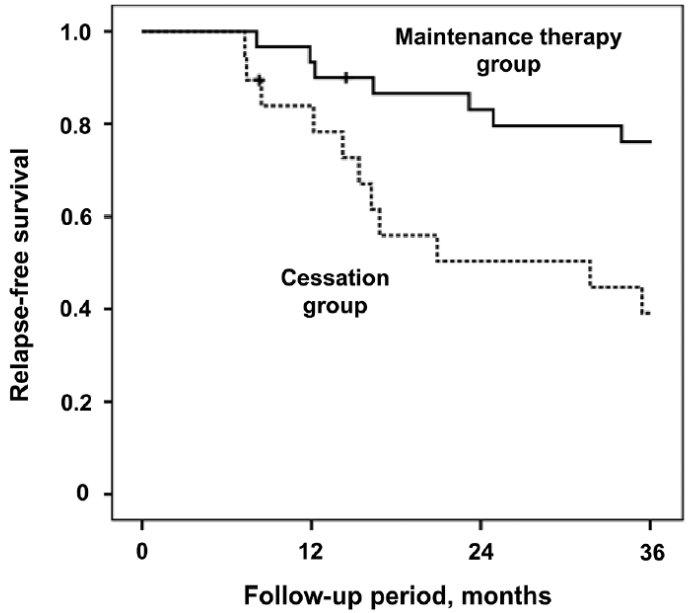


Table 4. Adverse events observed during glucocorticoid treatment in patients with IgG4-RD.

Adverse events	Number of cases	%
Expected		
Glucose intolerance	25	41.0%
Newly diagnosed with DM	12	19.7%
Aggravation from chronic DM	13	21.3%
Infection	11	18.0%
Fungus	6	9.8%
Bacteria	3	4.9%
Virus	1	1.6%
Acid-fast Bacillus	1	1.6%
Dyslipidemia	16	26.2%
Hypertension	9	14.8%
Psychosis	3	4.9%
Glaucoma	3	4.9%
Pathological fracture	2	3.3%
Myopathy	2	3.3%
Femur head necrosis	1	1.6%
Cataract	1	1.6%

Traitement- 4: quel traitement en épargne CTC

Table 1. Available therapeutic strategies for inducing and maintaining remission of IgG4-related disease.

Agent	Initial dose	Tapering	Maintenance	Study Design	Results	Ref
Glucocorticoids	p.o. PDN 0.6 mg/kg/day (2–4 weeks)	5 mg/1-2 weeks (2–6 months)	p.o. 2.5–10 mg/day (6–36 months)	Retrospective cohort studies	CR: 66% PR: 93% Relapse: 26% vs 45%	[38,42,43,56]
	p.o. PDN 30–60 mg/day (2–4 weeks)	5 mg/1-2 weeks (2–6 months)	p.o. 2.5–10 mg/day (6–36 months)		CR:100%	[39,40]
	i.v. MPDN 250–500 mg/day (3–5 days) → switch p.o.	-	-		CR:100%	[38,56]
	p.o. PDN 0.5 vs 1 mg/kg/day (4 weeks)	5–10% q2weeks	p.o. 7.5–10 mg/day (24 weeks)	Randomized controlled trial	CR: 95% vs 80%	[38,56]
	p.o. PDN 0.6 mg/kg/day (2–4 weeks)	(12 weeks)	p.o. 5–7.5 mg/d vs 0 mg/day (36 months)	Randomized controlled trial	Relapse: 23% vs 58%	[57]
Immunosuppressive agents						
Azathioprine	p.o. 0.5–2.5 mg/kg/day	-	p.o. 0.5–2.5 mg/kg/day (median 29–60 months)	Case series	Relapse 30%	[49]
Methotrexate	p.o./s.c.15–20 mg/week	-	p.o./s.c. 15–20 mg/week (median 15–60 months)	Case series	DR: 60% PR: 40%	[46,54]
Leflunomide	p.o. 10–20 mg/day	-	p.o. 10–20 mg/day (mean 12 months)	Case series	CR 67% Relapse 17%	[45]
Mycophenolate Mofetil	p.o. 1–1.5 gr/day (6 months)	p.o. 0.5–1.0 gr/d ^ (6 months)	p.o. 0.5–1.0 gr/day (19 ± 6 months)	Randomized controlled trial	CR 51 vs 76% Relapse: 40 vs 21%	[46,58]
	p.o. 1–2 gr/day	-	p.o. 1–2 gr/d^ (15–47 months)	Retrospective cohort studies		[46,50]
Cyclophosphamide	p.o. 50–100 mg/day (3 months)	-	p.o. 50 mg/day or maintain starting dose (≥ 9 months)	Prospective cohort study	Relapse: 38 vs 12%	[47,58]
Cyclosporin	p.o. 100 mg/day	-	p.o. 100 mg/day	Case report		[50]
Tacrolimus	p.o. 1–2.5 mg/day	-	p.o. 1–2.5 mg/day	Case series		[48,50]
6 Mercapto-purine	p.o. 0.7–2.6 mg/kg/day	-	p.o. 0.7–2.6 mg/kg/day	Case report		[53]
Iguratimod	p.o. 50 mg/day	-	p.o. 50 mg/day	Prospective cohort study	CR: 14% PR: 79%	[51,52]

Lanzillota M et al. Exp Rev Clin Immunol 2022

Traitement

Ajouter series plus recentes

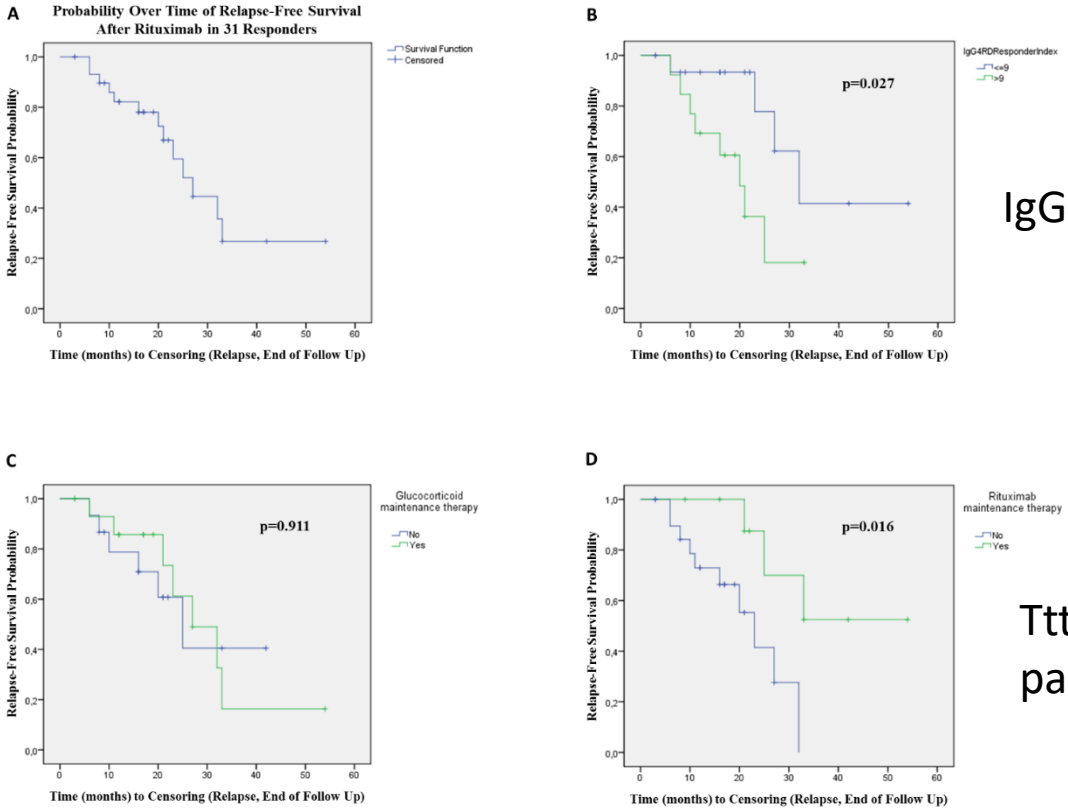
Traitement- 5: Anti CD20 et MAG4

Données dans la « vrai vie »
n=33 patients traités par RTX

Réponse 93,5% des patients

Suivi de 24,8 mois: 41,9% de rechute (délai médian 19 mois)

Taux d'infections sévères: 12,1/100 patient-années
3 patients hypogamma ≤ 5 g/L

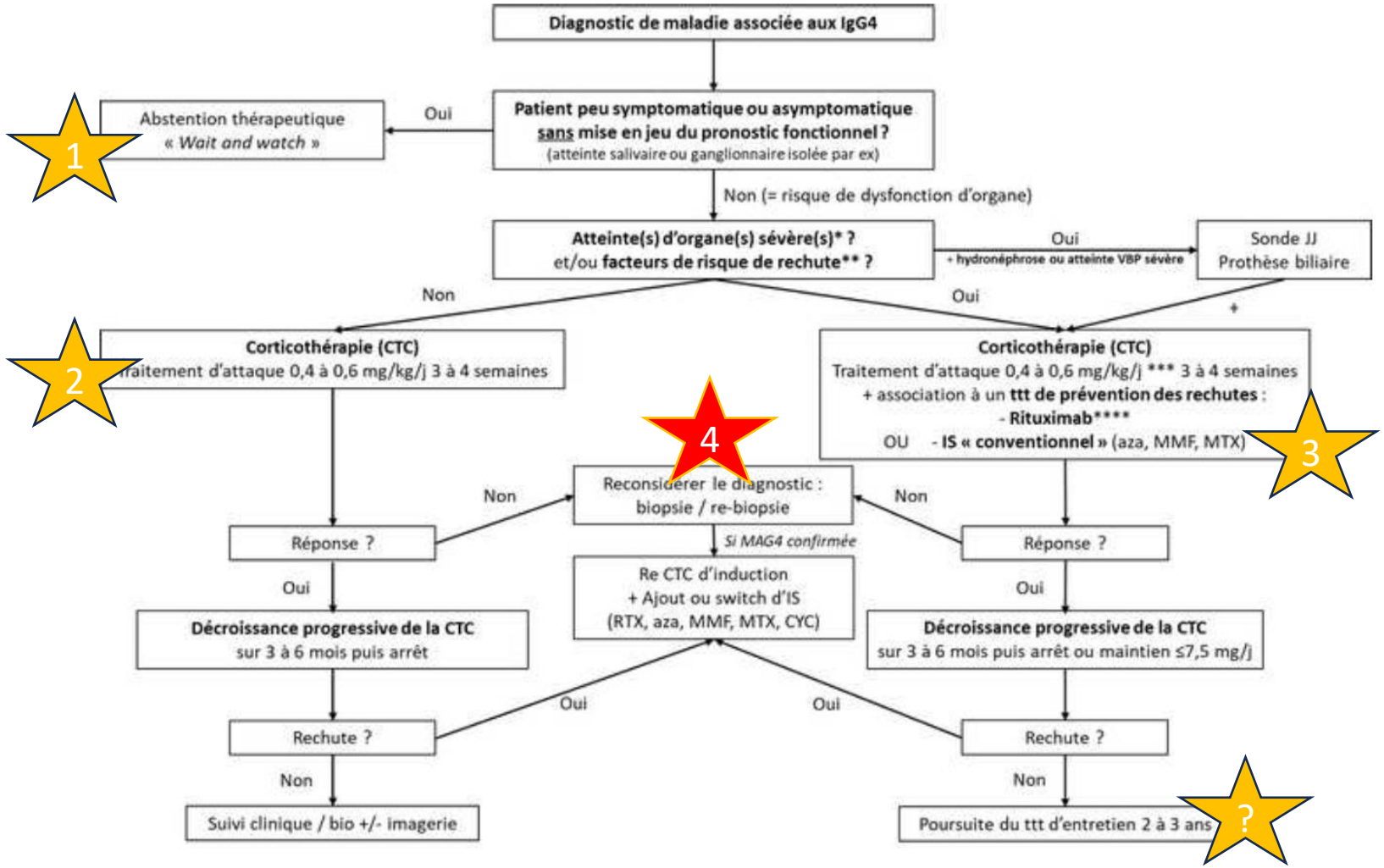


IgG4-RD RI >9

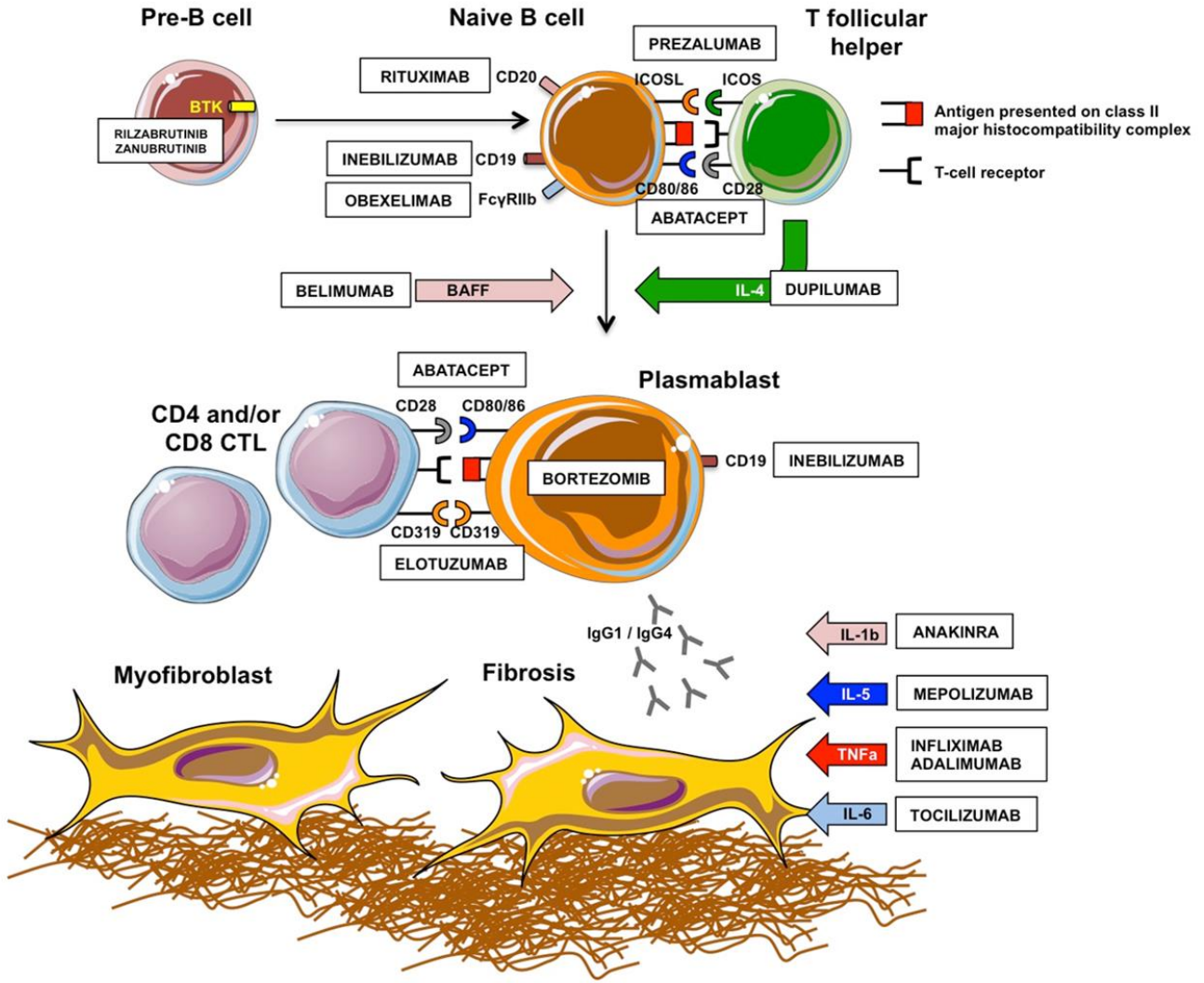
Ttt d'entretien par RTX

Ebbo et al, PLoS ONE 2017

Traitement


Diagnostic de maladie associée aux IgG4
Patient peu symptomatique ou asymptomatique sans mise en jeu du pronostic fonctionnel ?
(atteinte salivaire ou ganglionnaire isolée par ex)
Oui
Abstention thérapeutique
« Wait and watch »
1
Non (= risque de dysfonction d'organe)
Atteinte(s) d'organe(s) sévère(s)* ?
et/ou facteurs de risque de rechute** ?
Oui
+ hydronéphrose ou atteinte VBP sévère
Sonde JJ
Prothèse biliaire
+
Non
Oui
2
Corticothérapie (CTC)
Traitement d'attaque 0,4 à 0,6 mg/kg/j 3 à 4 semaines
Corticothérapie (CTC)
Traitement d'attaque 0,4 à 0,6 mg/kg/j *** 3 à 4 semaines
+ association à un ttt de prévention des rechutes :
- Rituximab****
OU - IS « conventionnel » (aza, MMF, MTX)
3
4
Reconsidérer le diagnostic :
biopsie / re-biopsie
Si MAG4 confirmée
Non
Non
Réponse ?
Réponse ?
Oui
Oui
Re CTC d'induction
+ Ajout ou switch d'IS
(RTX, aza, MMF, MTX, CYC)
Décroissance progressive de la CTC
sur 3 à 6 mois puis arrêt
Décroissance progressive de la CTC
sur 3 à 6 mois puis arrêt ou maintien ≤7,5 mg/j
Oui
Oui
Rechute ?
Rechute ?
Non
Non
Suivi clinique / bio +/- imagerie
Poursuite du ttt d'entretien 2 à 3 ans
?

Traitement


Pre-B cell
Naive B cell
T follicular helper
BTK
RILZABRUTINIB
ZANUBRUTINIB
RITUXIMAB
CD20
INEBILIZUMAB
CD19
OBEXELIMAB
FcγRIIb
PREZALUMAB
ICOSL
ICOS
CD80/86
CD28
ABATACEPT
Antigen presented on class II major histocompatibility complex
T-cell receptor
BELIMUMAB
BAFF
IL-4
DUPILUMAB
ABATACEPT
CD4 and/or CD8 CTL
CD28
CD80/86
Plasmablast
BORTEZOMIB
CD19
INEBILIZUMAB
CD319
CD319
ELOTUZUMAB
IgG1 / IgG4
Myofibroblast
Fibrosis
IL-1b
ANAKINRA
IL-5
MEPOLIZUMAB
TNFa
INFLIXIMAB
ADALIMUMAB
IL-6
TOCILIZUMAB

Traitement

Table 1. Novel targeted therapies for IgG4-related disease.

B cells		
Drug	Target and effect	Reference
Obexelimab	CD19: depletion of plasma cells and plasmablasts	[111]ClinicalTrials.gov: NCT02725476
Inebilizumab	CD19: depletion of plasma cells and plasmablasts	[112]ClinicalTrials.gov: NCT04540497
Rilzabrutinib	BTK: hindering of B cell maturation	[113]ClinicalTrials.gov: NCT04520451
Zanubrutinib	BTK: hindering of B cell maturation	[114]ClinicalTrials.gov: NCT04602598
Belimumab	BAFF: hindering of germinal center formation and IgG4 class switch; induction of B cell apoptosis	[116]ClinicalTrials.gov: NCT04660565
T cells		
Drug	Target and effect	Reference
Elotuzumab	SLAM-7: depletion of CTLs and plasma cells through the activation of NK cells	[117]ClinicalTrials.gov: NCT04918147
Abatacept	CD80/CD86 on APCs (analogue of CTLA4): hindering of the interaction with the costimulatory molecule CD28 expressed by T lymphocytes, thus preventing maturation of naive CD4+ T lymphocytes into T_{FH} cells	[118]
Cytokines or their receptors		
Drug	Target and effect	Reference
Dupilumab	IL4-Rα: inhibition of both IL4 and IL13 cascades	[119,120]
Infliximab	TNF: inhibition of the TNF cascade	[121–123]

Note: BAFF: B cell-activating factor; SLAM-7: signaling lymphocytic activation molecule 7; CTLs: cytotoxic T lymphocytes; APCs: antigen-presenting cells; T_{FH}: T follicular helper; TNF: tumoral necrosis factor.

En conclusion

A évoquer souvent mais à diagnostiquer prudemment !

Pathologie multidisciplinaire

Pas d’urgence a traiter le plus souvent

Risque de rechutes +++

Nécessité d’avoir une épargne cortisonique