Manifestations Ophtalmologiques du Syndrome Hyper IgG4

3ème Journée du Club Médecine Interne et Œil :
Inflammation Oculaire et Médecine Interne

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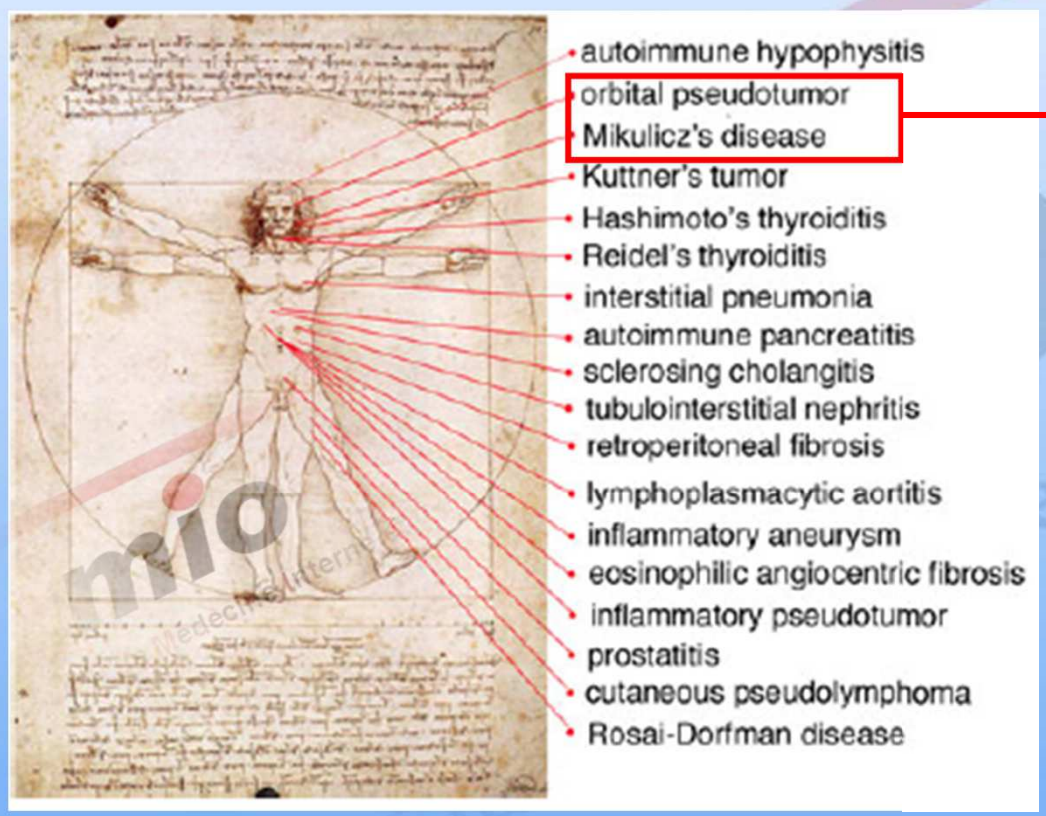
3ème journée du CMIO: 18/09/2015

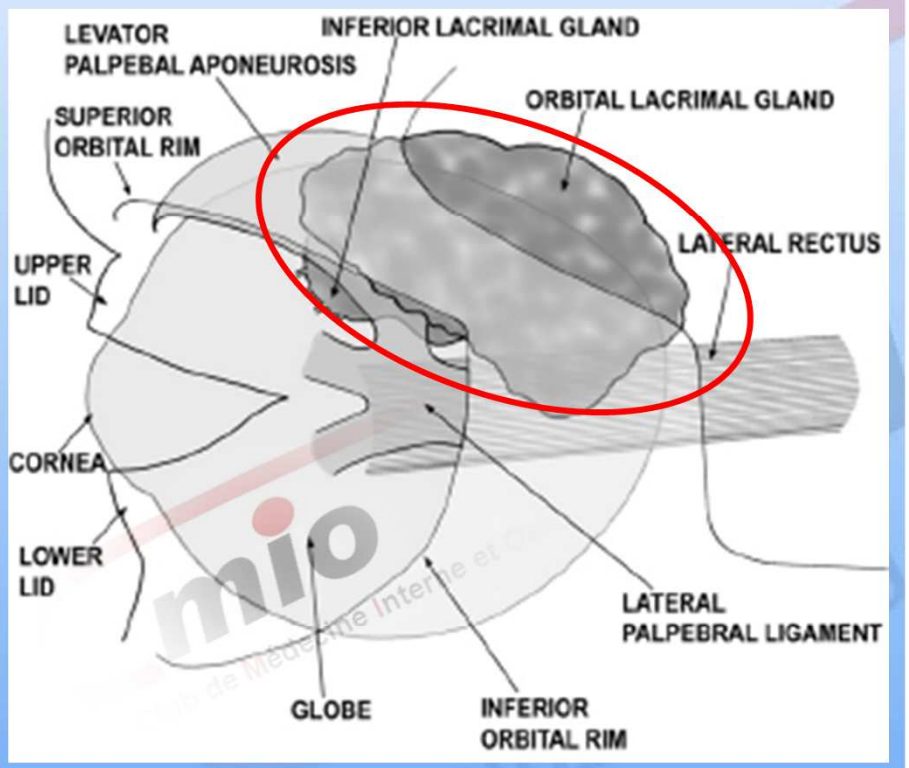
IgG4-related disease

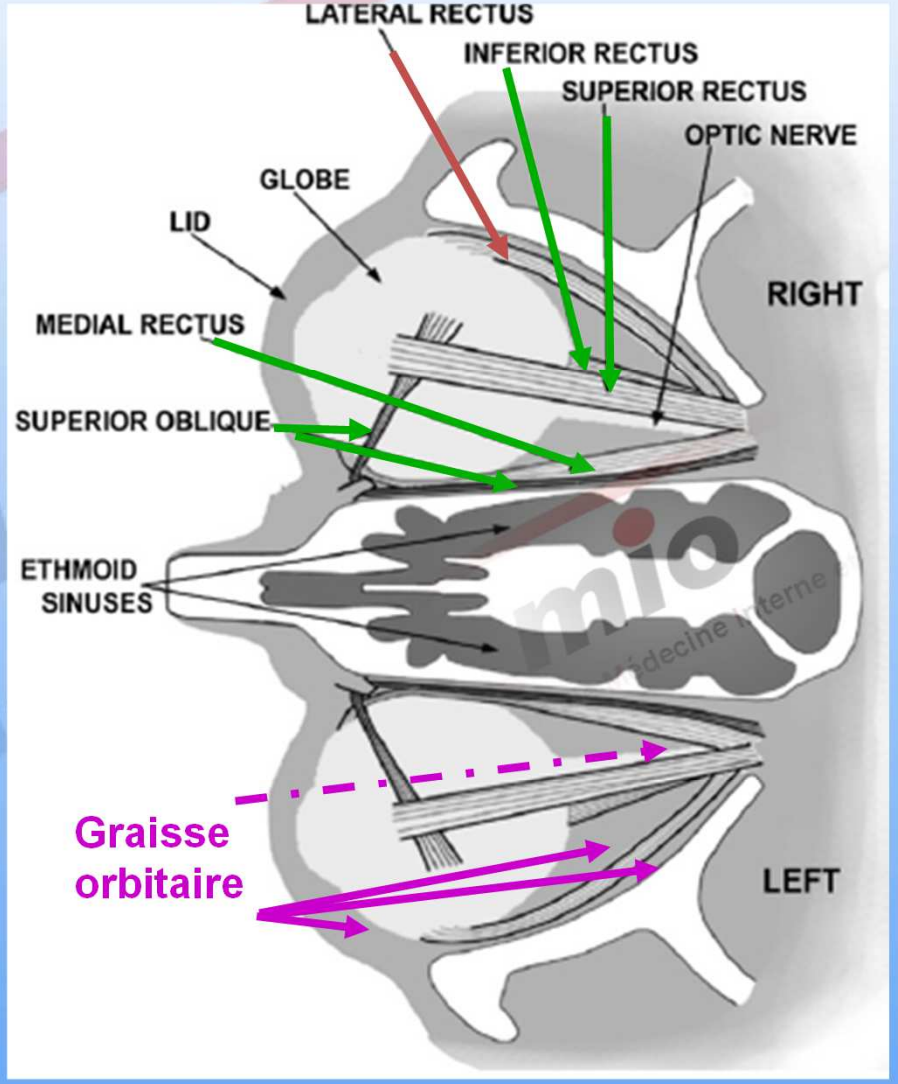
Stone JH et al. Arthritis Rheum 2012;64:3061–3067



→ Orbitopathies +++

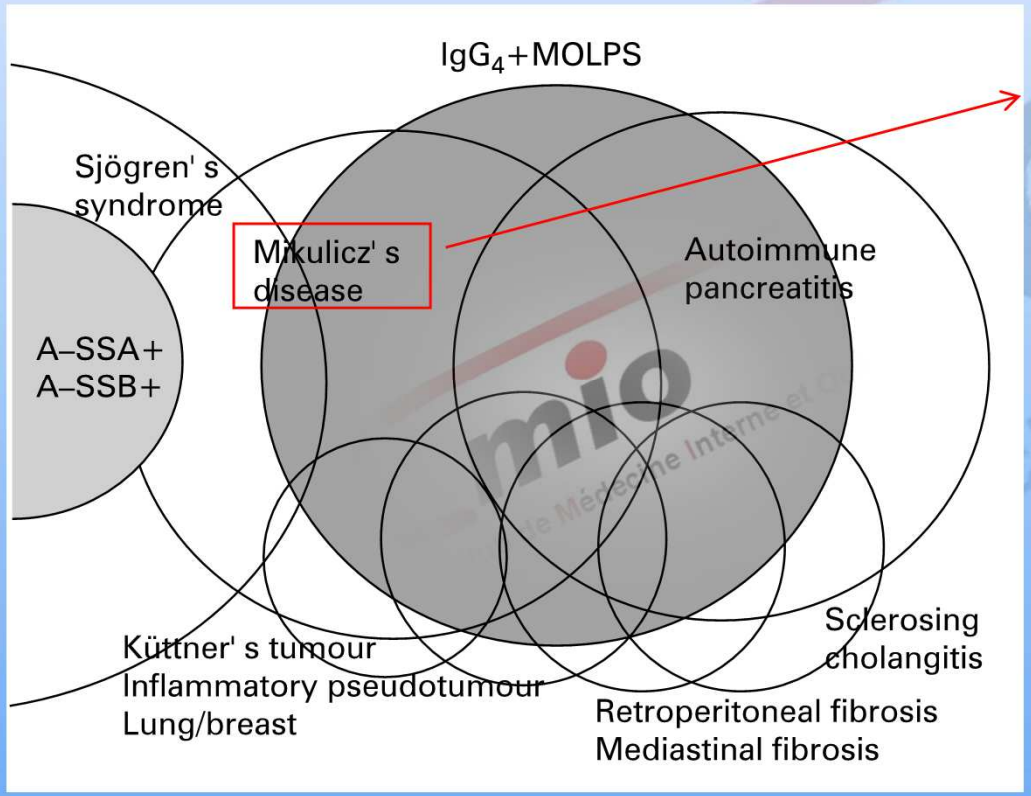
Structures orbitaires et annexes





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

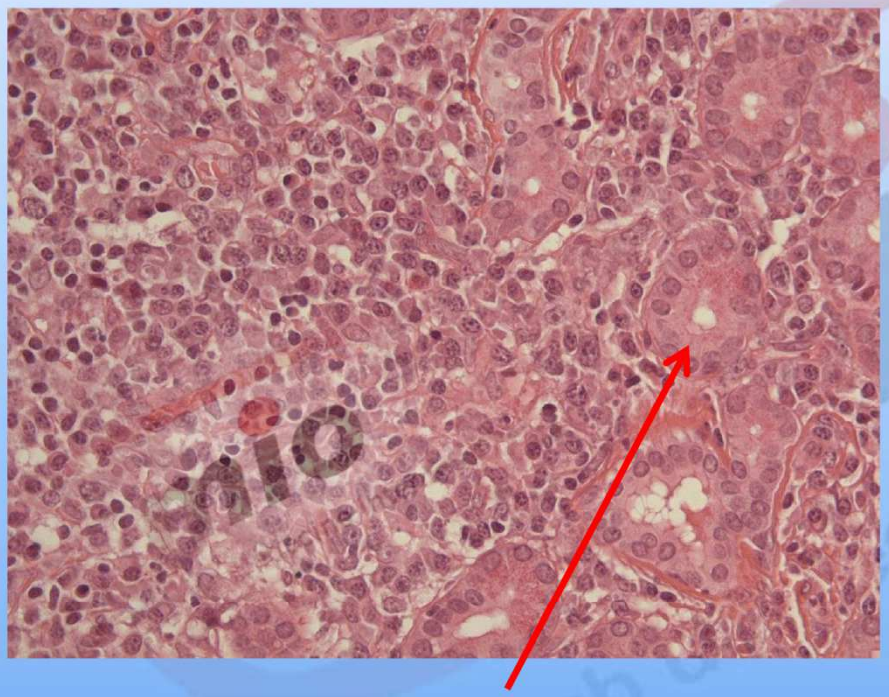
Masaki et al. Ann Rheum Dis 2009

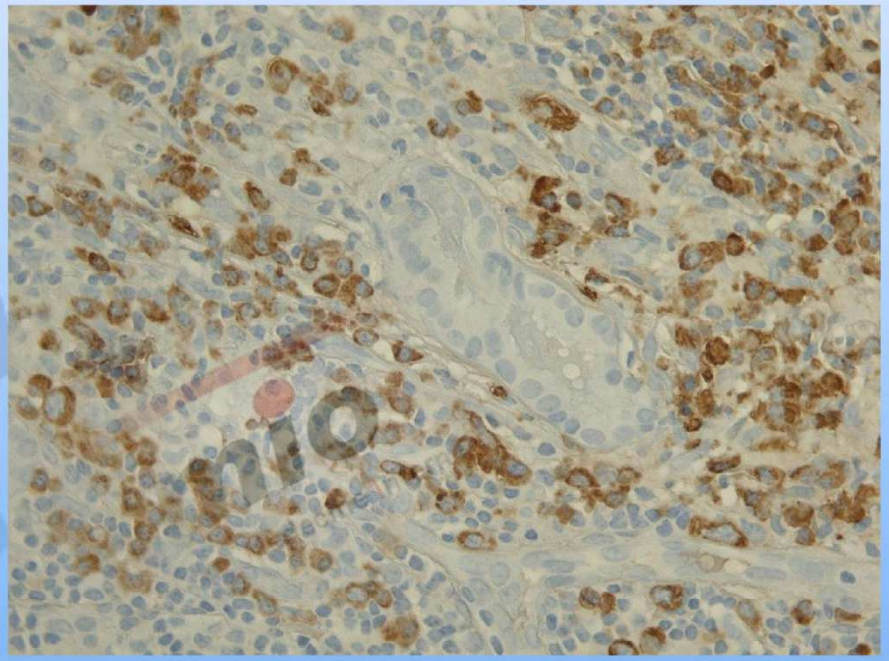


In 1888, Johann von Mikulicz-Radecki reported a man with symmetrical swelling of the lacrimal, submandibular and parotid glands of unknown aetiology.[1] Histologically, the swollen glands showed massive mononuclear cell infiltration,

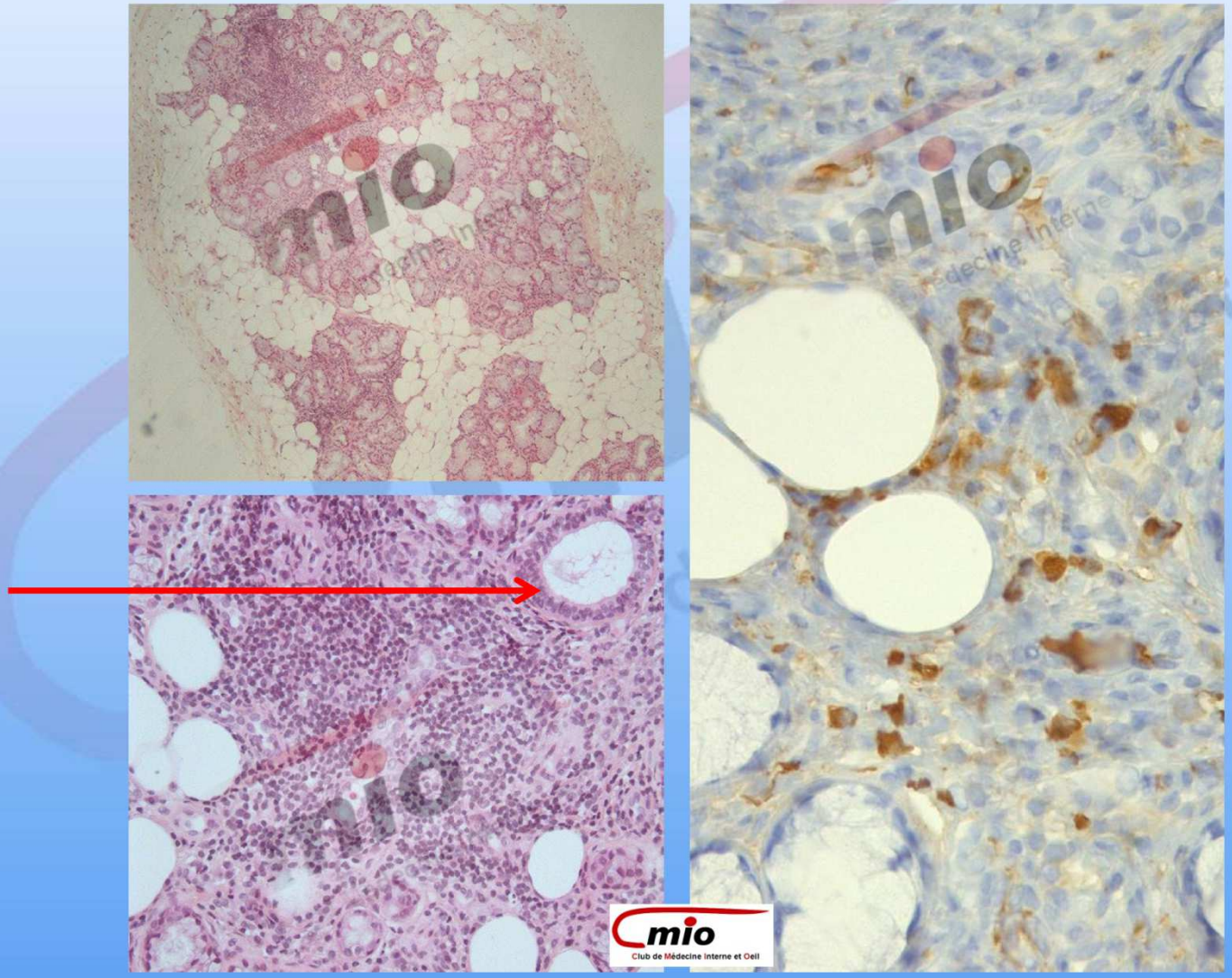
1/ Histologie:
- **Lympho-plasmocytes IgG4** (IgG4/IgG total plasma cells > 50%)
- Fibrose/ sclérose tissulaire

Glandes Lacrymales

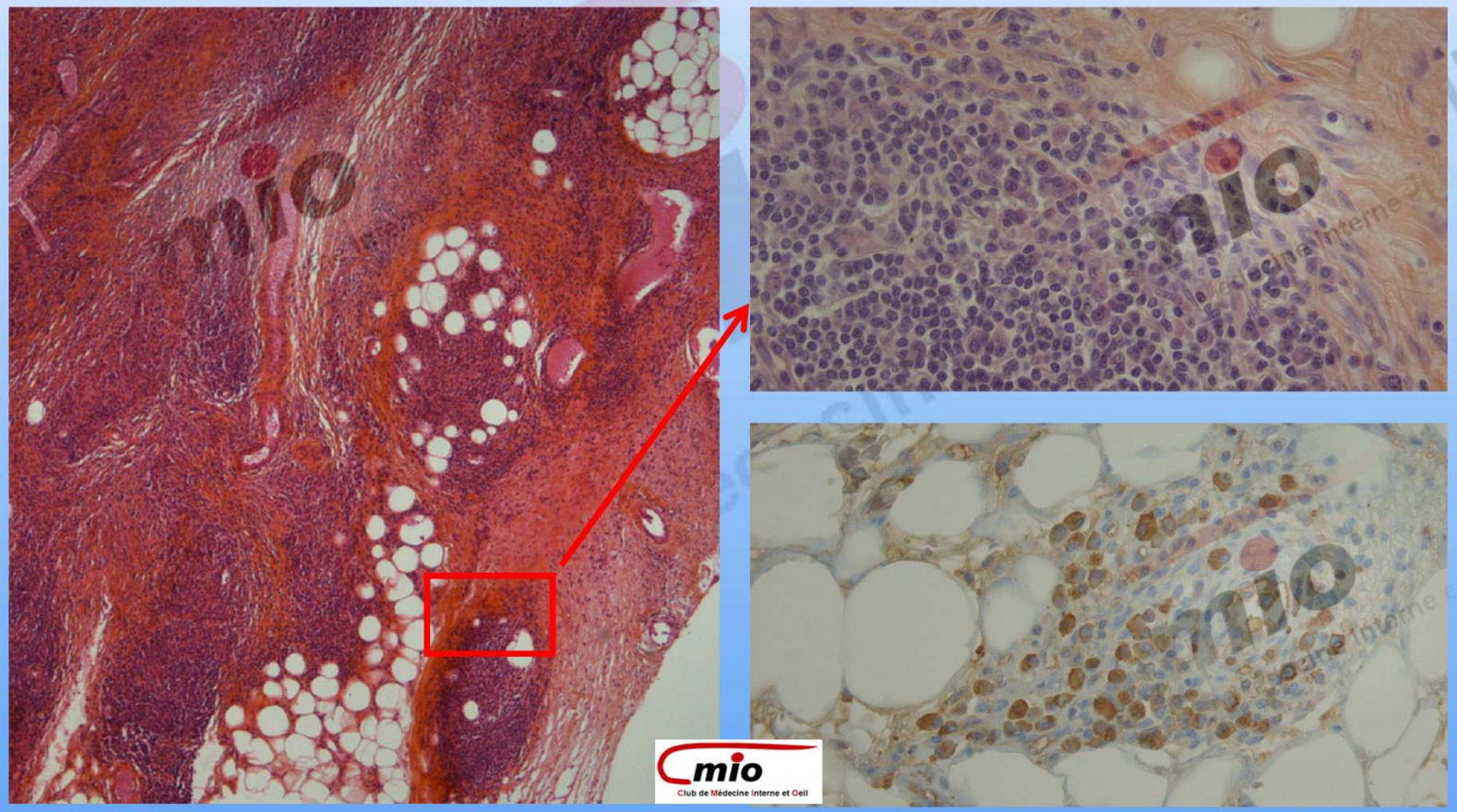




Glandes Salivaires



Orbite



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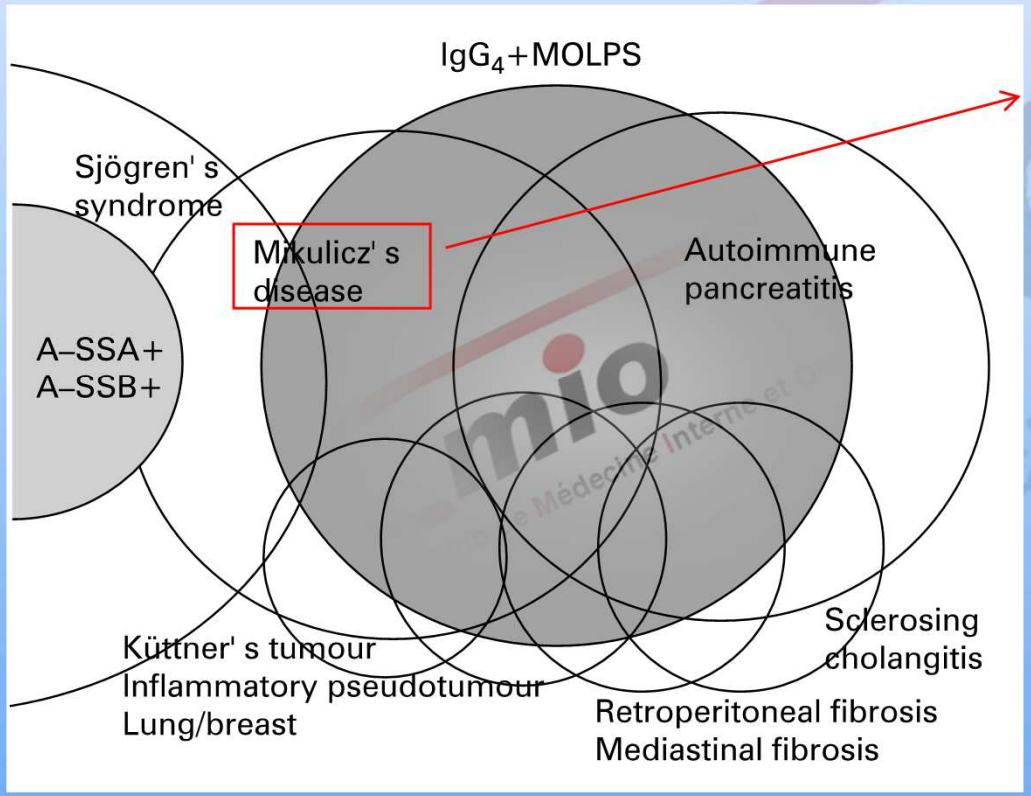

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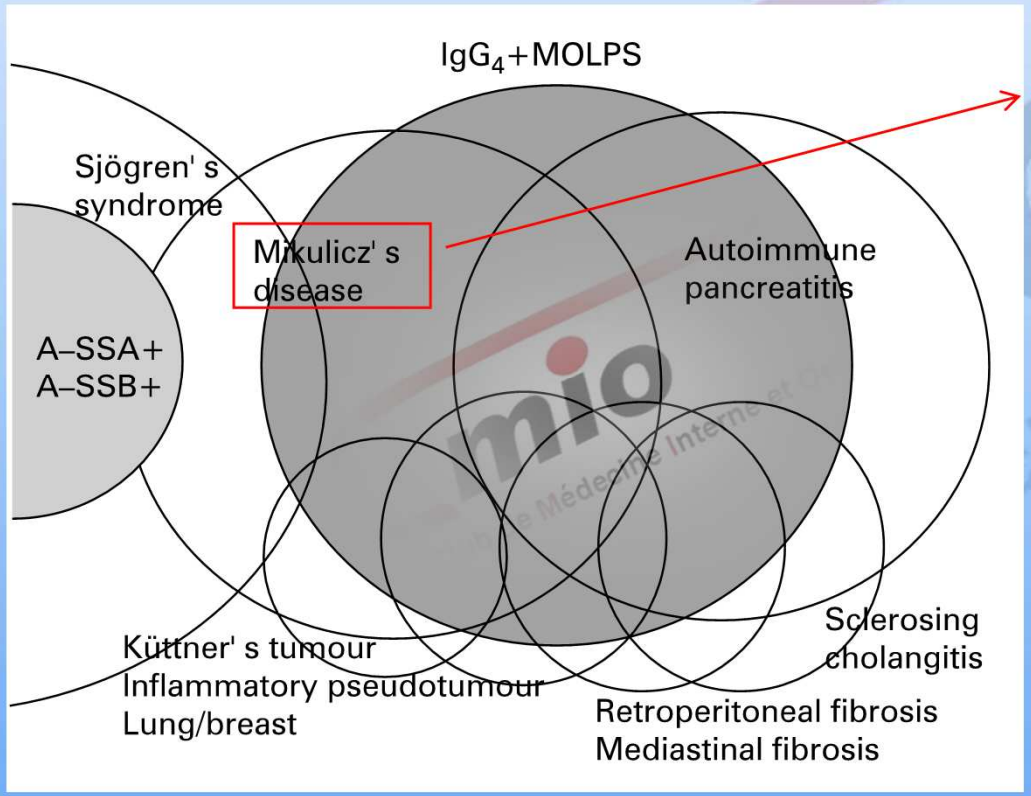

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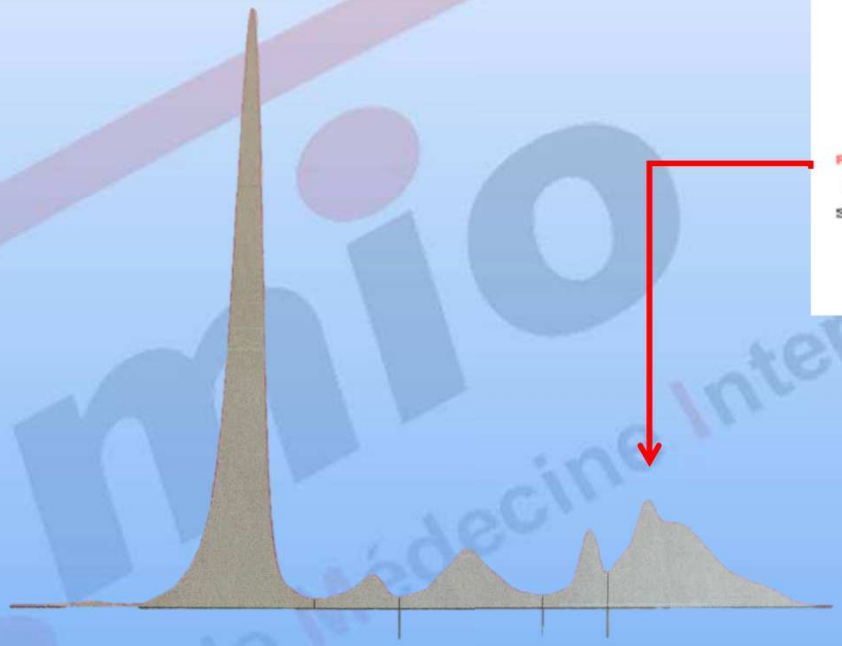
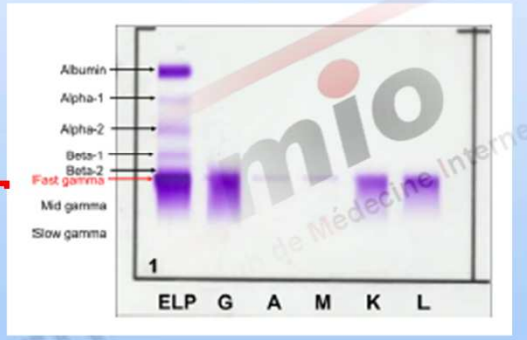
2/ **IgG4 sérique > 135 mg/l**

IgG4



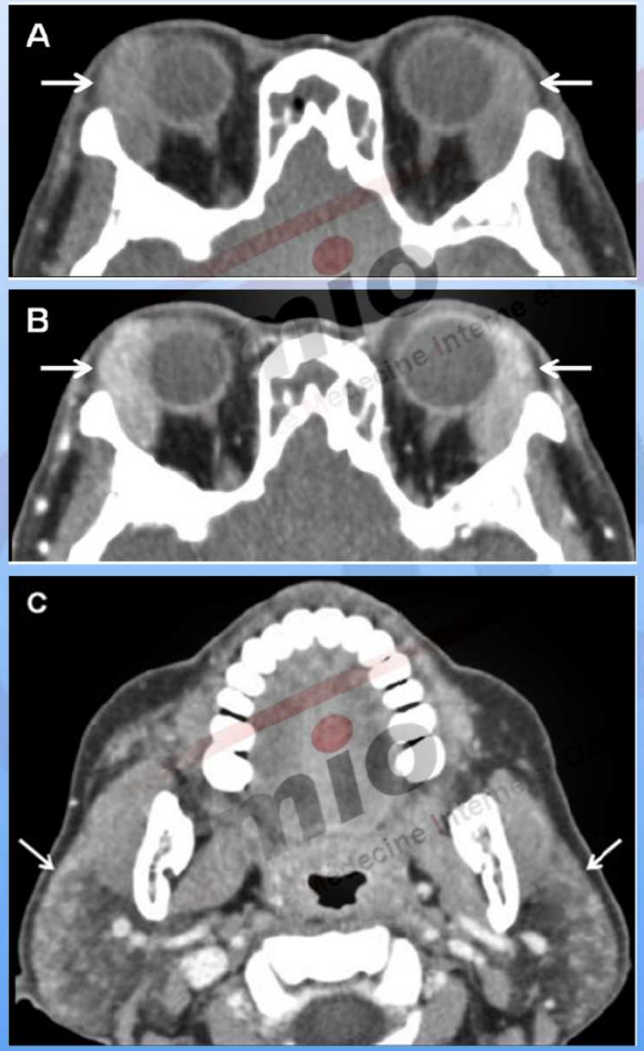


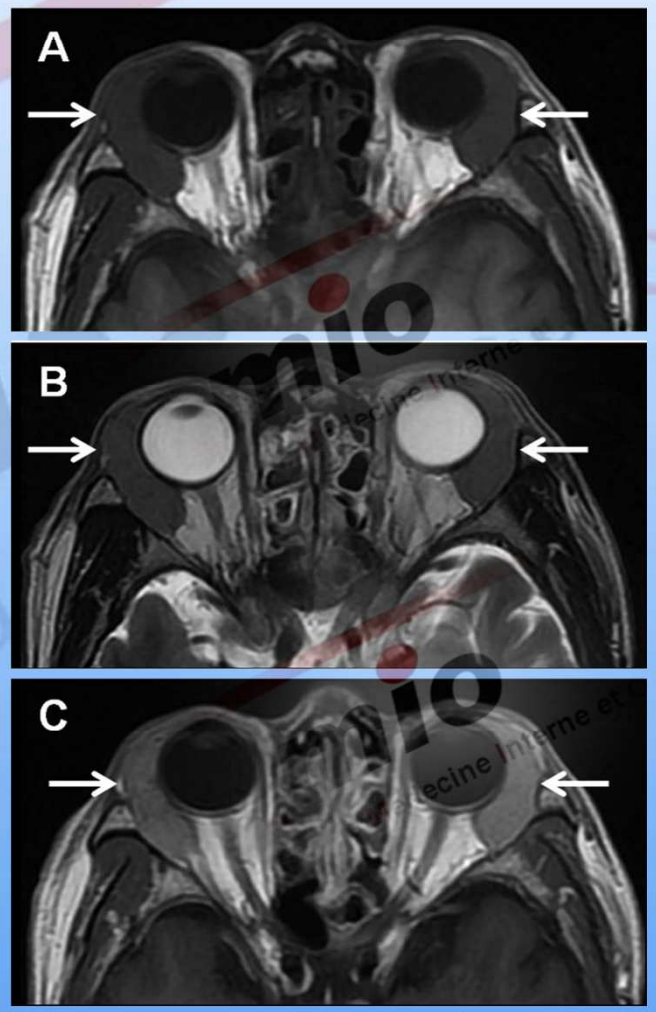
Nom	%	Normales %	g/l	Normales g/l
Albumine	56,2	55,8 - 66,1	42,2	40,2 - 47,6
Alpha 1	3,6	2,9 - 4,9	2,7	2,1 - 3,5
Alpha 2	10,0	7,1 - 11,8	7,5	5,1 - 8,5
Beta 1	5,8	8,4 - 13,1	4,4 <	6,0 - 9,4
Bet2+Gam	24,4	11,1 - 18,8	18,3 >	8,0 - 13,5

Chen L et al. Clinical Case Report 2015

Ocular adnexal IgG4-related disease: CT and MRI findings

Yong Sub Song,[1] Ho-Kyung Choung,[2,3] Sun-Won Park,[1,4] Ji-Hoon Kim,[1] Sang In Khwarg,[3] Yoon Kyung Jeon[5]





Song YS, *et al. Br J Ophthalmol* 2013;**97**:412–418.

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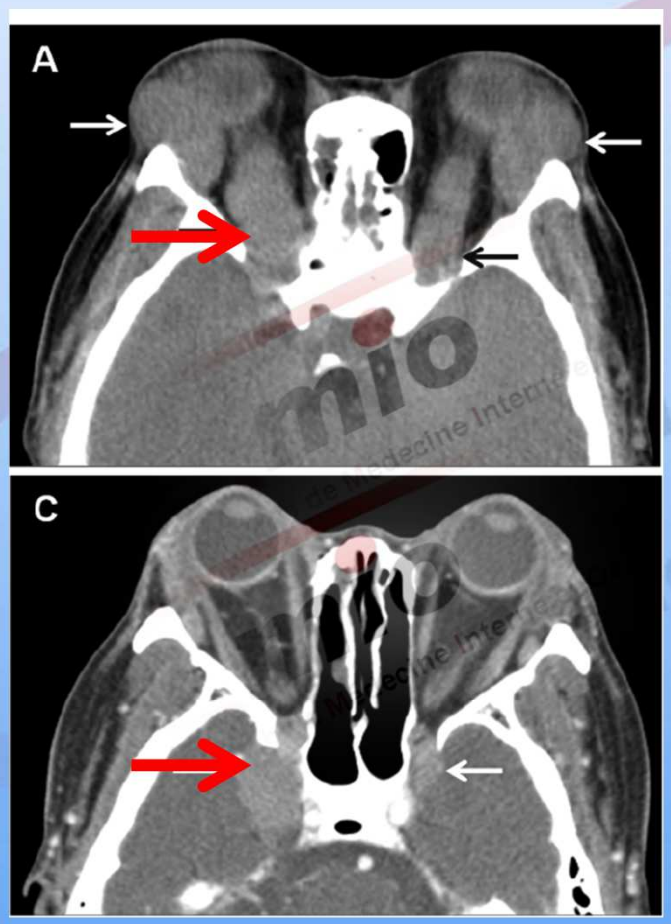

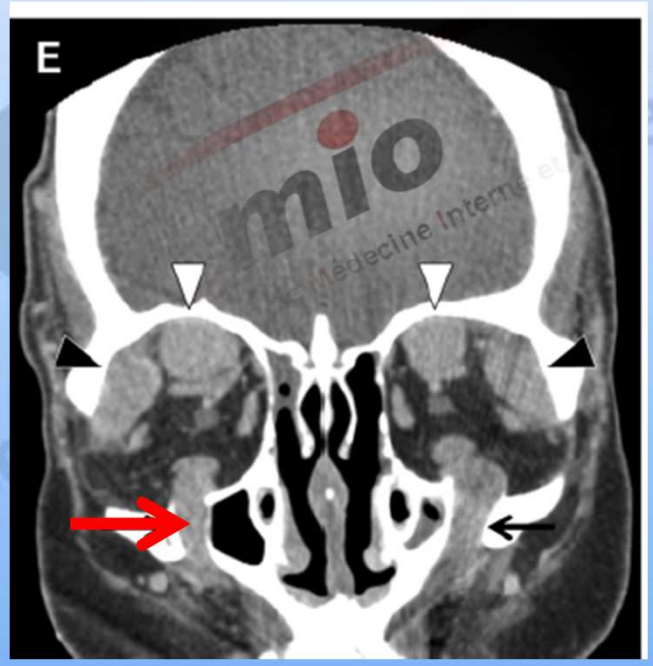

Song YS, *et al*. *Br J Ophthalmol* 2013;**97**:412–418.

Comprehensive clinical criteria for IgG4-RD

★ (1) Clinical examination shows characteristic diffuse/localized swelling or masses in single or multiple organs.
(2) Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dL).
(3) Histopathologic examination shows;
(1) marked lymphocyte and plasmacyte infiltration and fibrosis
(2) infiltration of IgG4-positive plasma cells: ratio of IgG4/IgG positive cells > 40% and > 10 IgG4-positive plasma cells/HPF.
Definite: (1) + (2) + (3), Probable: (1) + (3), Possible: (1) + (2)

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome) by additional histopathological examination. Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4RD.

Okazaki K et Umehara H. Int J Rheumatol. 2012

Orbitopathies IgG4 et IOI ?

TABLE 2. Organ Involvement of Patients With IgG4-RSD

Organ Involvement	No. (%) (n = 25)
Adenopathy	19 (76)
Sclerosing pancreatitis	13 (52)
Sialadenitis	11 (44)
Interstitial nephritis	11 (44)
Sclerosing cholangitis	8 (32)
Retroperitoneal fibrosis	8 (32)
Aortic involvement	6 (24)
Abdominal aorta	6 (24)
Thoracic aorta	3 (12)
Dacryoadenitis	3 (12)
Interstitial pneumonitis	3 (12)
Hypophysitis	2 (8)
Inflammatory pseudotumor	4 (16)
Orbital	1 (4)
Hepatic	2 (8)
Meningeal	1 (4)

Ebbo M et al. Medicine 2012

High prevalence of IgG4-related lymphoplasmacytic infiltrative disorder in 25 patients with orbital inflammation: a retrospective case series

Romain Deschamps,[1] Lydia Deschamps,[2] Raphael Depaz,[1] Sophie Coffin-Pichonnet,[3] Georges Belange,[4] Pierre Vincent Jacomet,[3] Catherine Vignal,[3] Paul Benillouche,[3] Marie Laure Herdan,[3] Marc Putterman,[5] Anne Couvelard,[2] Olivier Gout,[1] Olivier Galatoire[3]

Br J Ophthalmol 2013;**97**:999–1004. doi:10.1136/bjophthalmol-2013-303131

Table 2 Histomorphologic findings from biopsy specimens for IgG4-positive and IgG4-negative patients

Patient	Background fibrosis	Follicular hyperplasia	Phlebitis	Plasmacytic infiltrate	Lymphocytic infiltrate	Eosinop
IgG4 positive (n=10) (40%)						
1	3	1	0	3	2	0
2	3	0	1 (no obliterative)	3	1	0
3	3 (storiform)	3	1 (no obliterative)	3	3	1
4	3 (storiform)	3	1 (no obliterative)	3	3	0
5	3	3	0	3	2	0
6	2	1	1 (obliterative)	2	2	1
7	3	1	1 (no obliterative)	2	3	3
8	2	0	0	2	3	1
9	3	0	0	1	1	0
10	1	1	0	1	2	1
IgG4 negative (n=15)						
11	3	3	0	2	2	3
12	3	0	0	2	2	0
13	1	0	0	1	2	0
14	2	1	0	2	2	1
15	1	1	0	0	2	0
16	0	1	0	1	2	0
17	0	0	0	0	1	0
18	2	0	0	0	1	0
19	0	0	0	1	1	0
20	1	0	0	0	1	0
21	2	0	0	0	1	0
22	0	0	0	0	1	0
23	2	0	0	0	2	0
24	1	0	0	0	1	0
25	2	0	0	0	1	0

Critères Umehara

- Lympho-plasmocytes IgG4 (**> 10/ HpF et IgG4/IgG total plasma cells > 50%)**
- Fibrose (Storiforme)
- IgG4 sérique > 135 mg/l
- Eliminer diagnostics différentiels

Okazaki K et Umehara H. Int J Rheumatol. 2012

Clinical science

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Table 1 Clinical and radiographic data for IgG4-positive and IgG4-negative patients

Patient/ sex/age	Location	Pain	Eyelid or periocular swelling/mass	Other clinical history
IgG4 positive (n=10) (40%)				
1/F/31	LG, EOM, orb	Yes	Yes	Iodine allergy
2/F/81	LG	No	Yes	Breast carcinoma, pacemaker
3/M/40	Orb, ON	No	Yes	Malaria
4/F/57	LG, EOM, orb, ON	Yes	Yes	Ovarian cystectomy, eczema,chronic urticaria
5/F/52	Orb, LG	Yes	Yes	Retinal detachment
6/F/65	Orb, EOM,ON	No	Yes	Nephritis, bladder carcinoma, diabetes mellitus
7/F/28	LG, orb, apex, EOM	No	Yes	Asthma; recurrent sinusitis; left optic neuritis 1 and 4 years earlier
8/M/55	LG	No	Yes	Iodine allergy, bronchomediastinal lymphadenopathy
9/M/26	LG	No	Yes	
10/F/62	LG	No	Yes	Thyroidectomy
IgG4 negative (n=15)				
11/F/20	Orb	Yes	Yes	
12/F/26	LG	Yes	Yes	
13/F/32	LG	No	Yes	
14/M/83	Orb	No	Yes	Diabetes mellitus, pacemaker, hypertension
15/F/53	LG	No	Yes	Diabetes mellitus
16/F/53	LG, orb, ON	No	No	Hypertension, Hashimoto thyroiditis, collagenous colitis
17/M/20	LG, orb, ON	Yes	Yes	
18/F/43	EOM	Yes	Yes	
19/F/34	LG	No	Yes	
20/M/35	Orb, EOM, LG	No	Yes	Epilepsy
21/F/21	LG	No	Yes	Recurrent sinusitis
22/F/54	LG, EOM, ON	No	Yes	Myocardial infarction
23/M/53	Orb, ON	No	Yes	Amblyopia
24/F/58	Orb, apex, EOM, ON	Yes	No	Recurrent sinusitis, hearing loss 1 year earlier
25/M/65	Orb, Cav, ON, EOM, LG	No	Yes	

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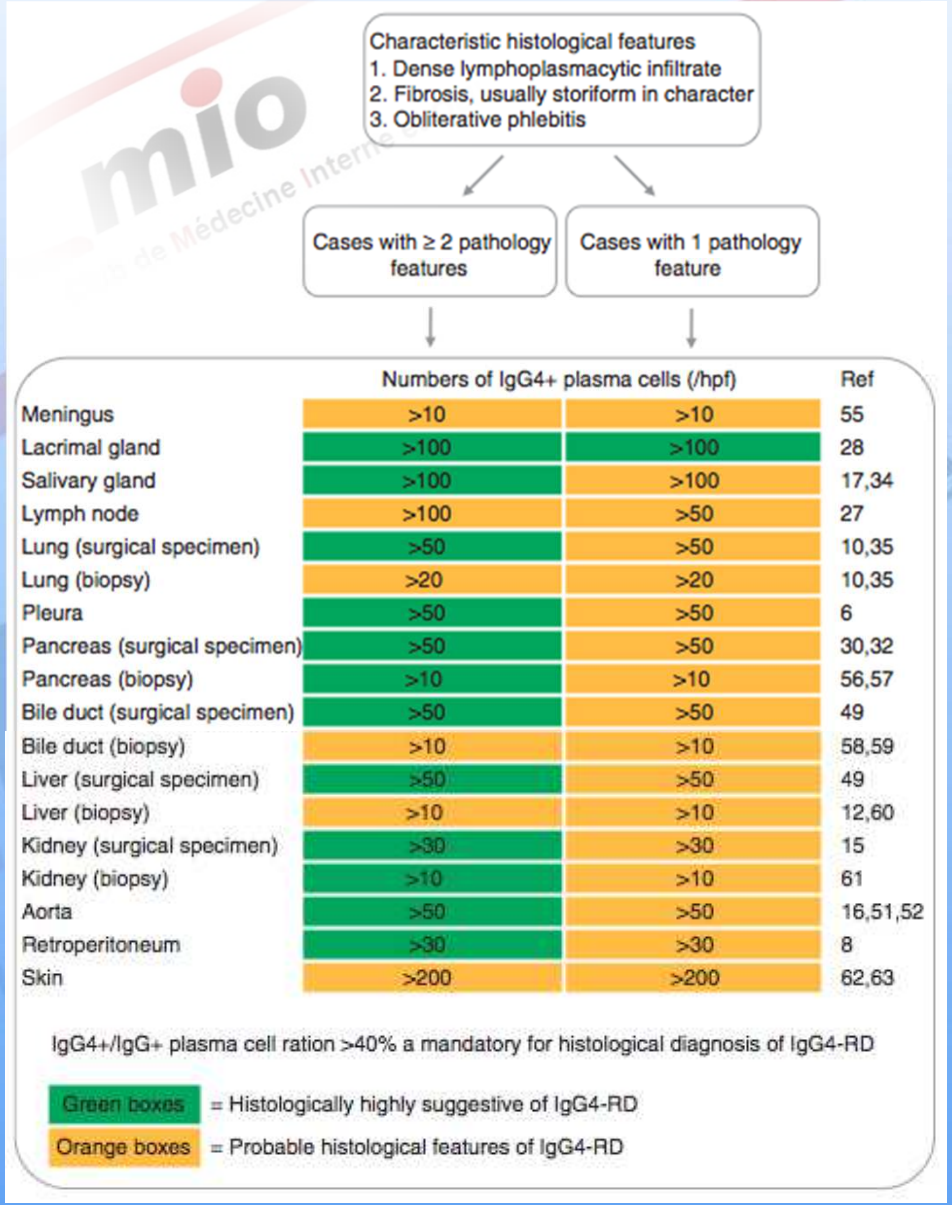
Okazaki K et Umehara H. Int J Rheumatol. 2012

Consensus statement on the pathology of IgG4-related disease

Deshpande V et al. Modern Pathology 2012



	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

An analysis of IgG4-related disease (IgG4-RD) among idiopathic orbital inflammations and benign lymphoid hyperplasias using two consensus-based diagnostic criteria for IgG4-RD

Nicholas H Andrew,[1] Nicole Sladden,[2] Daniel J Kearney,[2] Dinesh Selva[1]

Table 1 Proportion of cases assigned a diagnosis of IgG4-related orbital disease (ROD)

	Comprehensive diagnostic criteria, Umehara *et al*[15]		Consensus diagnostic criteria, Deshpande *et al*[16]	
Original pathological diagnosis	**IgG4-ROD cases (%)**	**95% CI**	**IgG4-ROD cases (%)**	**95% CI**
IOI (55 cases)	13 (23.6%)	12.4% to 34.8%	3 (5.4%)	−0.57% to 11.4%
OBLH (10 cases)	5 (50%)	19.0% to 81.0%	4 (40%)	9.6% to 70.3%

IOI, idiopathic orbital inflammation; OBLH, orbital benign lymphoid hyperplasia.

Table 2 Comparison of IgG4-related orbital disease (ROD) and non-IgG4-ROD cases: histopathology

	Comprehensive diagnostic criteria, Umehara *et al*[15] (IgG4+/HPF >10, IgG4 to IgG >40%)				Consensus diagnostic criteria, Deshpande *et al*[16] (IgG4+/HPF >100, IgG4 to IgG >40%)				IgG4-related disease (IgG4-RD) (comprehensive vs. consensus)
	IgG4-RD (18)	**Non-IgG4-RD (47)**	**p Value**	**95% CI***	**IgG4-RD (7)**	**Non-IgG4-RD (58)**	**p Value**	**95% CI***	**p Value (95% CI*)**
IgG4+/HPF: mean (SD)	110.2 (103.5)	6.4 (8.5)	0.0006	52.26 to 155.34	221.7 (76.4)	12.6 (17.4)	0.0004	138.2 to 280.1	0.01 (30.4 to 192)
IgG4+ to IgG+: mean (SD)	0.75 (0.24)	0.061 (0.11)	<0.0001	0.57 to 0.81	0.91 (0.11)	0.16 (0.25)	<0.0001	0.64 to 0.87	0.01 (0.04 to 0.4)
Lymphoplasmacytic infiltration: mean (SD)	2.3 (0.57)	1.8 (0.79)	0.03	0.14 to 0.86	2.6 (0.52)	1.8 (0.78)	0.004	0.47 to 1.4	0.1
Sclerosis: mean (SD)	2.5 (0.79)	1.8 (0.95)	0.01	0.23 to 1.17	1.9 (0.90)	2.1 (0.96)	0.6		0.1
Sclerosis: storiform	5.6%	4.7%	1.0		0%	5.2%	1.0		1.0
Eosinophilic infiltration: mean (SD)	1.7 (0.84)	0.65 (0.85)	0.002	0.57 to 1.5	1.6 (0.79)	0.85 (0.95)	0.06		0.9
Obliterative phlebitis	0%	0%	1.0		0%	0%	1.0		1.0
Lymphoepithelial lesions present	17%	28%	0.5		29%	24%	1.0		0.6
Germinal centre formation present	44%	10.6%	0.005	1.57 to 11.1	71%	14%	0.002	2.3 to 11.5	0.4
Blood eosinophilia at the time of orbital biopsy	3.5%	2.1%	0.02	1.25 to 87.3*	43%	3.5%	0.008	2.4 to 61	0.4
Precorticosteroid serum IgG4 measured	5 (28%)	10 (21%)	0.7		1 (14%)	14 (24.6%)	0.7		
Elevated ≥1.35 mg/dL	2 (40%)	0 (0%)	0.1		1 (100%)	1 (7.1%)	0.1		1.0

*95% CI for the risk ratio (categorical variables) or for the difference between the means (continuous and interval variables).
HPF, high power field.

Andrew NH, *et al*. *Br J Ophthalmol* 2015;**99**:376–381

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- **Eliminer diagnostics différentiels**

Okazaki K et Umehara H. Int J Rheumatol. 2012

Panel 2: **Differential diagnosis of IgG4-related disease, by organ system**

Orbits and periorbital tissues
- Lymphoma
- Graves' orbitopathy
- Granulomatosis with polyangiitis
- Sarcoidosis

Ears, nose, and sinuses
- Allergic disease
- Churg-Strauss syndrome
- Granulomatosis with polyangiitis
- Sarcoma
- Chronic infection

Salivary glands
- Lymphoma
- Sjögren's syndrome
- Sarcoidosis
- Sialodocholithiasis

Meninges
- Idiopathic hypertrophic pachymeningitis
- Inflammatory myofibroblastic tumour
- Lymphoma
- Granulomatosis with polyangiitis
- Giant-cell arteritis
- Langerhans-cell histiocytosis
- Sarcoidosis

Pituitary
- Neoplasms
- Histiocytosis
- Primary hypophysitis
- Secondary hypophysitis (sarcoidosis, ipilimumab-induced)

Lymph nodes
- Multicentric Castleman's disease
- Lymphoma
- Sarcoidosis
- Systemic lupus erythematosus

Thyroid gland
- Thyroid lymphoma
- Differentiated thyroid carcinoma (papillary variant)
- Other malignant disease

Lungs
- Malignancy (adenocarcinoma or bronchioloalveolar carcinoma)
- Inflammatory myofibroblastic tumour
- Sarcoidosis
- Granulomatosis with polyangiitis
- Castleman's disease
- Lymphomatoid granulomatosis
- Idiopathic interstitial pneumonitis
- Erdheim-Chester disease

Aorta
- Primary large-vessel vasculitis (giant-cell or Takayasu's arteritis)
- Sarcoidosis
- Erdheim-Chester disease
- Histiocytosis
- Lymphoma
- Infectious aortitis

Retroperitoneum
- Lymphoma
- Sarcoma
- Methysergide-induced retroperitoneal fibrosis
- Idiopathic retroperitoneal fibrosis

Kidney
- Lymphoma
- Renal-cell carcinoma
- Drug-induced tubulointerstitial nephritis
- Idiopathic membranous glomerulonephritis
- Pauci-immune, necrotising glomerulonephritis
- Sarcoidosis
- Sjögren's syndrome
- Systemic lupus erythematosus (membranous nephropathy)

Pancreas
- Pancreatic cancer

Biliary tree
- Pancreatic cancer
- Cholangiocarcinoma
- Primary sclerosing cholangitis

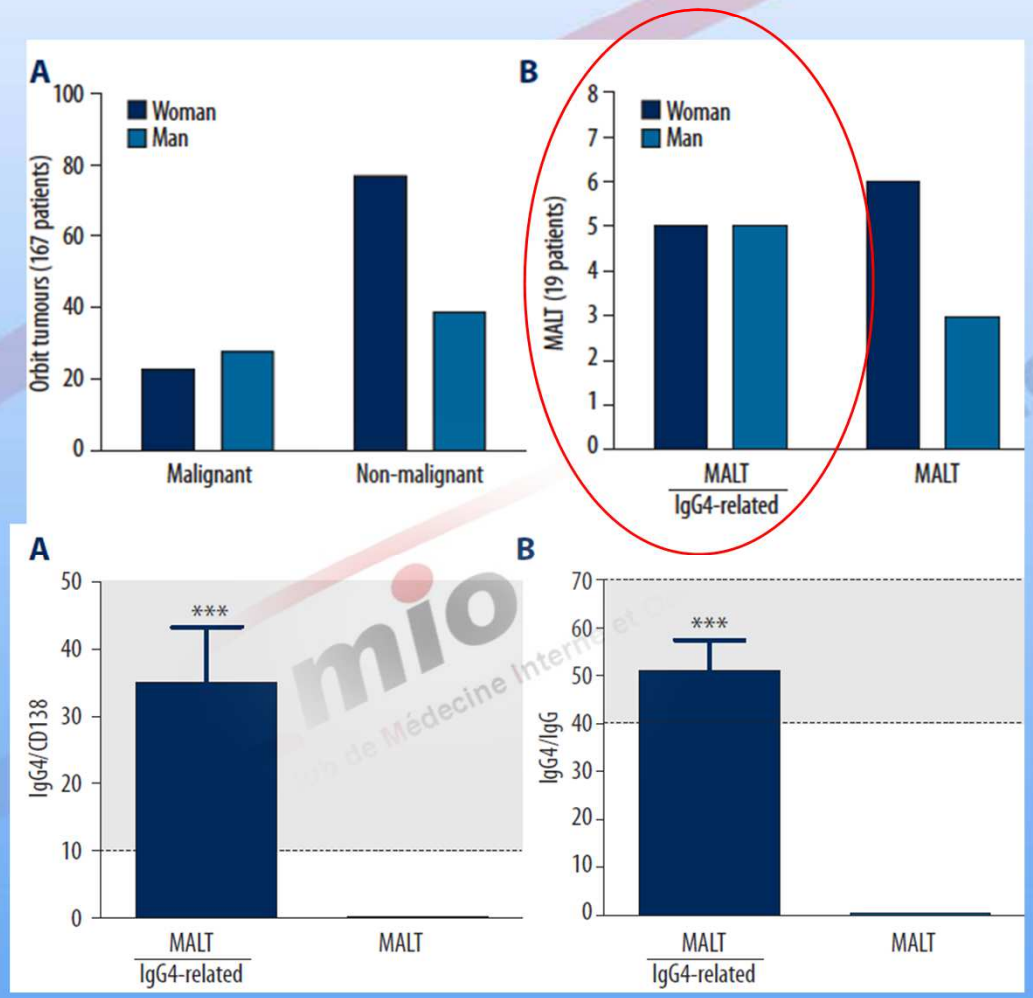
Liver
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Primary sclerosing cholangitis

Prostate
- Benign prostatic hypertrophy

Skin
- Cutaneous lymphoma

Kamisawa T et al. Lancet 2015

Immunoglobulin G4-Related Disease (IgG4-RD) in the Orbit: Mucosa-Associated Lymphoid Tissue (MALT)-Type Lymphomas



Oles K et al. Med Sci Monit 2015

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PLOS ONE

IgG4 Immunostaining and Its Implications in Orbital Inflammatory Disease

Table 2. A minority of subjects with inflamed orbits have markedly high IgG4+PC counts.

	IgG4+ PC/hpf				IgG4+ PC/hpf >30 and IgG4+PC/IgG+PC ≥0.4
	<10	10–29	30–99	≥100	
Lacrimal Gland	-	+	++	+++	
Control	7	-	-	-	-
TED	4	-	-	-	-
NSOI	15	4	2	1	1
Sarcoidosis	3	3	1	-	-
Orbital fat					
Control	15	-	-	-	-
TED	25	-	-	-	-
GPA	1	1	3	1	4
NSOI	11	2	5	2	2
Sarcoidosis	5	1	-	-	-

The number of subjects in each category is shown.

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Wong AJ et al. PloS One 2014

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IgG4 Immunostaining and Its Implications in Orbital Inflammatory Disease

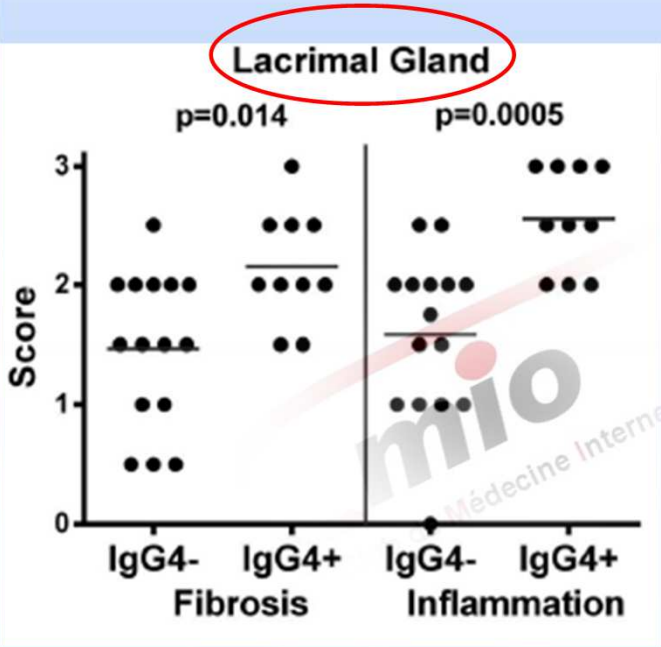

Table 5. Examples of gene expression differences comparing IgG4+ to IgG4- lacrimal gland tissue from subjects with NSOI, GPA, or sarcoidosis.

Probe sets with increased levels					
Probe Set	**Gene Symbol**	**FC**	**FDR p value**	**Gene Title**	**Gene Ontology Biological Process**
228599_at	MS4A1	3.51	0.004	Membrane-spanning 4-domains, A1	B cell activation
221969_at	PAX5	3.48	0.005	Paired box 5	Regulation of transcription
217422_s_at 38521_at 204581_at	CD22	2.87 2.48 2.14	0.016 0.028 0.009	CD22 molecule	Cell adhesion
219014_at	PLAC8	2.83	0.030	Placenta-specific 8	Regulation of cell proliferation
209995_s_at	TCL1A	2.74	0.031	T-cell leukemia/lymphoma 1A	Multicellular organismal development
1558662_s_at 222915_s_at	BANK1	2.55 2.44	0.012 0.020	B-cell scaffold protein with ankyrin repeats 1	B cell activation
221601_s_at	FAIM3	2.37	0.023	Fas apoptotic inhibitory molecule 3	Regulation of apoptotic process
235400_at	FCRLA	2.37	0.017	Fc receptor-like A	Cell differentiation
1564310_a_at	PARP15	2.35	0.047	Poly (ADP-ribose) polymerase family, member 15	Regulation of transcription
205544_s_at	CR2	2.27	0.032	Complement component receptor 2	Complement receptor mediated signaling
35974_at 204674_at	LRMP	2.26 2.19	0.009 0.008	Lymphoid-restricted membrane protein	Veside targeting
211861_x_at	CD28	2.18	0.038	CD28 molecule	Inflammatory response to antigenic stimulus

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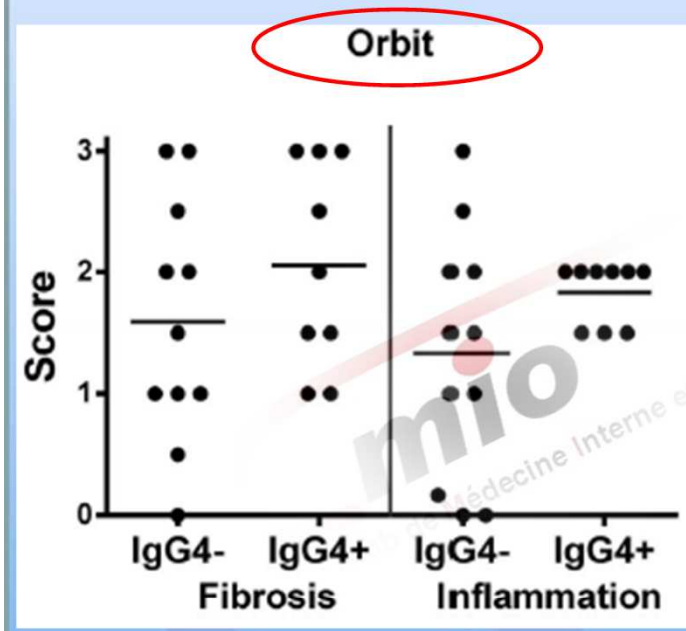

Table 4. Examples of gene expression differences comparing IgG4+ to IgG4- orbital tissue from subjects with NSOI, GPA, or sarcoidosis.

Probe Set	Gene Symbol	Fold Change	FDR P-value	Gene Title	A Gene Ontology Biological Process
Probe sets with increased levels					
211639_x_at	IGH; IGHA1; IGHA2; IGHD; IGHG1; IGHG3; IGHG4; IGHM; IGHV4-31	3.33	0.029	Immunoglobulin heavy locus	Immune response
216829_at	IGK; IGKC	3.06	0.013	Immunoglobulin kappa locus; immunoglobulin kappa constant	Immune response
205242_at	CXCL13	2.99	0.045	Chemokine (C-X-C motif) ligand 13	T and B cell chemotaxis
242020_s_at	ZBP1	2.80	0.048	Z-DNA binding protein 1	Positive regulation of type I interferon-mediated signaling pathway
234477_at	IGHA1; IGHV4-31	2.52	0.022	Immunoglobulin heavy constant alpha 1; immunoglobulin heavy variable 4-31	Immune response
205884_at	ITGA4	2.40	0.049	Integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	Cell adhesion
217227_x_at	IGLV1-44	2.40	0.039	Immunoglobulin lambda variable 1-44	Immune response
216541_x_at	IGHG1; IGHM	2.18	0.045	Immunoglobulin heavy constant gamma; immunoglobulin heavy constant mu	Immune response
211648_at	IGHG1; IGHM	1.98	0.034	Immunoglobulin heavy constant gamma 1; immunoglobulin heavy constant mu	Immune response
223565_at	MZB1	2.13	0.011	Marginal zone B and B1 cell-specific protein	Positive regulation of immunoglobulin biosynthetic process
204562_at	IRF4	2.08	0.026	Interferon regulatory factor 4	interferon-gamma-mediated signaling pathway
1558561_at	HM13	2.01	0.002	Histocompatibility (minor) 13	Proteolysis
208083_s_at	ITGB6	1.96	0.043	Integrin, beta 6	Cell adhesion
201688_s_at	TPD52	1.86	0.019	Tumor protein D52	B cell differentiation
225435_at	SSR1	1.86	0.020	Signal sequence receptor, alpha	Activation of signaling protein activity involved in unfolded protein response

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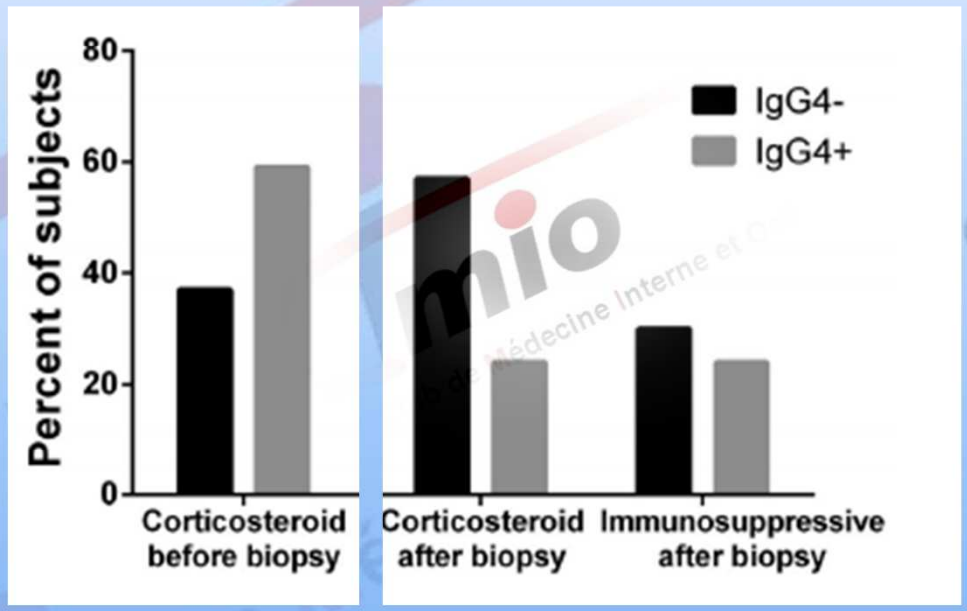

IgG4- 52,5±18,9 mg/day

IgG4+ 55,8±27,1 mg/day

NS

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Traitements ?

International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease

Table 2. International consensus guidance statements on the treatment of IgG4-related disease (IgG4-RD), voting agreement, level of evidence, and citations

Statement	% agreement	Evidence level/grade of recommendation	References
1. The most accurate assessment of IgG4-RD are based on a full clinical history, physical examination, selected laboratory investigations, and appropriate radiology studies.	96	4/C	37, 51, 53, 54, 66, 67
2. Diagnostic confirmation by biopsy is strongly recommended for the exclusion of malignancies and other IgG4-RD mimics.	94	5/D	26, 57, 68
3. All patients with symptomatic, active IgG4-RD require treatment, some urgently. A subset of patients with asymptomatic IgG4-RD require treatment.	87	4/C	39, 47, 48, 51, 55, 67, 69–74
4. Glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD unless contraindications to such treatment are present.	94	2b/B	38, 39, 47, 50, 51, 53, 54, 57, 66, 67, 69, 70, 72–77
5. Some but not all patients require the combination of glucocorticoids and a steroid-sparing immunosuppressive agent from the start of treatment. This is because glucocorticoid monotherapy will ultimately fail to control the disease and long-term glucocorticoid toxicities pose a high risk to patients.	46	4/C	38, 55, 56, 66, 78
6. Following a successful course of induction therapy, certain patients benefit from maintenance therapy.	94	2b/B	38, 47, 48, 50, 51, 54, 55, 67, 73
7. Re-treatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction. Following relapse, the introduction of a steroid-sparing agent for continuation in the remission maintenance period should be considered.	81	4/C	45, 56, 57, 59, 60, 77, 78

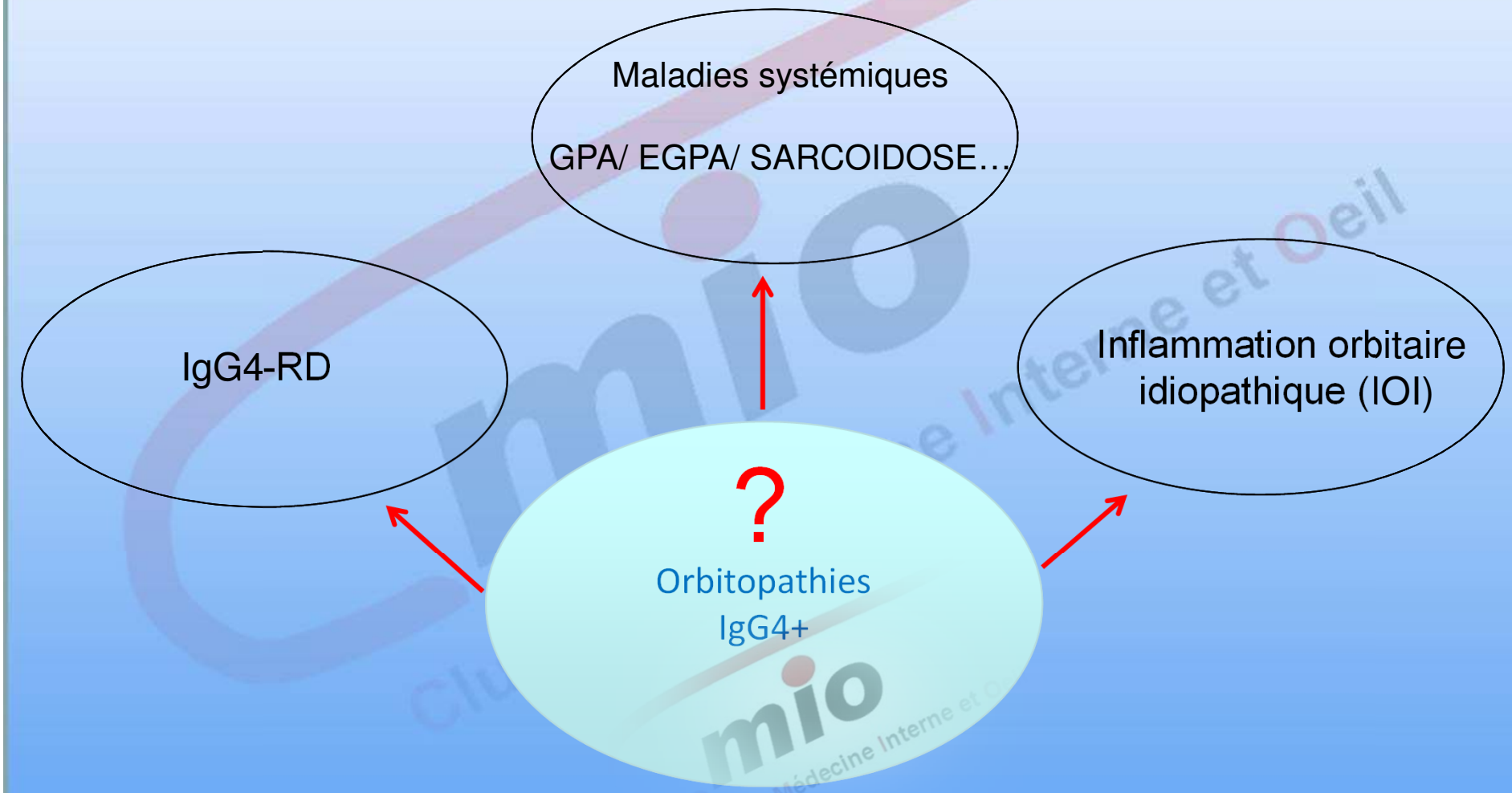
Khosroshahi A et al. Arthritis & Rheumatology 2015.

Conclusion

- L'orbite est une cible importante !
- Spécificité du critère histologique (seuil à 100 hpf)?
  - Diagnostic:
    - Confrontation de critères cliniques/ biologiques/ morphologiques et histologiques
    - Eliminer diagnostics différentiels
- Facteur pronostic: Marquage IgG4?
  - Etude de cohorte

  → Suivi prospectif +++

Conclusion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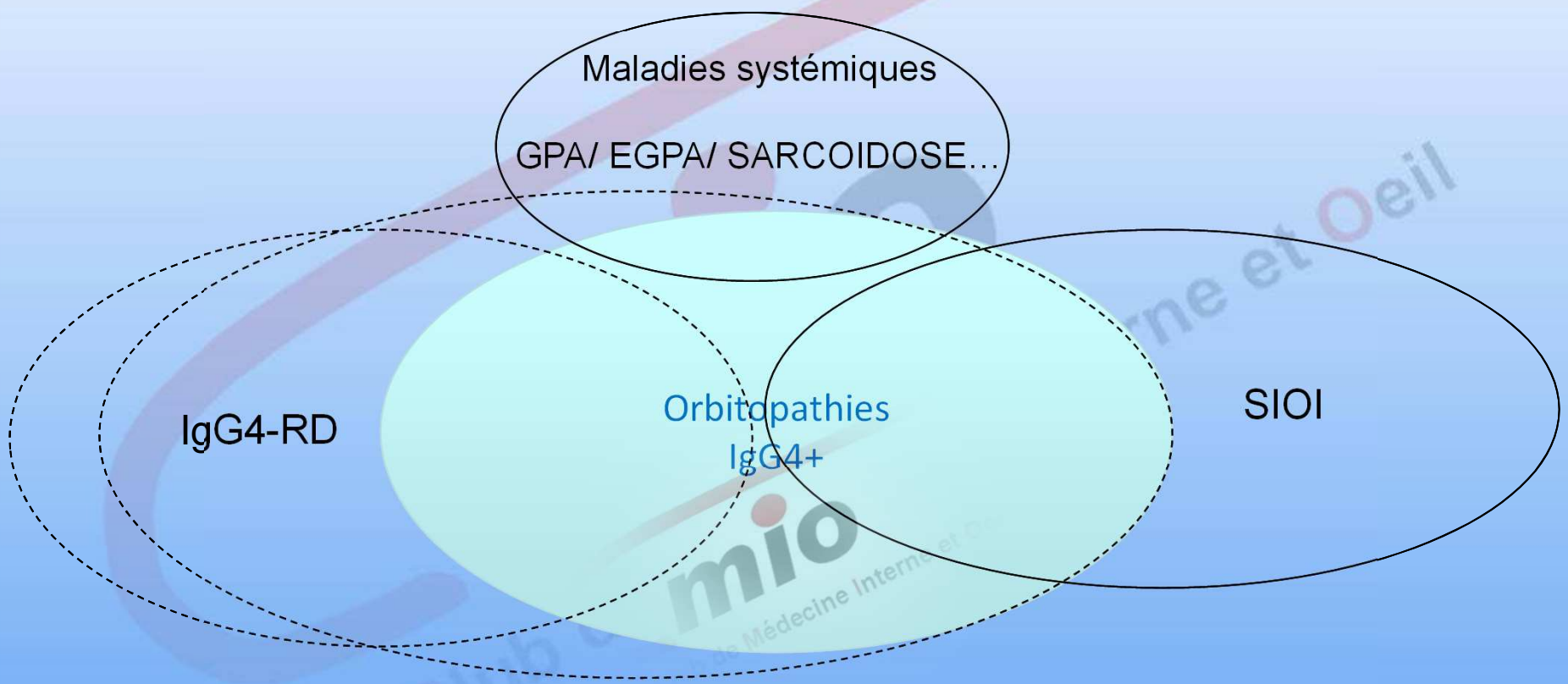
GPA/ EGPA/ SARCOIDOSE…
IgG4-RD
Inflammation orbitaire idiopathique (IOI)
?
Orbitopathies IgG4+

Conclusion


Maladies systémiques
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SIOI

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  - Etude de cohorte

  → Suivi prospectif +++

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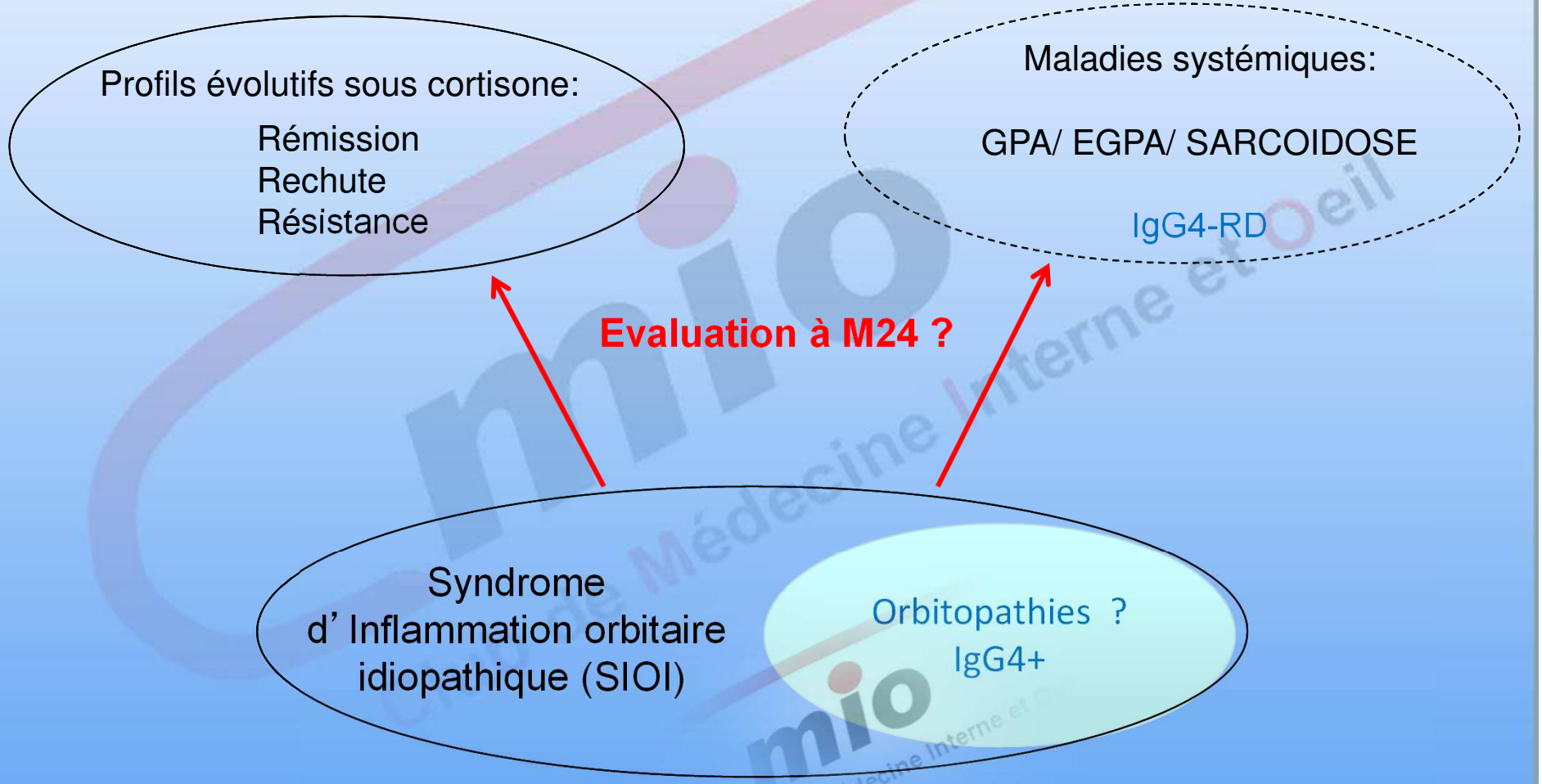
PHRC national 2009



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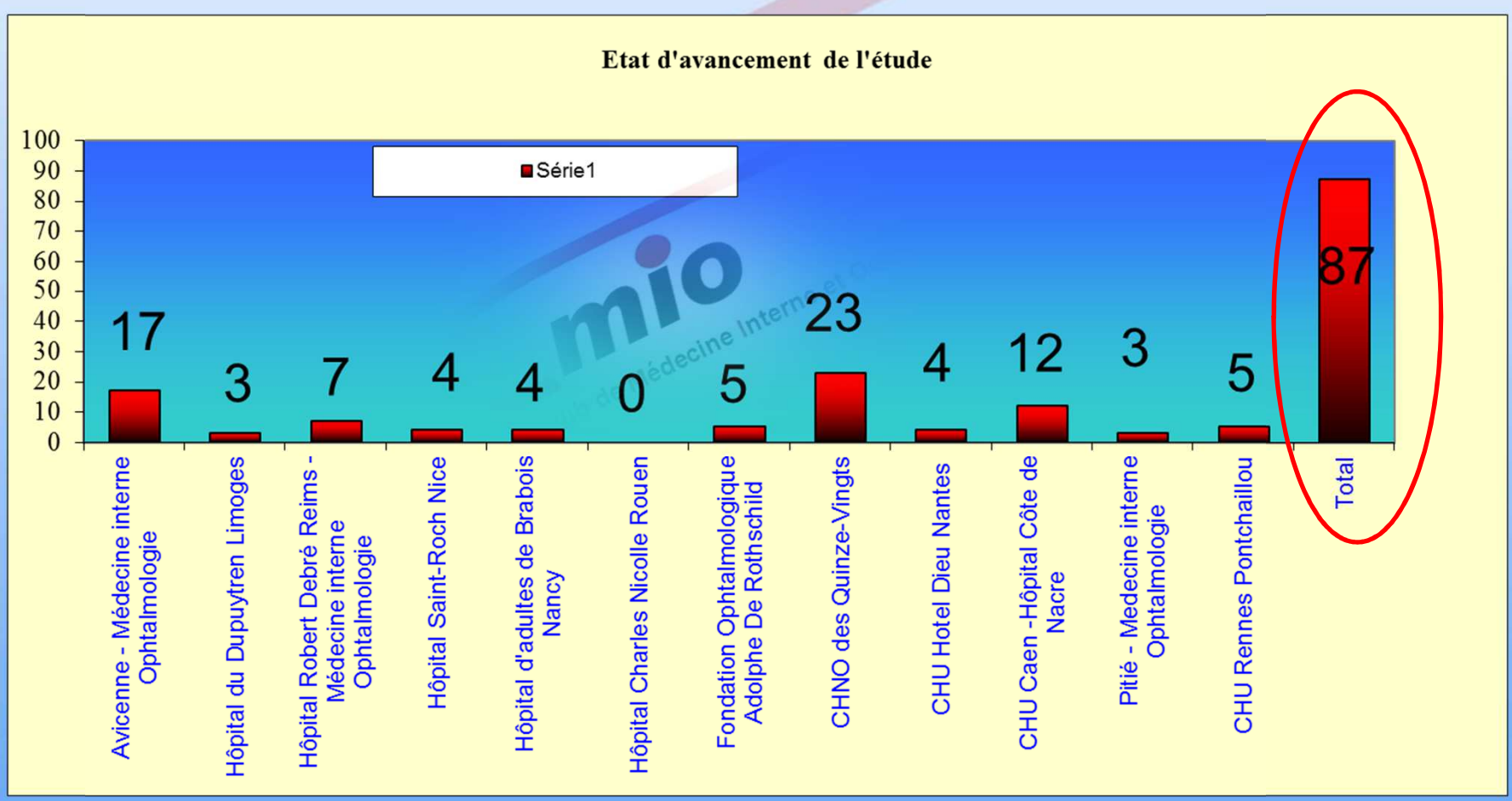
INCLUSIONS PAR CENTRE



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- Fin des inclusions: Juillet 2015
- 1er résultats:

Congrès SNFMI

Tours, Décembre 2015