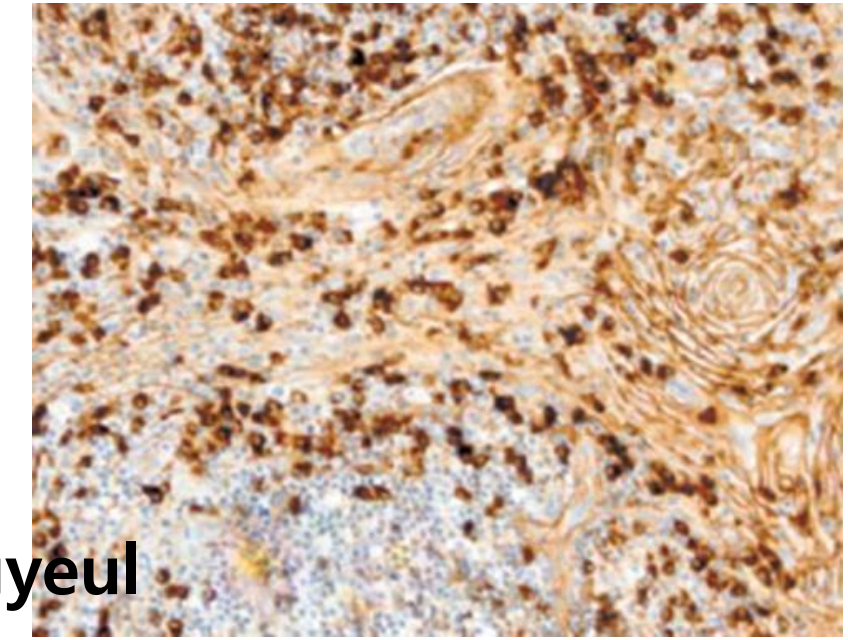
IgG4-Related Lung Disease

Department of internal medicine, respiratory medicine, intensive care medicine, Inje University Busan-Paik Hospital, Busan, Korea



Lee Hongyeul

IgG4-Related Disease (IgG4-RD)

- Rare multi-organ immune-mediated condition characterized by three pathology features

1) Lymphoplasmacytic infiltration
2) Storiform fibrosis
3) Obliterative phlebitis

History of IgG4 Related disase

- Mikulicz's disease (MD) (1892)

: Symmetrical swelling of the lachrymal, parotid, and submandibular glands, with massive infiltration of these glands by mononuclear cells

- Manifestation of Sjo¨gren's syndrome(1953)

: rheumatoid arthritis accompanied by keratoconjunctivitis sicca and severe swelling of the parotid glands

- AutoImmune Pancreatitis (1991)

: characteristic histopathological finding lymphoplasmacytic sclerosing pancreatitis (LPSP)

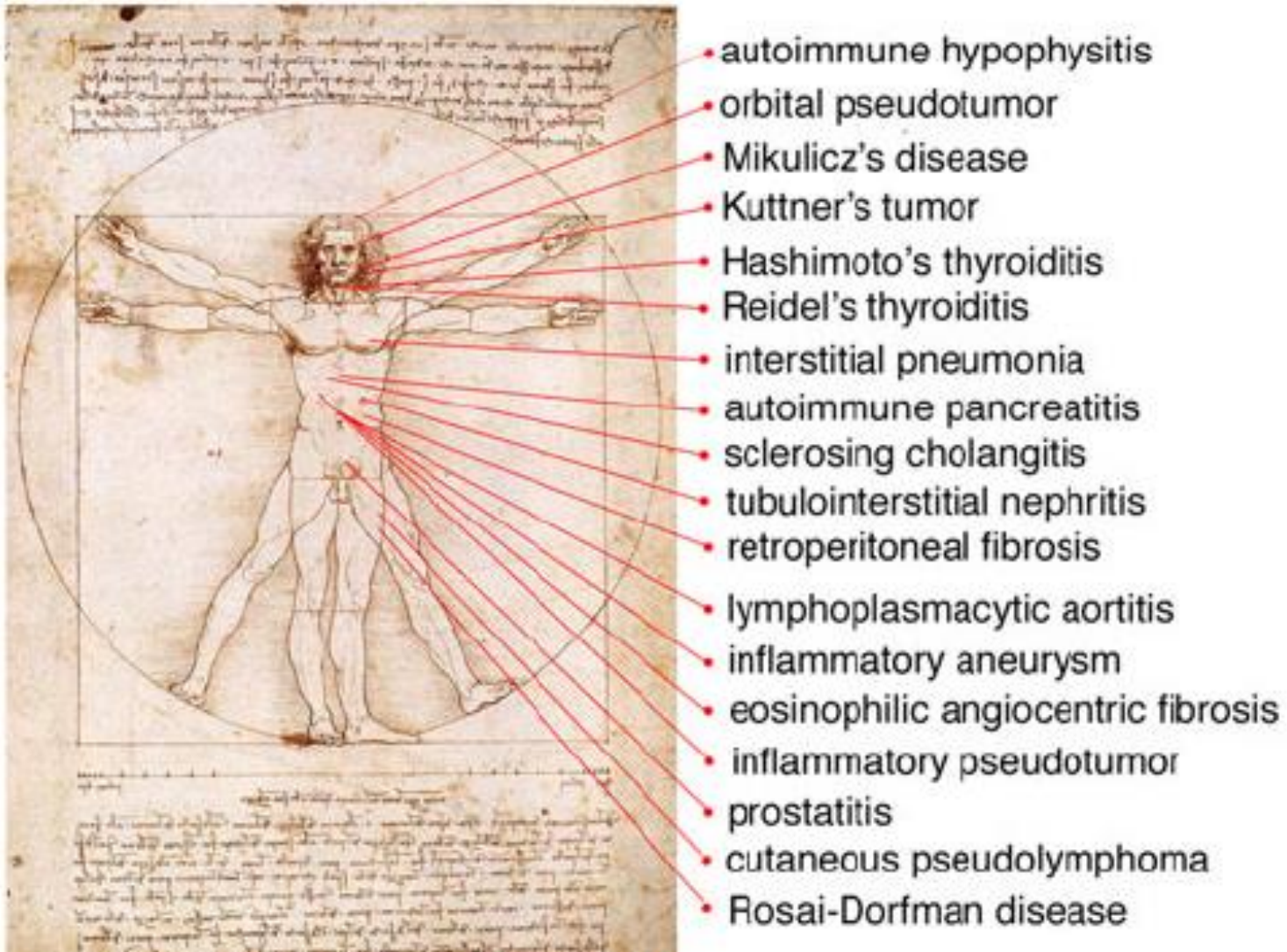
HIGH SERUM IgG4 CONCENTRATIONS IN PATIENTS WITH SCLEROSING PANCREATITIS

HIDEAKI HAMANO, M.D., SHIGEYUKI KAWA, M.D., AKIRA HORIUCHI, M.D., HIROSHI UNNO, M.D., NAOYUKI FURUYA, M.D., TAIJI AKAMATSU, M.D., MANA FUKUSHIMA, M.D., TOSHIO NIKAIDO, PH.D., KOHZO NAKAYAMA, PH.D., NOBUTERU USUDA, M.D., AND KENDO KIYOSAWA, M.D.

CHARACTERISTIC	NORMAL SUBJECTS (N=20)	PATIENTS WITH SCLEROSING PANCREATITIS (N=20)	P VALUE†
Age — yr	61±11	61±11	1.00
Male sex — no. (%)	15 (75)	15 (75)	1.00
	median (5th, 95th percentiles)		
Serum IgG1 — mg/dl			
Single radial immunodiffusion	664 (498, 1036)	868 (401, 1784)	0.25
ELISA	859 (698, 1077)	1095 (464, 1991)	0.03
Serum IgG2 — mg/dl			
Single radial immunodiffusion	592 (403, 902)	617 (330, 1234)	0.99
ELISA	510 (326, 726)	366 (263, 639)	0.03
Serum IgG3 — mg/dl			
Single radial immunodiffusion	34 (3, 100)	53 (13, 174)	0.12
ELISA	38 (11, 76)	51 (17, 101)	0.38
Serum IgG4 — mg/dl			
Single radial immunodiffusion	51 (15, 128)	663 (136, 1150)	<0.001
ELISA	41 (14, 156)	597 (24, 1230)	<0.001
Serum IgA — mg/dl‡	247 (144, 392)	226 (85, 552)	0.44
Serum IgM — mg/dl‡	142 (73, 221)	91 (40, 236)	0.11
Serum IgE — IU/ml§	79 (10, 240)	176 (62, 405)	0.09

N Engl J Med. 2001;344:732–8.

Many disease :IgG4 related conditions



IgG4-related autoimmune disease

IgG4-associated multifocal systemic fibrosis

IgG4-related systemic disease

IgG4-related sclerosing disease

Hyper-IgG4 disease

IgG4-related disease (IgG4-RD)

Systemic IgG4 plasmacytic syndrome (SIPS)

IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS)

IgG4-associated disease

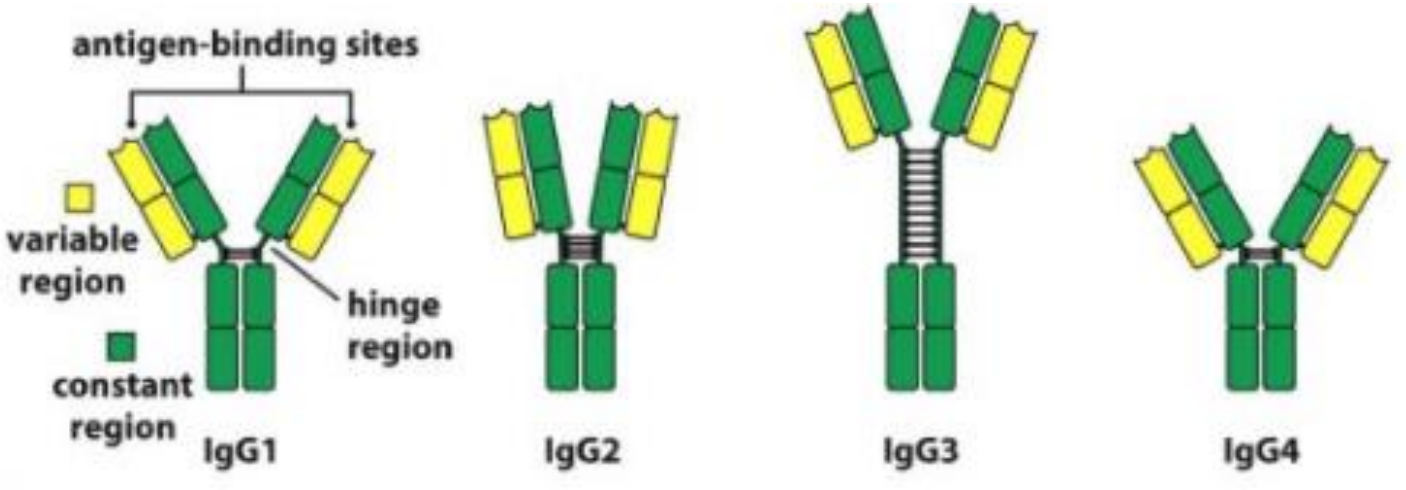
Individual disorders -> part of IgG4 RD

Panel 1: Conditions once regarded as individual disorders now recognised to be part of IgG4-related disease

- Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
- Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
- Fibrosing mediastinitis
- Hypertrophic pachymeningitis
- Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
- Küttner's tumour (affecting the submandibular glands)
- Mikulicz's disease (affecting the salivary and lacrimal glands)
- Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
- Periaortitis and periarteritis
- Inflammatory aortic aneurysm
- Retroperitoneal fibrosis (Ormond's disease)
- Riedel's thyroiditis
- Sclerosing mesenteritis

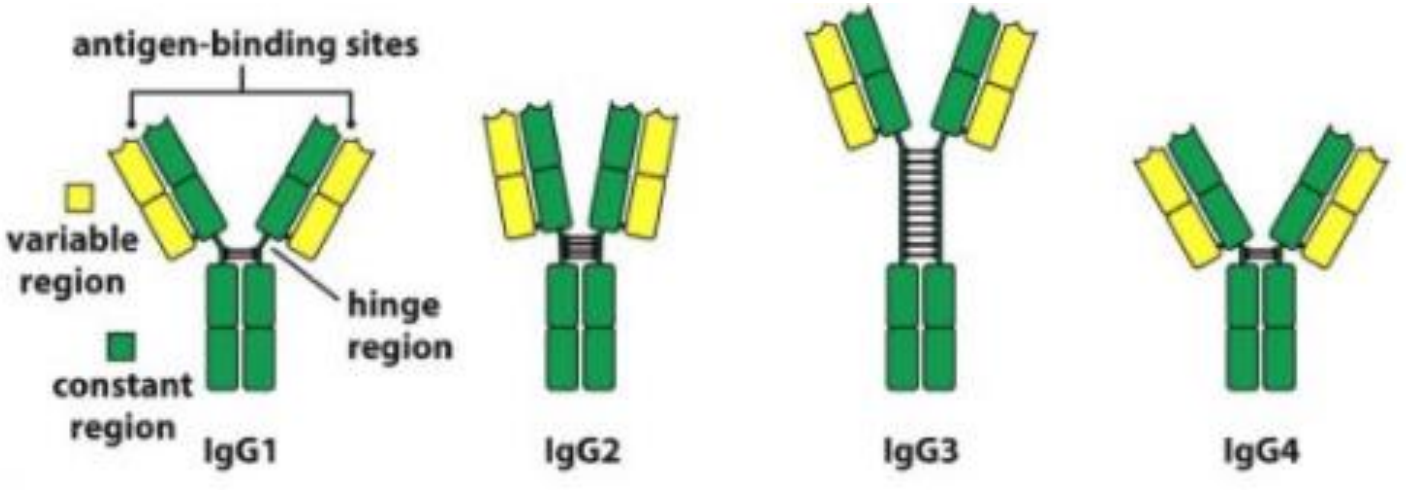
IgG4

- Unique antibiotics in boththructure and fuction
- Less than 5% of the total IgG in healthy persons
- Normal range in healthy people : 0.01 – 1.4 mg / mL
  but, Stable concentration in individual person



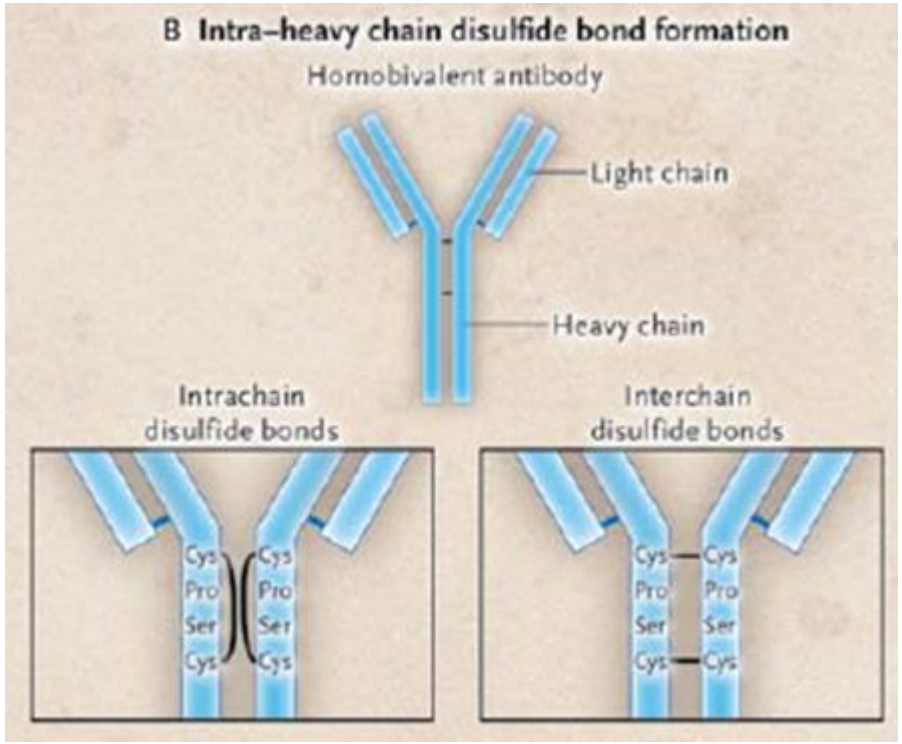
IgG4

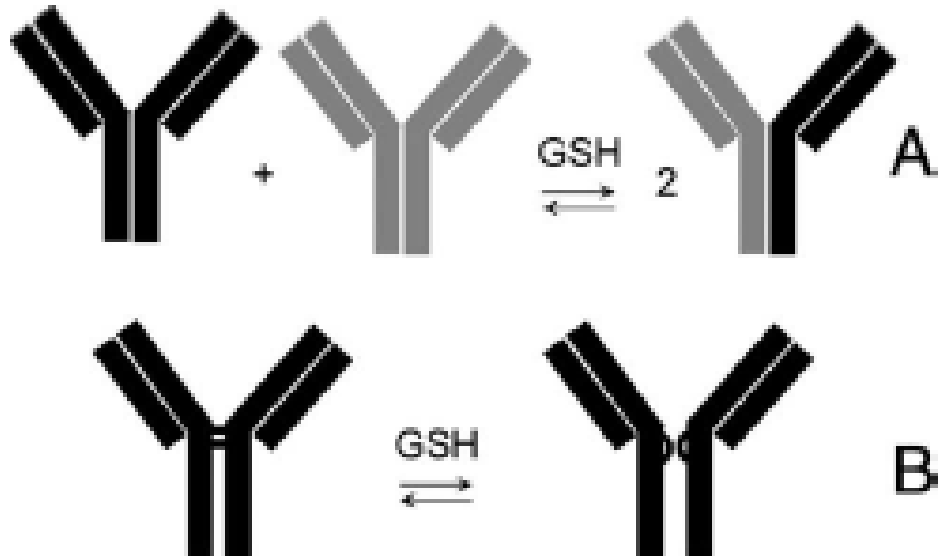
- Heavy chain – 90% shared IgG
- Amino acid difference within 2nd constant domain
  - week or negligible binding to both C1q and Fcr Rx
  -> No activation of classic complement pathway
  Only limited role in immune activation



IgG4- Half antibody exchange reaction

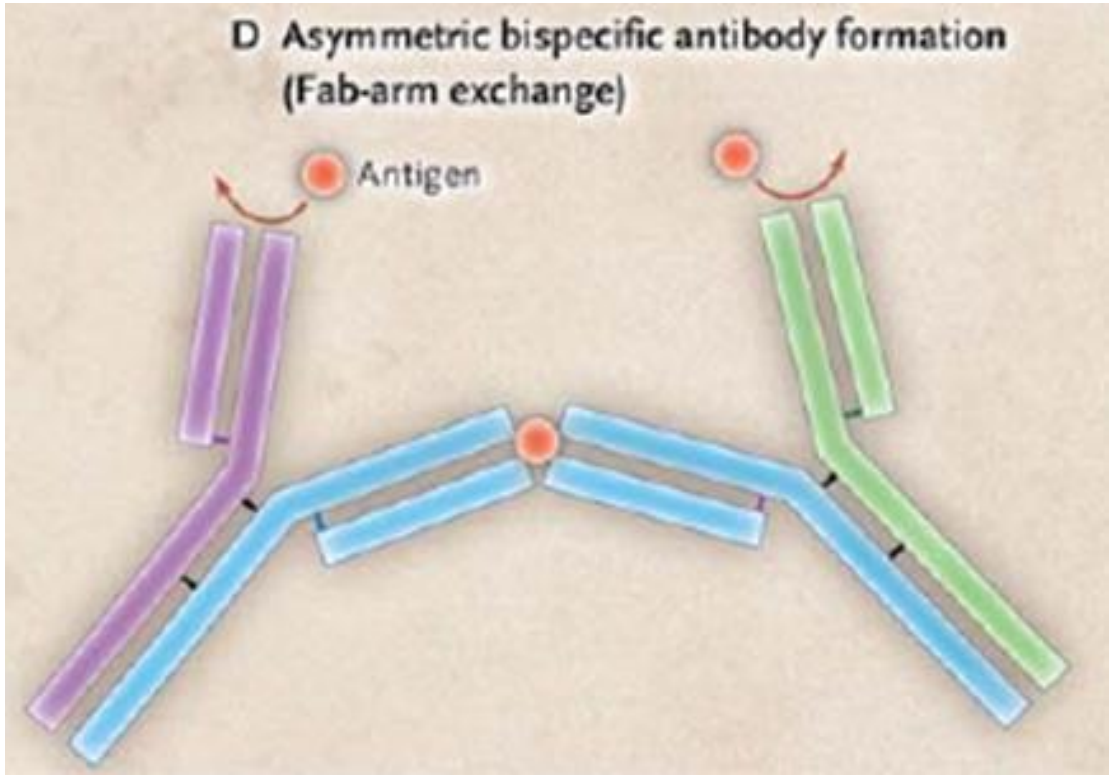
- Unique characteristic of IgG4
- Fragment antigen binding (Fab)- arm exchange

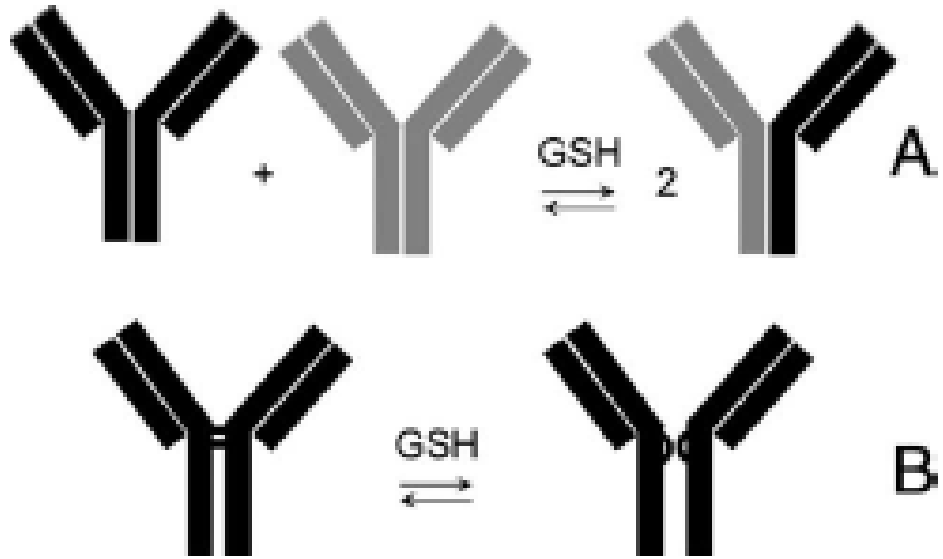


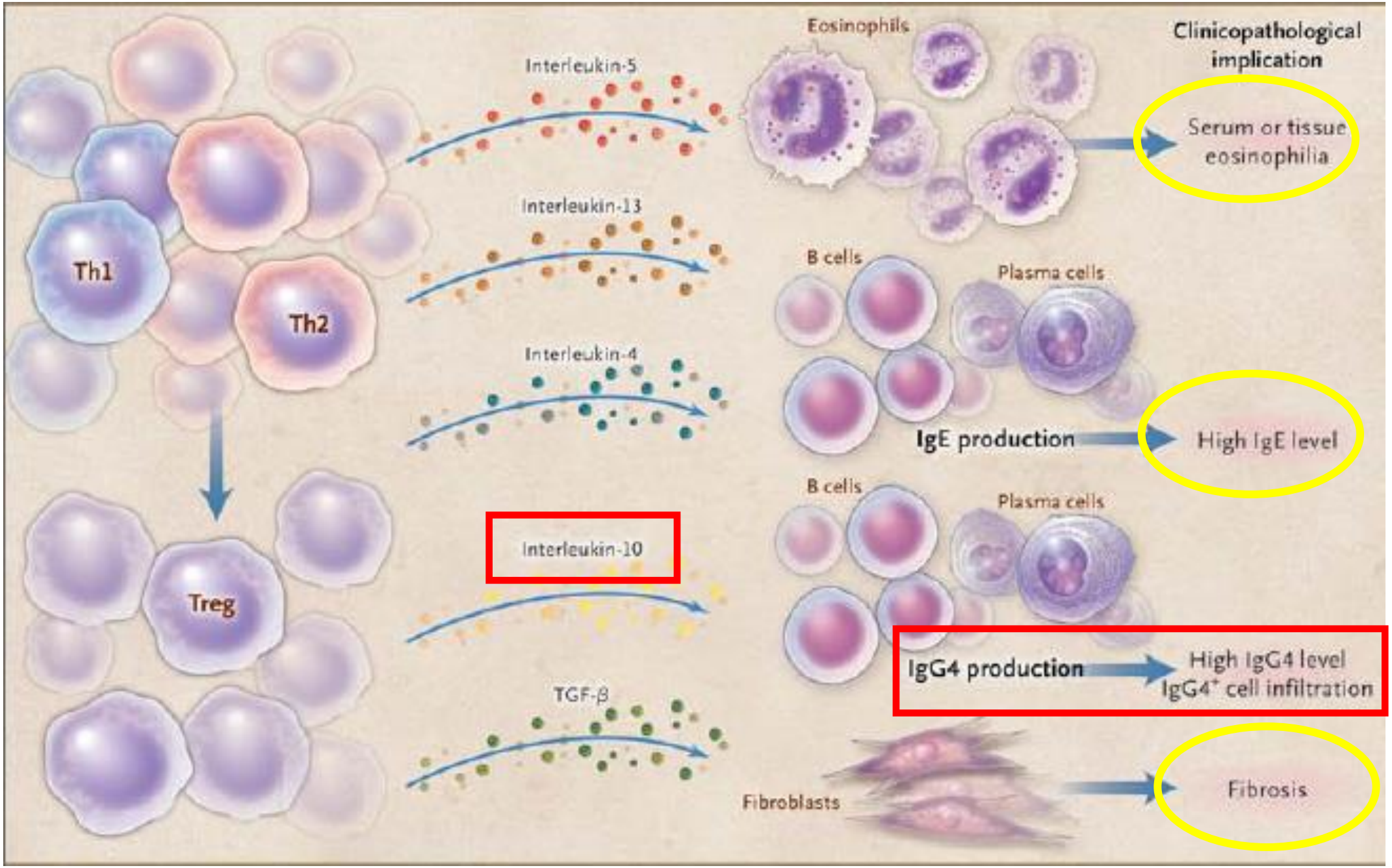


IgG4- Half antibody exchange reaction

- Unique characteristic of IgG4
- Fragment antigen binding (Fab)- arm exchange





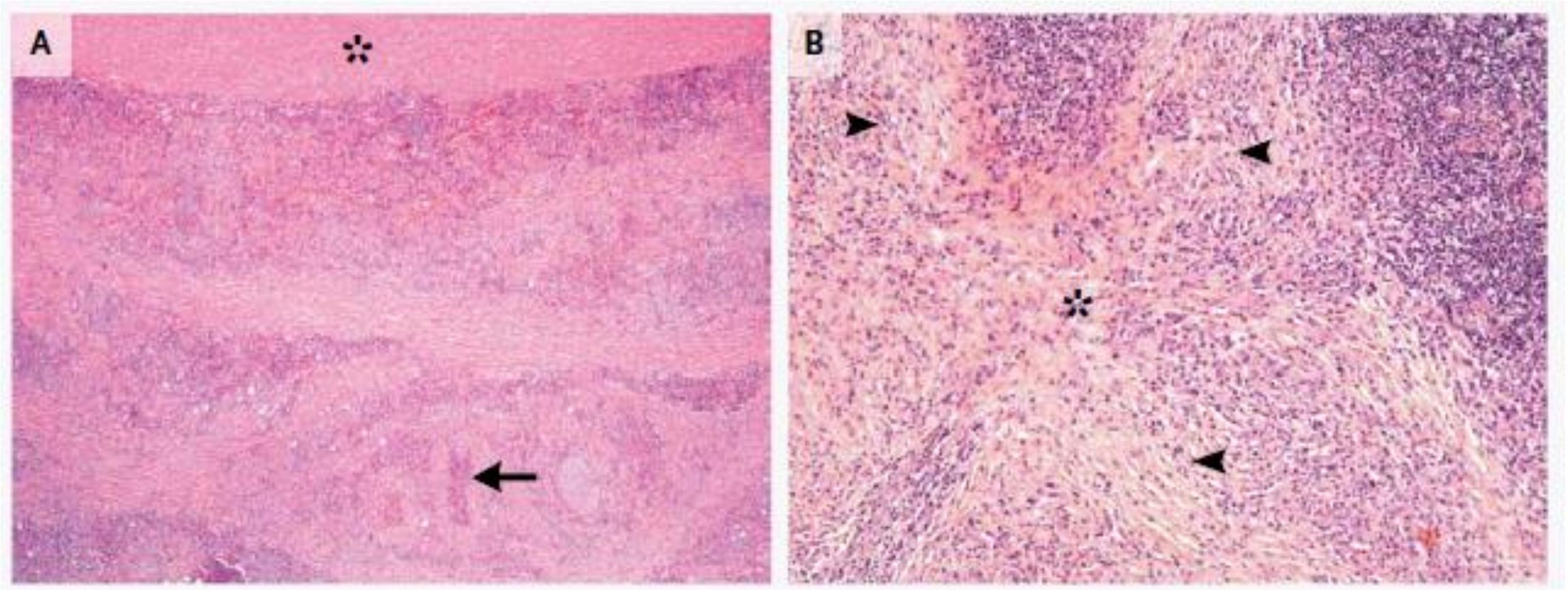

Th1
Th2
Treg
Interleukin-5
Interleukin-13
Interleukin-4
Interleukin-10
TGF-β
Eosinophils
Clinicopathological implication
Serum or tissue eosinophilia
B cells
Plasma cells
IgE production
High IgE level
B cells
Plasma cells
IgG4 production
High IgG4 level
IgG4+ cell infiltration
Fibroblasts
Fibrosis

Histopathologic feature

- Regardless of serum IgG4 concentration
  1) Lymphoplasmacytic infiltration
  2) Storiform fibrosis
  3) Obliterative phlebitis

- Mild to moderate eosinophilic infiltration

Histopathologic feature

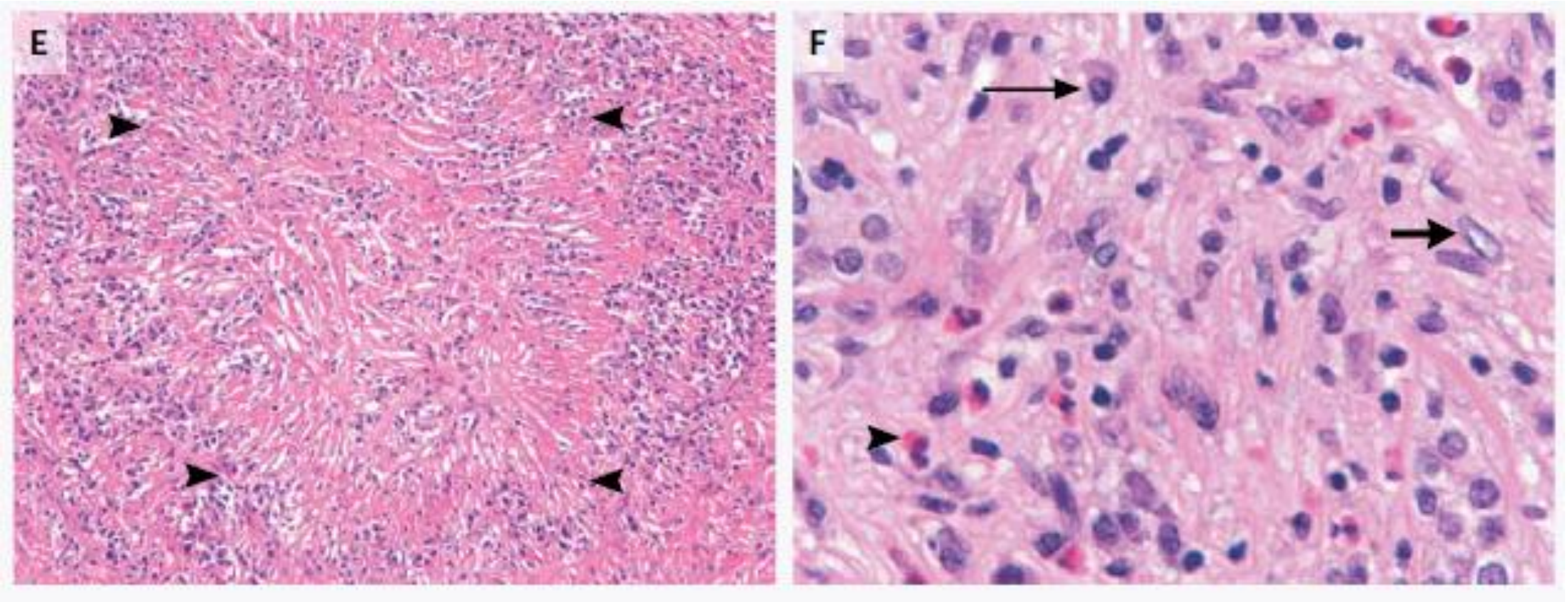


Obliterative phlebitis

storiform pattern

N Engl J Med 2012;366:539-51.

Histopathologic feature

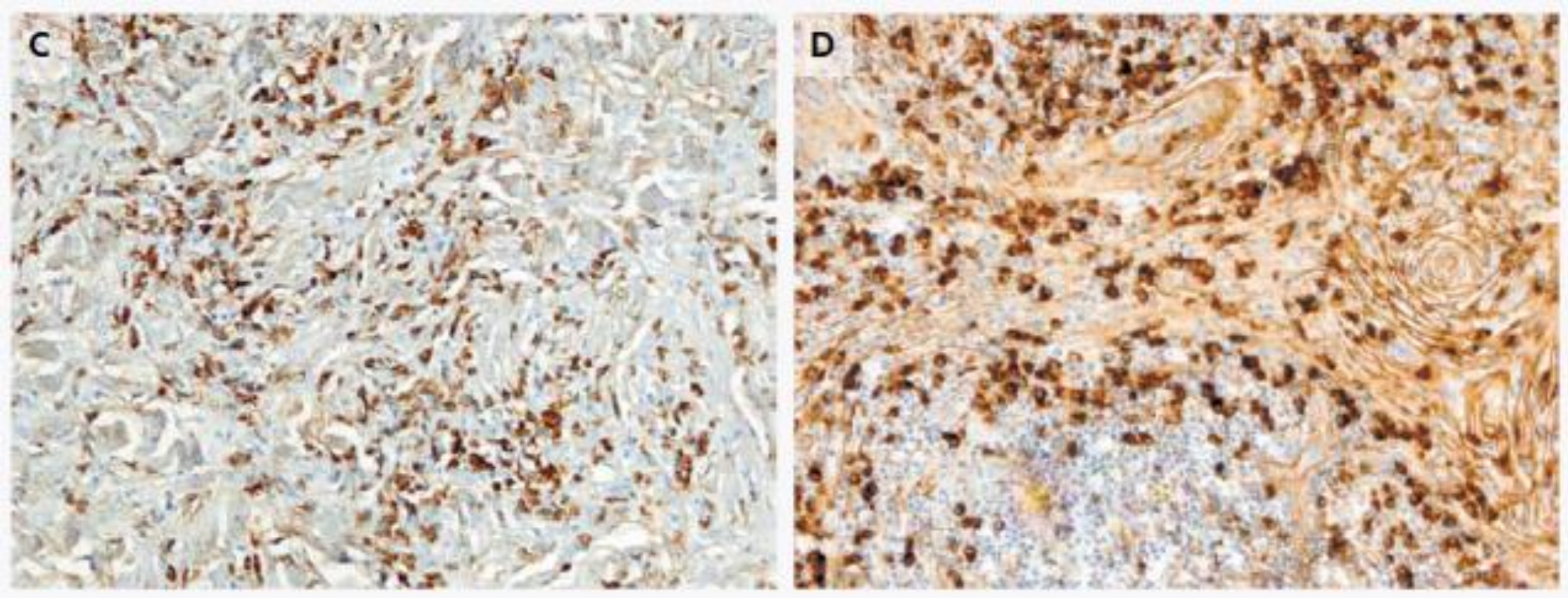


Obliterative phlebitis in venus channel
: totally occulded

plasam cell / fibroblast / eosinophilic

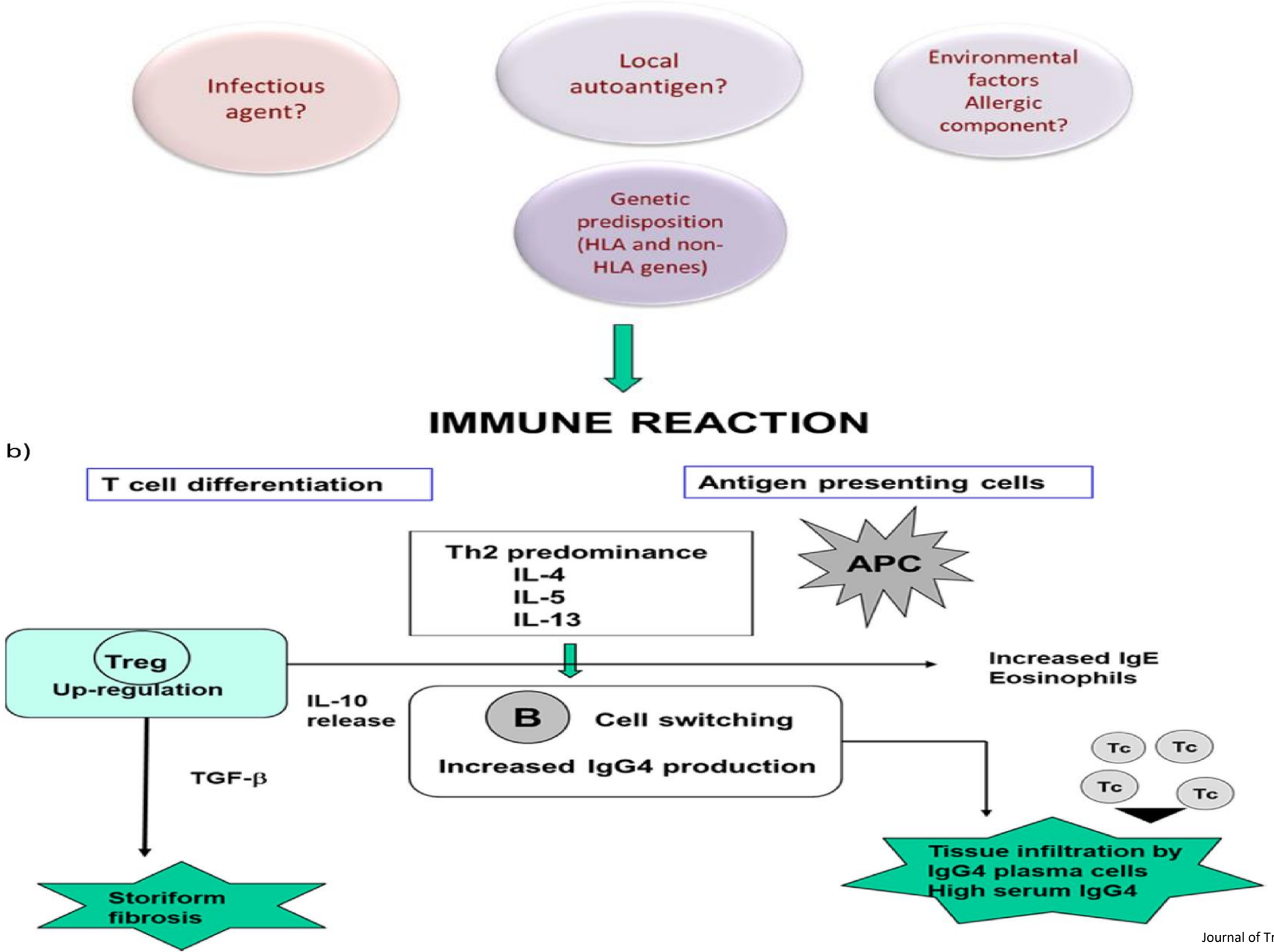
N Engl J Med 2012;366:539-51.

Histopathologic feature



plasama cell stained except lymphocyte

N Engl J Med 2012;366:539-51.


Infectious agent?
Local autoantigen?
Environmental factors Allergic component?
Genetic predisposition (HLA and non-HLA genes)
IMMUNE REACTION
b)
T cell differentiation
Antigen presenting cells
Th2 predominance
IL-4
IL-5
IL-13
APC
Treg
Up-regulation
Increased IgE
Eosinophils
IL-10 release
B
Cell switching
Increased IgG4 production
TGF-β
Tc
Tc
Tc
Tc
Storiform fibrosis
Tissue infiltration by IgG4 plasma cells
High serum IgG4

Potential initiating mechanisms

- Genetic risk factor
- Bacterial infection and Molecular mimicry
- Autoimmunity

Genetic risk factor

Table 2. Analysis of the Associations With Amino Acid at the 57 Residue of DQβ1 in the Relapse and Nonrelapse Groups

Amino acid residue	Position	Encoding alleles	Relapse group (n = 13)	Nonrelapse group (n = 27)	*P* value	Odds ratio (95% confidence interval)
Nonaspartic acid (V, S, A)[a]	B1 57	DQB1*0201 DQB1*0202 DQB1*0302 DQB1*0501 DQB1*0502 DQB1*0604 DQB1*0609	13 (100%)	8 (29.6%)	.00003	3.38 (1.9–6.0)

V, valine; S, serine; A, alanine.
[a]DQB1*0301, DQB1*0303, DQB1*0401, DQB1*0402, DQB1*0503, DQB1*0601, DQB1*0602, and DQB1*0603 are encoded by aspartic acid at DQβ1 57.

- DQbeta1 – 57 without aspartic acid in Korea

- HLA DRB1*0405-DQB1*0401 haplotype in Japan

Gastroenterology 2008;134:440-6.
Gastroenterology 2002;122:1264-9.

Bacterial infection and Molecular mimicry

Table 2. Peptides Used in the Study and Sequence Homologies.*

Synthetic peptides												
S	K	D	E	R	R	F	E	Q	P	R	V	AIP peptide$_{1-12}$
S	K	D	E	R	R	F						AIP peptide$_{1-7}$
R	F	E	Q	P	R	V						AIP peptide$_{6-12}$
A	K	E	E	R	R	Y						*Helicobacter pylori* PBP (298-304) O25249
Sequence homology between AIP$_{1-7}$ and *H. pylori* PBP												
S	K	D	E	R	R	F						AIP peptide$_{1-7}$
:	|	:	|	|	|	:						
A	K	E	E	R	R	Y						*H. pylori* PBP (298-304) O25249
Sequence homology between *H. pylori* PBP and UBR2												
A	K	E	E	R	R	Y						*H. pylori* PBP (298-304) O25249
|	|	|	:	|	|							
A	K	E	Q	R	R	Q						UBR2 (1186-1192) Q8IWV8

* PBP denotes plasminogen-binding protein, and UBR2 ubiquitin-protein ligase E3 component n-recognin 2. Identity is indicated by a vertical line, and a conservative substitution is indicated by a colon.

N EnglJ Med 2009;361:2135-42.

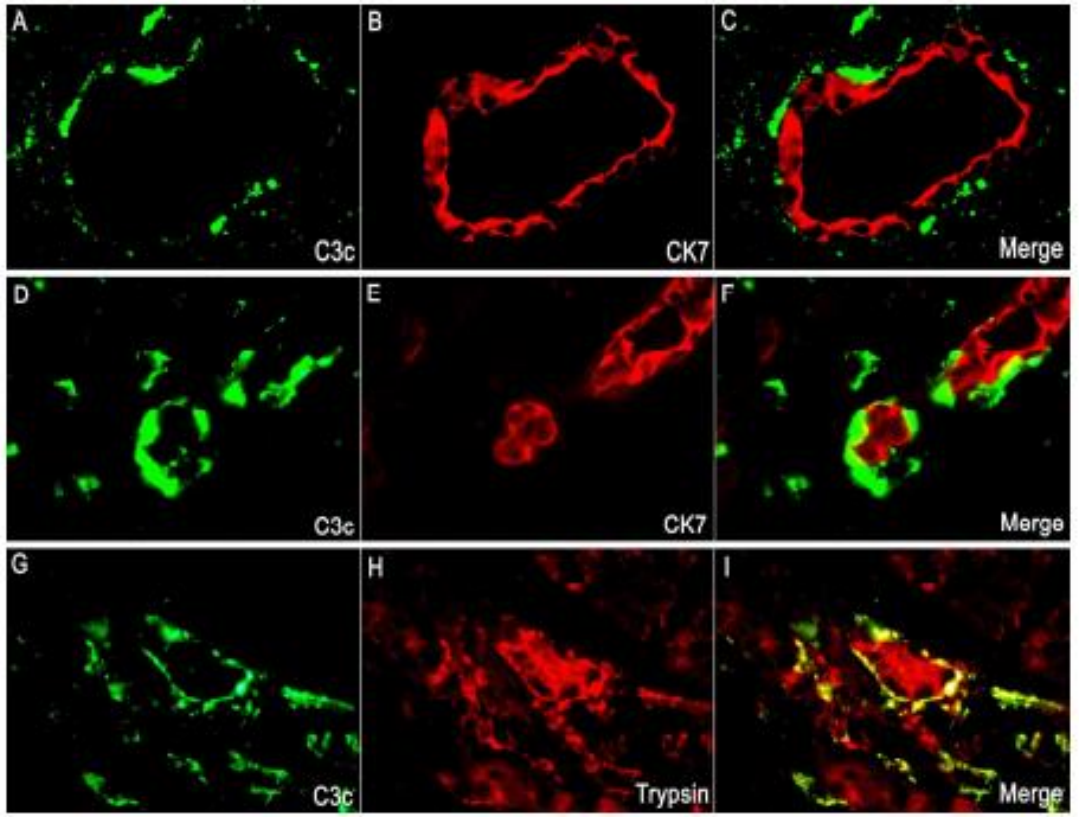
Autoimmunity

- Widely regarded as the initial immunologic stimulus

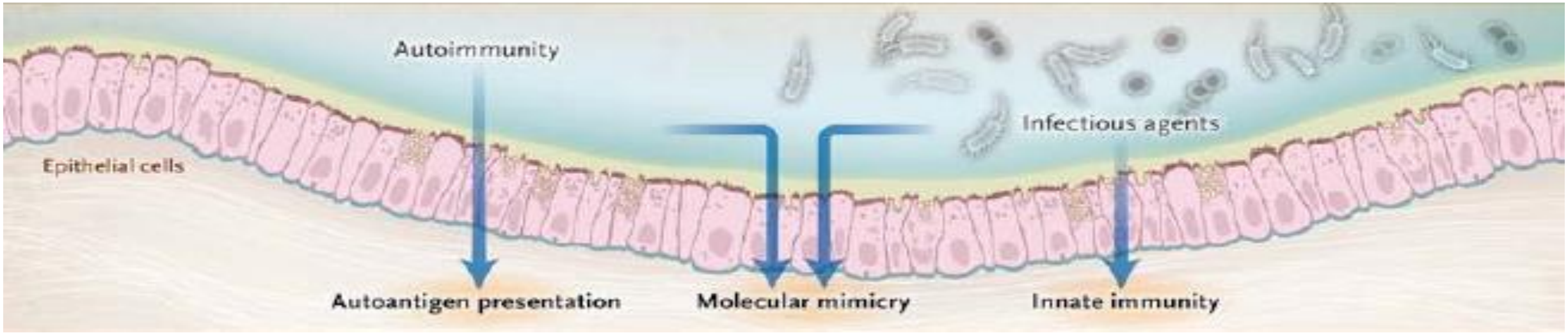
  : But non specific

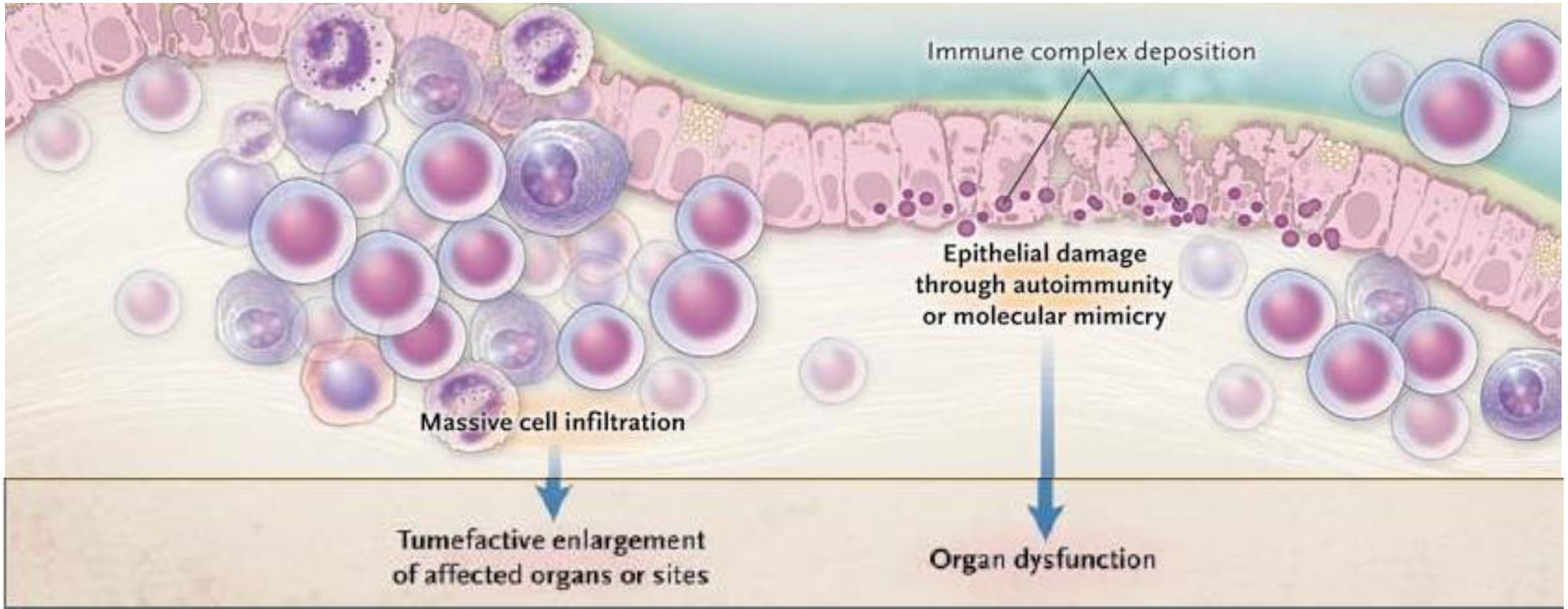
- Immune complex depotsit of IgG4 and C3

: Fab-arm exchange and Fc interaction between IgG4 and IgG or not



Histopathology 2010;57:825-35


Autoimmunity
Epithelial cells
Infectious agents
Autoantigen presentation
Molecular mimicry
Innate immunity


Immune complex deposition
Epithelial damage
through autoimmunity
or molecular mimicry
Massive cell infiltration
Tumefactive enlargement
of affected organs or sites
Organ dysfunction

Major clinical presentations

- Tumefactive lesion
- Subacute major tissue damage and organ failure
- Allergic disease (up to 40%)
  : atopy, eczema, asthma modest peripheral blood eosinophilia
- Unusual : Fever and elevated CRP

Eur J Gastroenterol Hepatol 2009;21:1136-9.

Tumefactive lesion

Spectrum of IgG4 RD

Pacreaticobiliar involvement

Salivary and lacrimal gland

Retroperitoneal fibrosis

Renal involvement

Aortitis

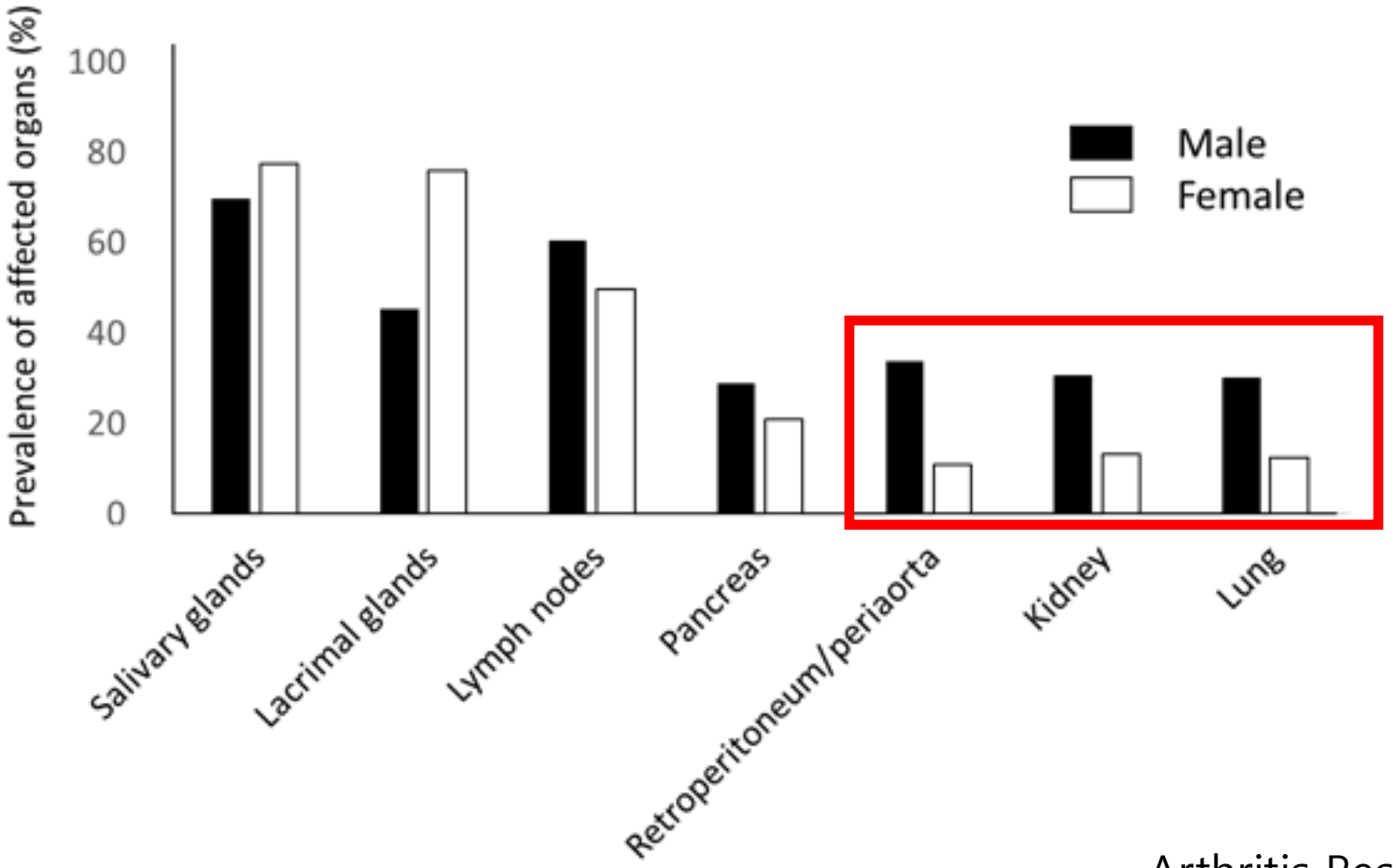
Head and neck	
Orbits and periorbital tissue	IgG4-related orbital disease
Salivary and lacrimal glands	IgG4-related sialadenitis
Thyroid	IgG4-related thyroiditis
Ear, nose, throat	IgG4-related sinusitis
Thorax	
Lungs	IgG4-related lung disease
Pleura	IgG4-related pleural disease
Mediastinum	IgG4-related mediastinitis
Breast	IgG4-related mastitis
Abdomen and pelvis	
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Pancreas	IgG4-related pancreatitis
Biliary tree	IgG4-related sclerosing cholangitis
Liver	IgG4-related autoimmune hepatitis
Kidney	IgG4-related tubule-interstitial nephritis/ glomerulonephritis
Gastrointestinal tract	IgG4-related gastrointestinal disease
Mesentery	IgG4-related sclerosing mesenteritis
Prostate	IgG4-related prostatitis
Testis	IgG4-related epididymitis-orchitis
Nervous system	
Pituitary gland	IgG4-related hypophysitis
Peripheral nerves	IgG4-related neuropathy
Meninges	IgG4-related pachymeningitis
Cardiovascular system	
Heart and pericardium	IgG4-related cardiac disease
Aorta	IgG4-related periaortitis
Lymph nodes	IgG4-related lymph adenopathy
Skin	IgG4-related skin disease
Bone	IgG4-related disease of the bone

Immunol. 181 (2015) 191–206.

Epidemiology of IgG4 RD

Author	Year	Country	N. pts	M:F ratio	Age at onset	Organ involvement
Ebbo[49]	2012	France	25	2.6:1	58	Lymph nodes, pancreas
Fernandez-Codina[50]	2015	Spain	55	3:1	56	Retroperitoneum, orbital pseudotumor
Lin[51]	2015	China	118	2.3:1	53.1	Pancreas, lymph nodes, salivary glans
Wallace[52]	2015	USA	125	1.6:1	50.3	Pancreas, lymph nodes, submandibular glands
Quero[53]	2019	Spain	15	4:1	60.7	Pancreas, lymph nodes, Kidney, salivary glands, lungs, vascular system
Campochiaro[54]	2016	Italy	41	1.9:1	62	Pancreas, retroperitoneum
Li[55]	2017	Hong Kong	104	3:1	62	Hepatobiliary system, lungs, retroperitoneum, CNS, eye, skin
Fong[56]	2018	Singapore	42 (35 definite)	2.9:1	66.3	Pancreas, lymph nodes, bile ducts
Inoue[57]	2015	Japan	235	4:1	67	Pancreas, salivary glands, kidney
Wang[58]	2019	China	403	1.69:1	55	Salivary glands, pancreas, Lung, retroperitoneum, kidney, lymph nodes, liver, gastrointestinal tract, skin, prostate, sinus, orbits, thyroid
Jamada[59]	2017	Japan	334	1.5:1	63.8	Salivary and lacrimal glands, lymph nodes, retroperitoneum/periaorta, lung, prostate, biliary tree, skin, thyroid

Gender differences in affected organ



Arthritis Research & Therapy (2017) 19:262

Ethiology of lung involvement

Affected organs, *n* (%)	
Salivary glands	242 (72.7)
Lacrimal glands	190 (57.1)
Lymph nodes	188 (56.5)
Pancreas	85 (25.5)
Retroperitoneum/periaorta	83 (24.9)
Kidney	79 (23.7)
Lung	78 (23.4)
Prostate	32 (9.6)
Bile duct	18 (5.4)
Skin	5 (1.5)
Thyroid glands	3 (0.9)
Mean number (range) of affected organs	3.2 (1–11)

Arthritis Research & Therapy (2017) 19:262

IgG4-related disease: Lung involvement

IgG4-Related Disease A Cross-sectional Study of 114 Cases in America

	n	Locations of the Lesions (No. Patients)
Head and neck	23	Salivary gland (17), lacrimal gland (10)
Thoracic	16	Lung (11), pleura (5), breast (1)
HPB	27	Pancreas (17), bile duct (25), gallbladder (5), liver (8)
Retroperitoneal	13	Retroperitoneal fibrosis (6), aorta/artery (7)
Systemic	35	Salivary gland (22), lacrimal gland (4), lung (15), pancreas (11), bile duct (8), gallbladder (4), liver (3), retroperitoneal fibrosis (7), aorta/artery (3), kidney (10), paravertebra (2), mediastinal fibrosis (1), prostate (1), peripheral nerve (1), systemic lymph nodes (2).

	n	Plasma cells (> 50/hpf) (%)	Neutrophils (> 5/hpf)	Eosinophils (> 5/hpf) (%)	Lymph follicle (> 10/lpf)	Obliterative Phlebitis (%)	Obliterative Arteritis	Granuloma (%)
Head and neck	23	23 (100)	0	12 (52)	15 (65%)*	17 (74)	0	2 (9)
Thoracic	16	16 (100)	2 (13%)	9 (56)	0	9 (56)	5 (31%)‡	1 (6)
HPB	27	27 (100)	0	17 (63)	0	23 (85)	0	3 (11)
Retroperitoneal	13	12 (92)	0	7 (54)	0	8 (62)	0	1 (8)
Systemic	35	34 (97)	1 (3%)	19 (54)	6 (17%)†	26 (74)	2 (6%)	2 (6)

Am J Surg Pathol. 2010 Dec;34(12):1812-9.

Factor analysis

Factor	1	2	3
Pancreas	-0.042	0.21	0.228
Lacrimal glands	0.340	-0.136	-0.355
Salivary glands	0.394	-0.086	-0.068
Kidney	0.127	0.179	0.324
RP/periaorta	-0.002	0.598	0.029
Lung	-0.044	-0.048	0.405
Lymph node	0.528	0.156	0.103

Arthritis Research & Therapy (2017) 19:262

Type of affected organ biopsied

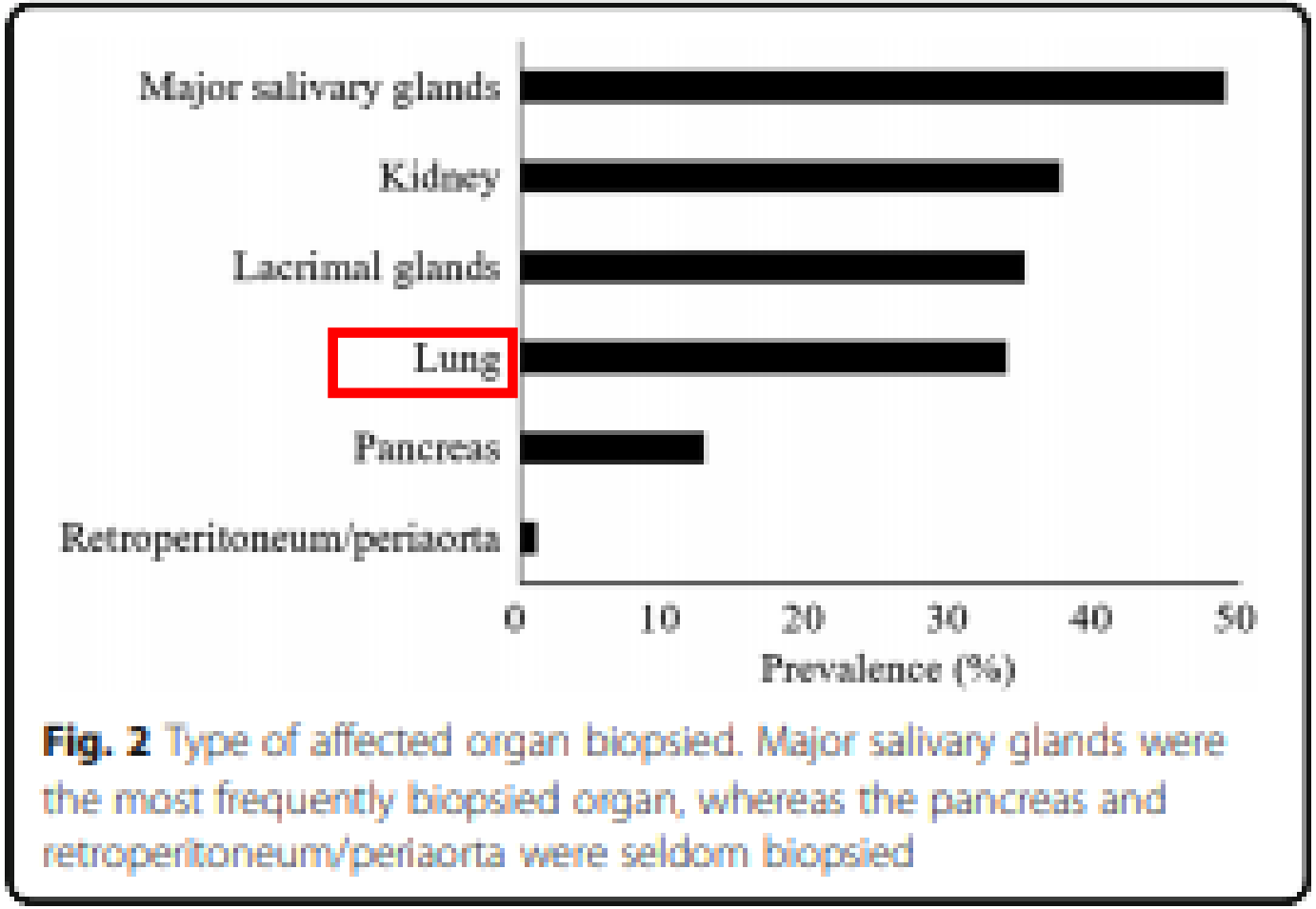


Fig. 2 Type of affected organ biopsied. Major salivary glands were the most frequently biopsied organ, whereas the pancreas and retroperitoneum/periaorta were seldom biopsied

Arthritis Research & Therapy (2017) 19:262

Diagnostic criteria for IgG4- Mikulicz's disease

1. Symmetrical swelling of at least two pairs of lachrymal, parotid, and submandibular glands continuing for more than 3 months;

and

2. Elevated serum IgG4 (>135 mg/dl);

or

3. Histopathological features including lymphocyte and IgG4+ plasma-cell infiltration (IgG4+ plasma cells/IgG+ plasma cells >50%) with typical tissue fibrosis or sclerosis

Differential diagnosis is necessary from other disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. Although the diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different

Mod Rheumatol (2012) 22:21–30

Clinical diagnostic criteria for autoimmune pancreatitis in Japan

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular walls and diffuse or localized enlargement of the pancreas on imaging modalities, including abdominal ultrasound, computed tomography, and magnetic resonance imaging
2. High-serum F-globulin, IgG, or IgG4 concentration or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells to the periductal area, occasionally accompanied by lymphoid follicles in the pancreas

For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3

However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers

Mod Rheumatol (2012) 22:21–30

Diagnostic criteria for IgG4-related kidney disease

1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG or IgE or hypocomplementemia
2. Abnormal renal radiologic findings:
   a. Multiple low-density lesions on enhanced computed tomography
   b. Diffuse kidney enlargement
   c. Hypovascular solitary mass in the kidney
   d. Hypertrophic lesion of the renal pelvic wall without irregularities of the renal pelvic surface
3. Elevated serum IgG4 level (>135 mg/dl)
4. Histological findings in the kidney:
   a. Dense lymphoplasmacytic infiltration by >10 IgG4+ plasma cells/high power field (HPF) and/or IgG4+/IgG+
   b. Characteristic (sclero-) fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histological findings in extra-renal organ(s):
   Dense lymphoplasmacytic infiltration by >10 IgG4+ plasma cells/HPF and/or IgG4+/IgG+ plasma cells >40%

Definite:	1 + 3 + 4 a, b
	2 + 3 + 4 a, b
	2 + 3 + 5
	1 + 3 + 4 a + 5
Probable:	1 + 4 a, b
	2 + 4 a, b
	2 + 5
	3 + 4 a, (b)
Possible:	1 + 3
	2 + 3
	1 + 4 a
	2 + 4 a

Mod Rheumatol (2012) 22:21–30

Comprehensive clinical diagnostic criteria for IgG4-RD

1. Clinical examination showing 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+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF

Definite: 1) + 2) + 3)

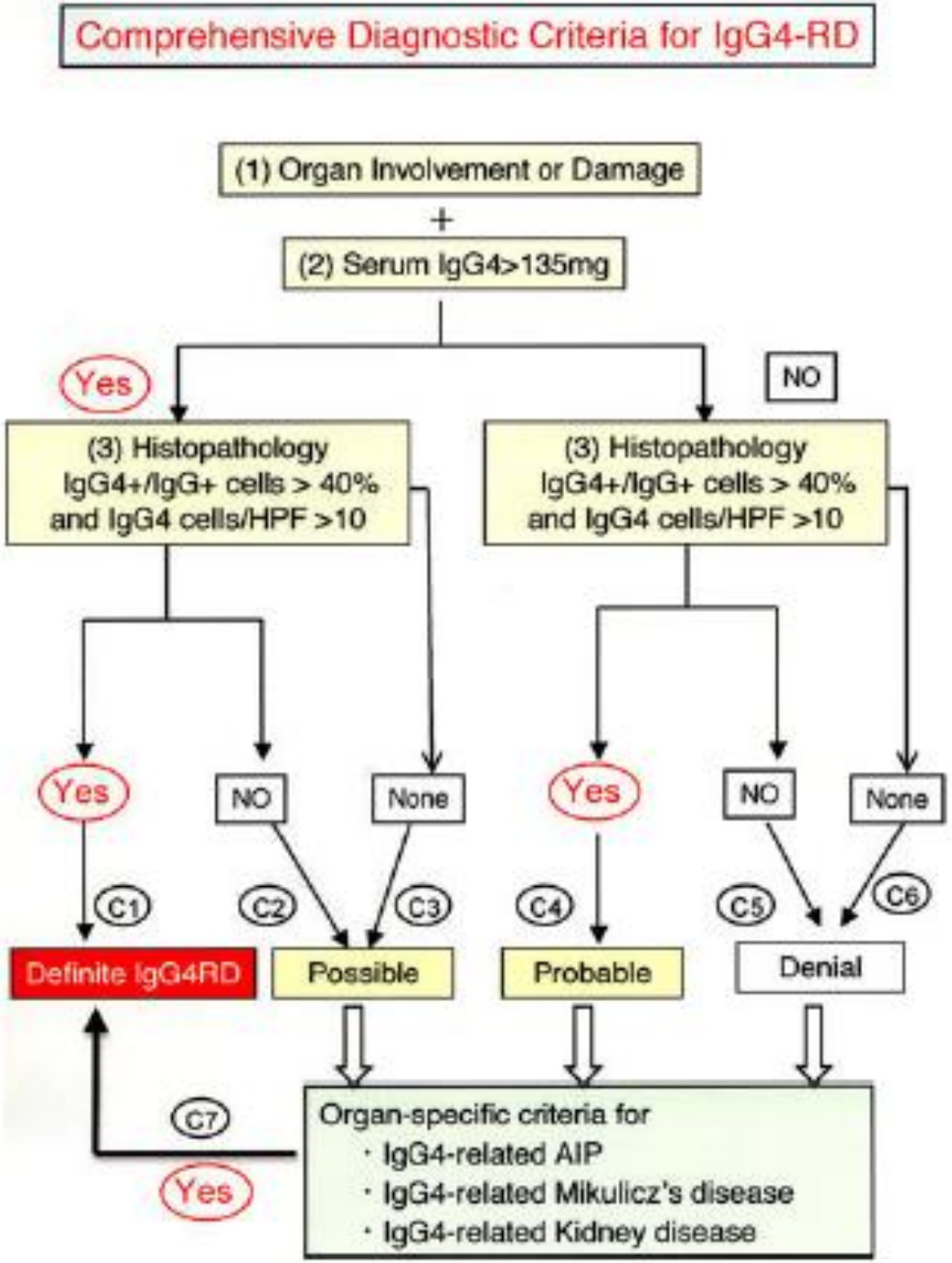
Probable: 1) + 3)

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, 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

Mod Rheumatol (2012) 22:21–30



1. Clinical examination showing 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+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF

Definite: 1) + 2) + 3)

Probable: 1) + 3)

Possible: 1) + 2)

Mod Rheumatol (2012) 22:21–30

Conditions that mimic IgG4-RD

- 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

ARTHRITIS & RHEUMATOLOGY Vol. 67, No. 7, July 2015

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

A. Khosroshahi,[1] Z. S. Wallace,[2] J. L. Crowe,[3] T. Akamizu,[4] A. Azumi,[5] M. N. Carruthers,[6] S. T. Chari,[7] E. Della-Torre,[8] L. Frulloni,[9] H. Goto,[10] P. A. Hart,[11] T. Kamisawa,[12] S. Kawa,[13] M. Kawano,[14] M. H. Kim,[15] Y. Kodama,[16] K. Kubota,[17] M. M. Lerch,[18] M. Löhr,[19] Y. Masaki,[20] S. Matsui,[21] T. Mimori,[16] S. Nakamura,[22] T. Nakazawa,[23] H. Ohara,[23] K. Okazaki,[24] J. H. Ryu,[7] T. Saeki,[25] N. Schleinitz,[26] A. Shimatsu,[27] T. Shimosegawa,[28] H. Takahashi,[29] M. Takahira,[14] A. Tanaka,[30] M. Topazian,[7] H. Umehara,[20] G. J. Webster,[31] T. E. Witzig,[7] M. Yamamoto,[29] W. Zhang,[32] T. Chiba,[16] and J. H. Stone[2]

Total	42
Specialty	
Gastroenterology	18
Rheumatology	13
Ophthalmology	3
Pulmonary–critical care	2
Hematology/oncology	2
Internal medicine	2
Nephrology	1
Endocrinology	1

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 7, July 2015, pp 1688–1699
DOI 10.1002/art.39132

Indication of Treatment

- Not all manifestation for IgG4-RD require immediate treatment
- Asymptomatic nonprogressive and limited disease : "Watchful waiting"
- Asymptomatic disease with progressive disease
: Organ dysfunction in laboratory or radiology findings
- All patient with symptomatic active IgG4-RD : Some urgent

Manifestation	Rationale for urgent treatment
Aortitis	Inflammatory aortic aneurysms can continue to enlarge and are at risk for dissection.
Retroperitoneal fibrosis	Progressive disease may lead to irreversible nerve damage/pain and/or ureteral obstruction/renal failure.
Proximal biliary strictures*	Untreated disease may lead to superimposed infectious cholangitis and eventually irreversible fibrosis and cirrhosis.
Tubulointerstitial nephritis	Untreated disease may lead to irreversible chronic kidney disease.
Pachymeningitis	Untreated disease puts the patient at risk for neurologic deficits and/or seizures.
Pancreatic enlargement	Untreated disease may lead to irreversible pancreatic exocrine and endocrine failure.
Pericarditis	Untreated disease may lead to tamponade or constrictive pericarditis

ARTHRITIS & RHEUMATOLOGY 2015, pp 1688–1699

Regimen of remission induction

- Glucocorticoid
  - At a dosage of 30-40mg / day (Prednisolone 0.6mg/kg)
  - Initial dosage for 2-4week
  - Tappering and discontinue 3-6months

J Gastroenterol 2014;49:961–70.

- Remission nearly all patient with Autoimmune hepatitis
- Remission 83% patient with sclerosing cholnagitis

Gut 2013;62:1607–15.

Alterantive Tx : Rituximab

- Ritiuximab : 1g iv every 15days for two dose

- Alternative Treatment of glucocorticoid
  - not respond to up to 40 mg/day of steroid
  - cannot be tapered to <5 mg daily
  - strong relative contraindications to glucocorticoid therapy

Other agent
: Azathioprine, methotrexate, mcophenolate mofetil

Therapeutic approach to IgG4-related disease

A systematic review

Pilar Brito-Zerón (MD, PhD)[a,b,c], Belchin Kostov (MSc, PhD)[d,e], Xavier Bosch (MD, PhD)[f], Nihan Acar-Denizli (MSc)[g], Manuel Ramos-Casals (MD, PhD)[b,c,h,*], John H. Stone (MD, MPH)[i]

Efficacy of first-line therapies	
Global efficacy	1246/1293 (96.4%)
Glucocorticoids alone	1186/1220 (97.2%)
Glucocorticoids + surgery	20/22 (91%)
Immunosuppressive/biological agents*	17/22 (77%)
Surgery alone	14/17 (82%)
Radiotherapy	9/12 (75%)
No therapy	68/159 (43%)
Secondary outcomes	
Relapses	464/1395 (33%)
Stop glucocorticoids	51/191 (27%)
Spontaneous remission in untreated patients	68/159 (43%)
Death	26/294 (8.8%)

Organ-specific selection of patients	Patients (studies)
Autoimmune pancreatitis/sclerosing cholangitis	1651 (12)
Ocular involvement	101 (8)
Salivary gland involvement	173 (5)
Renal involvement	140 (5)
Lymph nodes/skin involvement	67 (4)
Other organ-specific involvements	207 (14)
Unselected patients (systemic)	695 (14)

Brito-Zerón et al. Medicine (2016) 95:26

Typical response of remission induction

- Response in several weeks
  - Symptomatic improvement
  - Reductions in the size of masses or organ enlargement,
  - Improvement in organ function
  - Decrease in serum levels of IgG4.

- Poor response
  - Advanced fibrotic change

Lancet Rheumatol. 2019;1:e55.

Maintenance therapy following remission induction

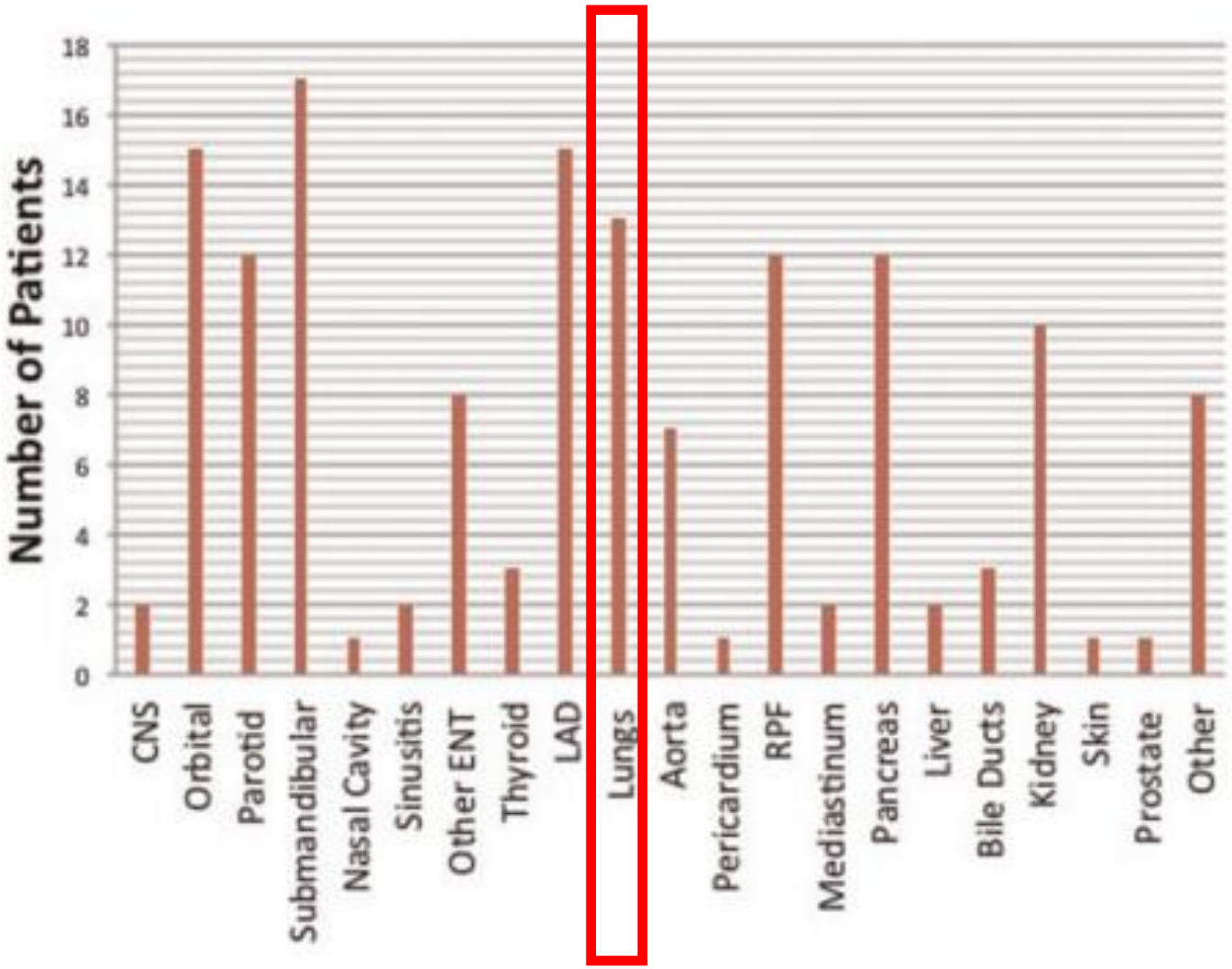
- low-dose glucocorticoids (eg, 2.5 to 5 mg/day) for up to 3 years

- High risk for disease relapse.
  - Multi-organ involvement
  - Significantly elevated serum IgG4 concentrations
  - Involvement of the proximal bile ducts
  - History of disease relapse

Ann Rheum Dis. 2015;74(6):1171.

Predictors of disease relapse in IgG4-related disease following rituximab

Zachary S. Wallace[1], Hamid Mattoo[2,3], Vinay S. Mahajan[2,3], Maria Kulikova[2,3], Leo Lu[1,4], Vikram Deshpande[5,6], Hyon K. Choi[1,6], Shiv Pillai[2,3,6] and John H. Stone[1,6]

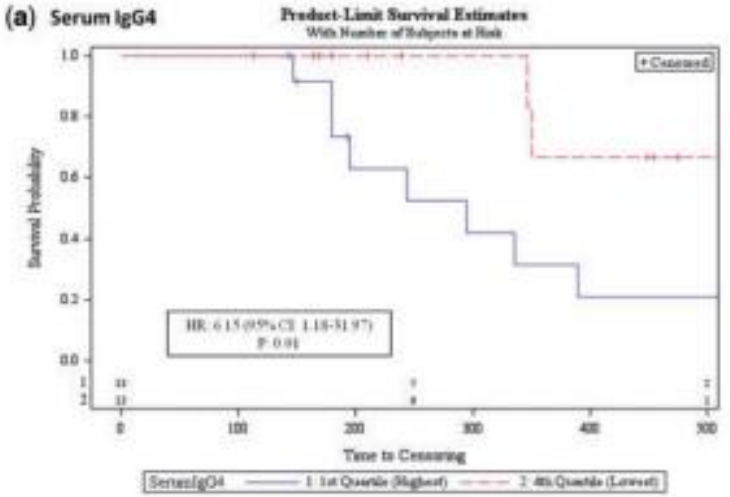


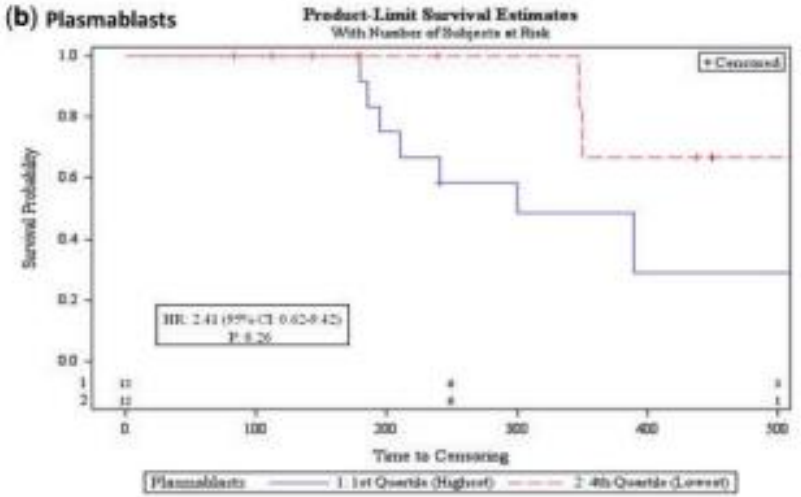
retrospective cohort study
: total 60patients

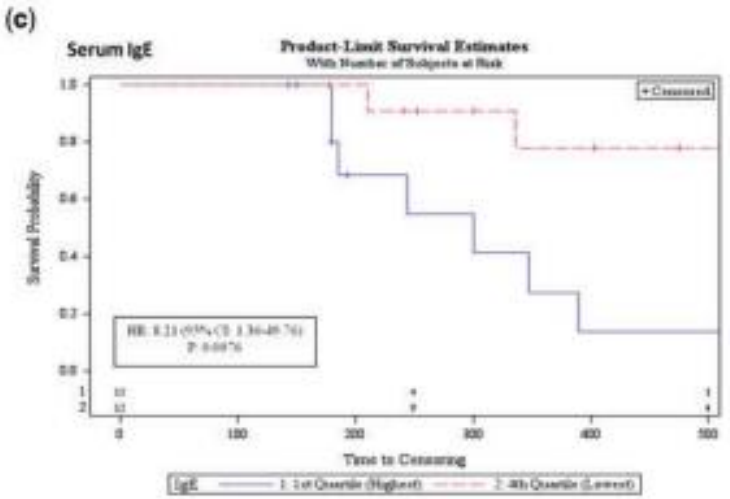
Rheumatology 2016;55

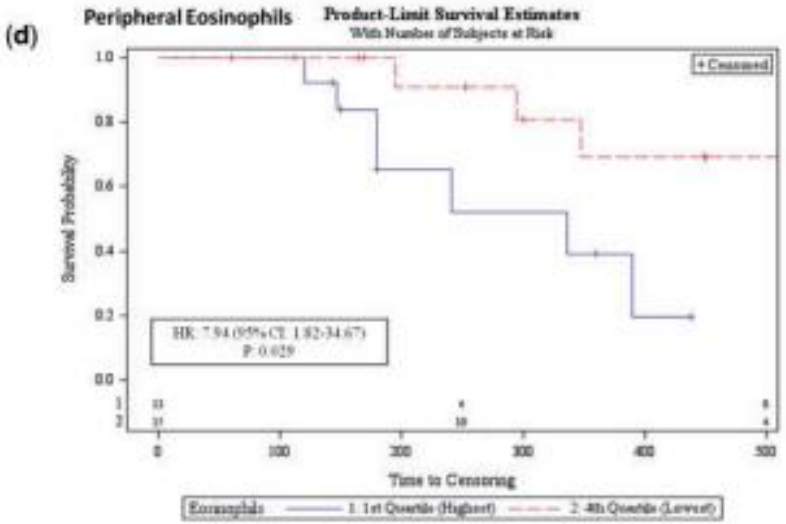
Predictors of disease relapse in IgG4-related disease following rituximab

Zachary S. Wallace[1], Hamid Mattoo[2,3], Vinay S. Mahajan[2,3], Maria Kulikova[2,3], Leo Lu[1,4], Vikram Deshpande[5,6], Hyon K. Choi[1,6], Shiv Pillai[2,3,6] and John H. Stone[1,6]









retrospective cohort study
: total 60patients

Serum IgG4

Plasmablasts

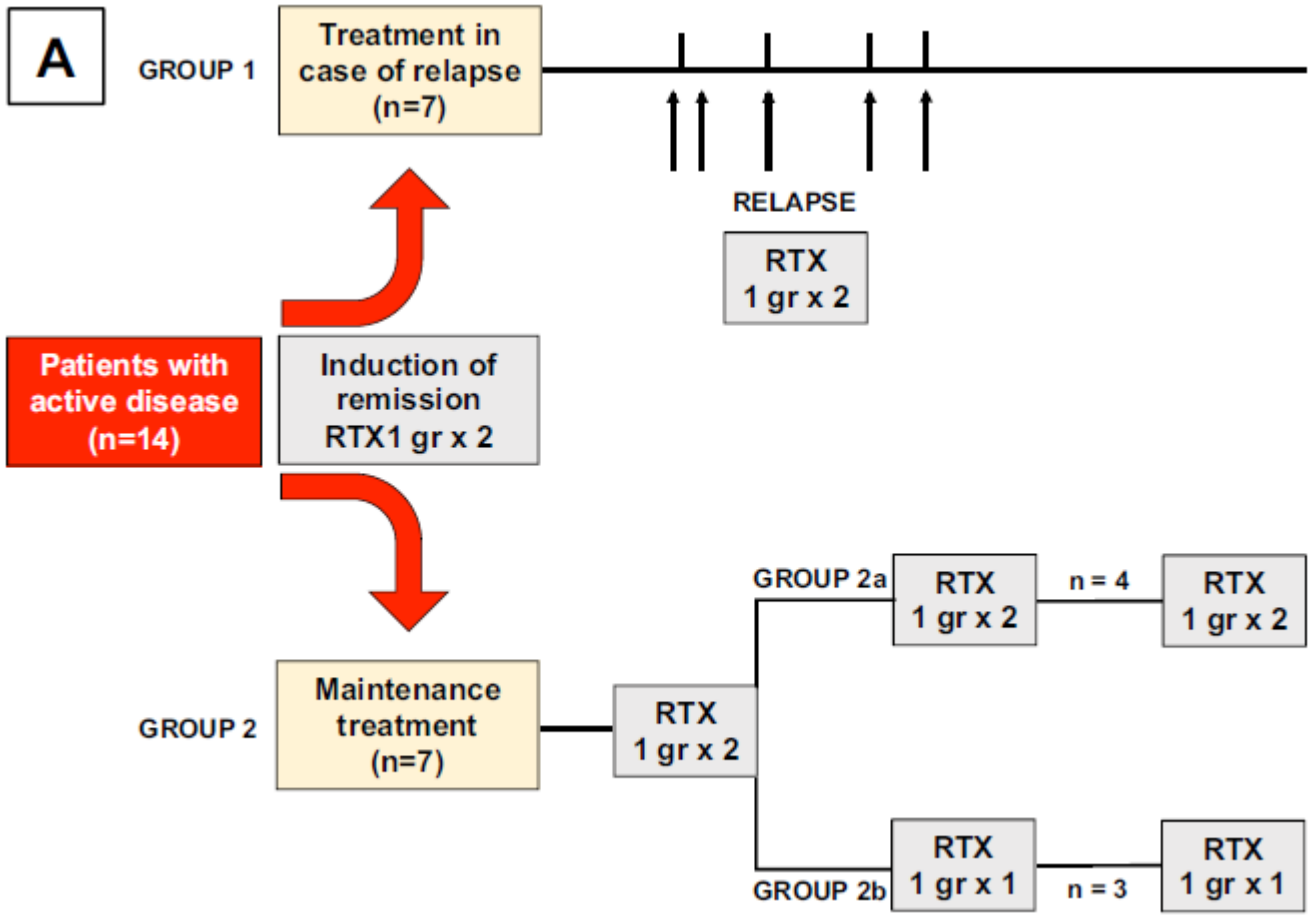
Serum IgE

Peripheral eosinophile

Rheumatology 2016;55

Long-term efficacy of maintenance therapy with Rituximab for IgG4-related disease

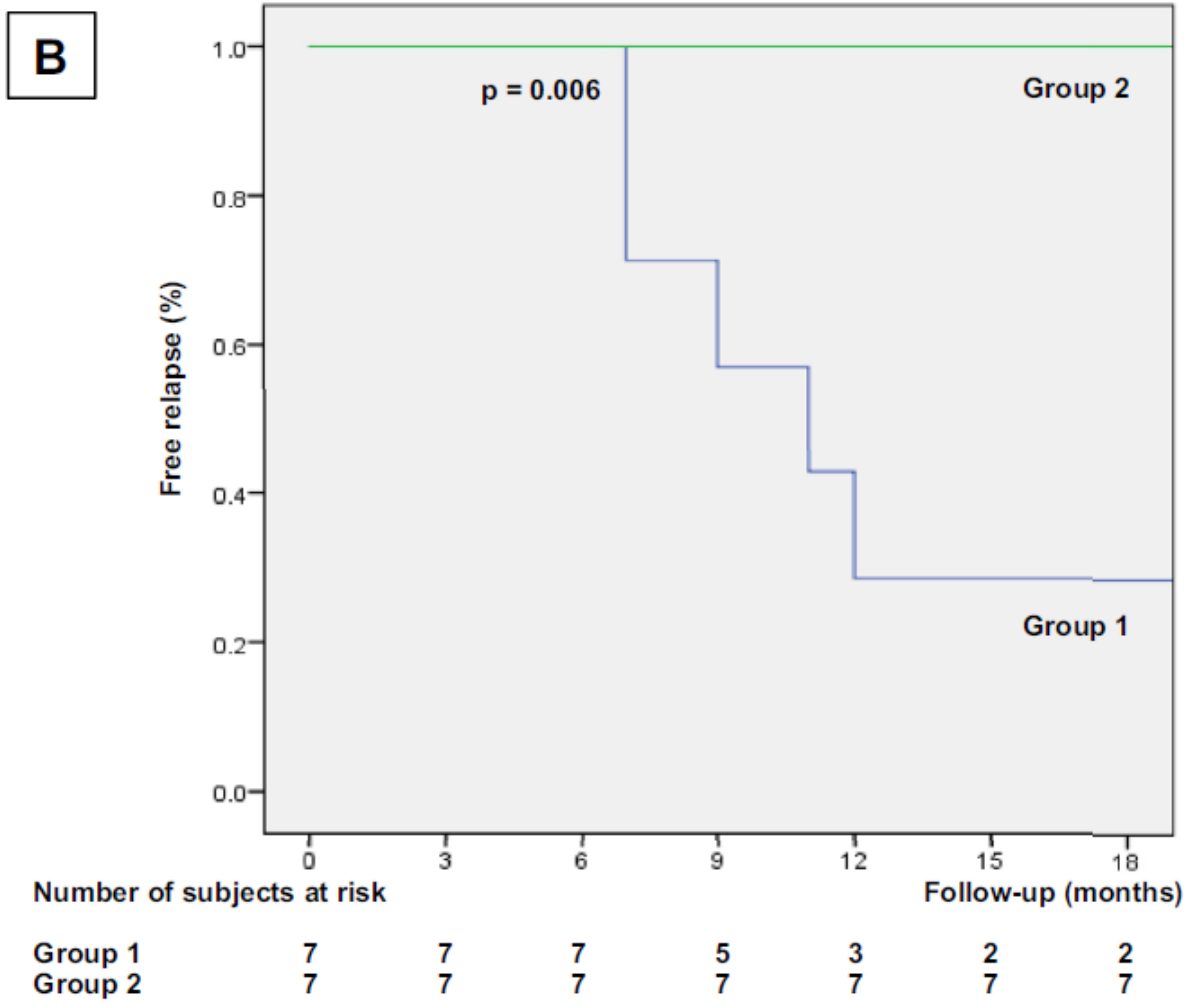
Corrado Campochiaro[a,b,f,#], Emanuel Della-Torre[a,b,f,*,#], Marco Lanzillotta[a,b,f], Enrica Bozzolo[b,f], Elena Baldissera[b,f], Raffaella Milani[c,f], Paolo Giorgio Arcidiacono[d,f], Stefano Crippa[b,e,f], Massimo Falconi[b,e,f], Lorenzo Dagna[a,b,f]



European Journal of Internal Medicine 74 (2020) 92–98

Long-term efficacy of maintenance therapy with Rituximab for IgG4-related disease

Corrado Campochiaro[a,b,f,#], Emanuel Della-Torre[a,b,f,*,#], Marco Lanzillotta[a,b,f], Enrica Bozzolo[b,f], Elena Baldissera[b,f], Raffaella Milani[c,f], Paolo Giorgio Arcidiacono[d,f], Stefano Crippa[b,e,f], Massimo Falconi[b,e,f], Lorenzo Dagna[a,b,f]

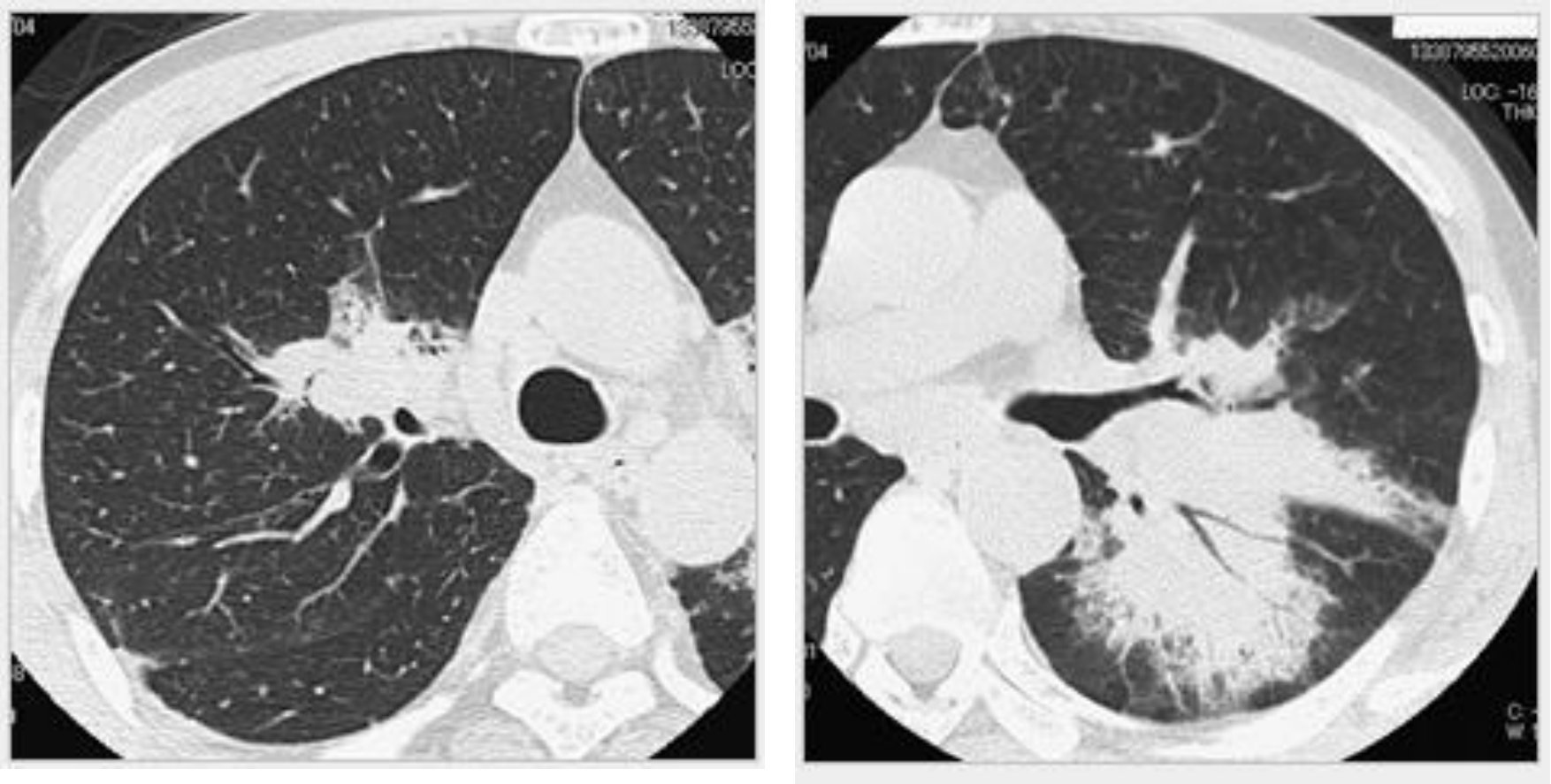


Free relase period : 18 months

Side-effect : infectious complication 6/14

European Journal of Internal Medicine 74 (2020) 92–98

IgG4-related lung disease (IgG4-RLD)



J Thorac Imaging Volume 22, Number 4, November 2007

IgG4-related lung disease (IgG4-RLD)

- Lymphoplasmacytic infiltration with Storiform
- Tumefactive lesion
- Fibrosis
- Allergic disease (up to 40%)
- Lung involvement : 10-23%

Mimiking condtion
Sarcoidosis and neoplasm
Interstitial lung disease associated with autoimmune diseases

IgG4+ plasma cells are frequent, although storiform fibrosis is not always present in lung biopsies

Neutrophilic aggregates might be seen in the lung, unlike in other tissues in IgG4-RD

the extension of the fibroinflammatory infiltrate along the perilymphatic

Clinical feature of IgG4-RLD

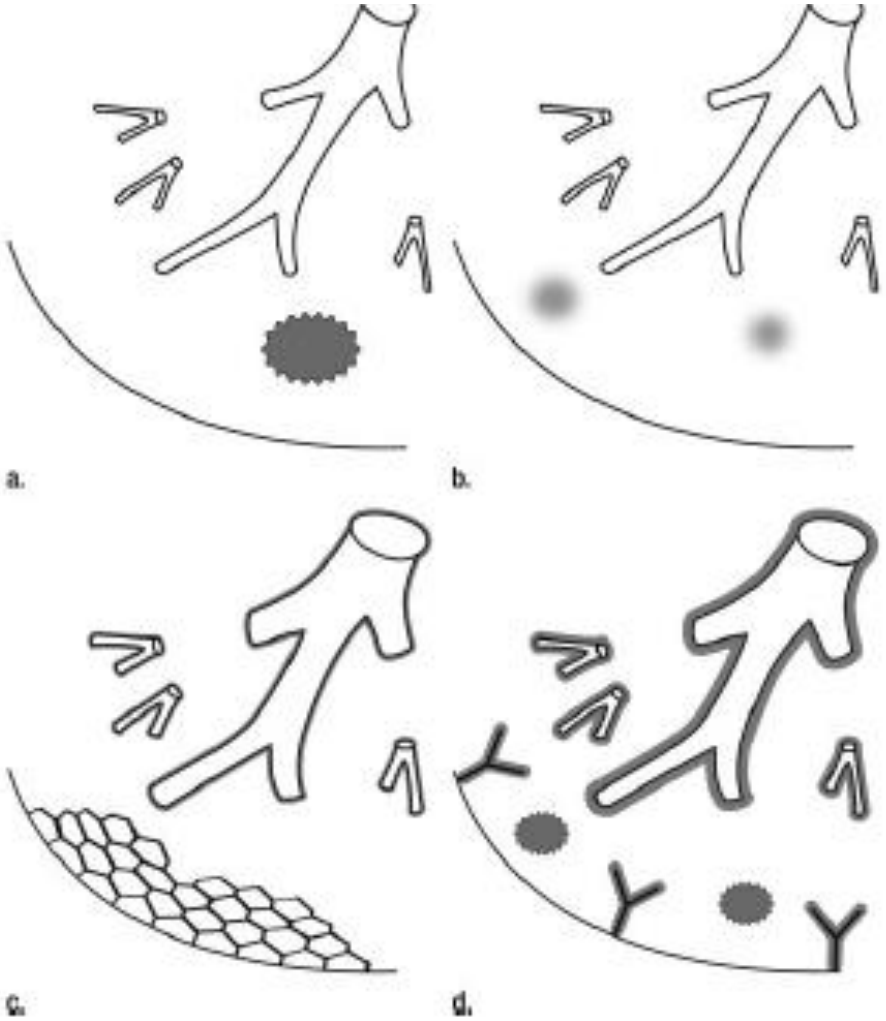
Clinical Symptom
Chest pain
None
Cough
Cough
Low-grade fever
None
Cough, dyspnea on exertion
Fever
Cough
Cough, low-grade fever
Cough
Cough, low-grade fever, dyspnea on exertion
None

Radiology 2009;251:260–270

respiratory symptoms (n=10)
cough (n=9)
expectoration (n=6)
hemoptysis (n=6)
chest tightness (n=2)
breathless (n=2)
No respiratory Symptoms (n=3)

中华医学杂志, 2018,98(42)

Immunoglobulin G4–related Lung Disease: CT Findings with Pathologic Correlations[1]



a. Solid nodular

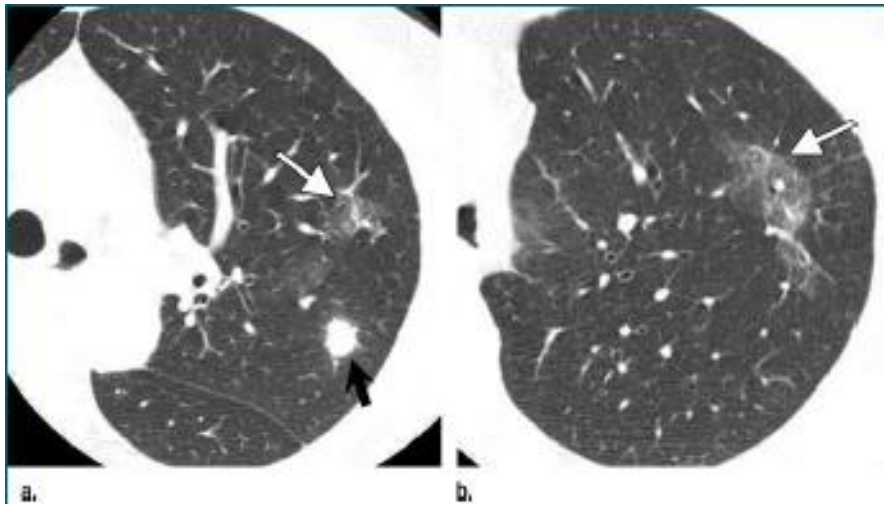
b.Round-shaped, ground-glass opacities

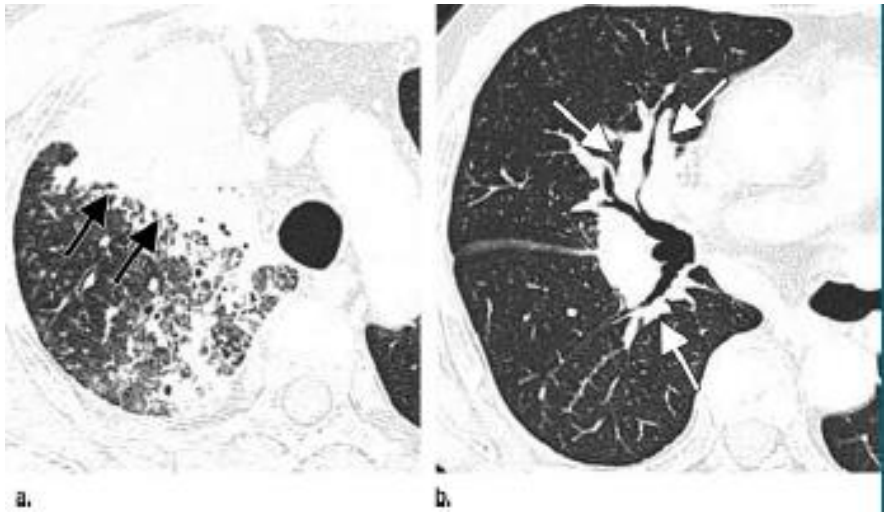
c. Alveolar interstitial (with honeycombing, ronchiectasis, and diffuse ground-glass opacities

d. Bronchovascular (with thickening of bronchovascular bundles and interlobular septa)

Radiology: Volume 251: Number 1—April 2009

Immunoglobulin G4–related Lung Disease: CT Findings with Pathologic Correlations[1]





a. Solid nodular

b.Round-shaped, ground-glass opacities

c. Alveolar interstitial (with honeycombing, ronchiectasis, and diffuse ground-glass opacities

d. Bronchovascular (with thickening of bronchovascular bundles and interlobular septa)

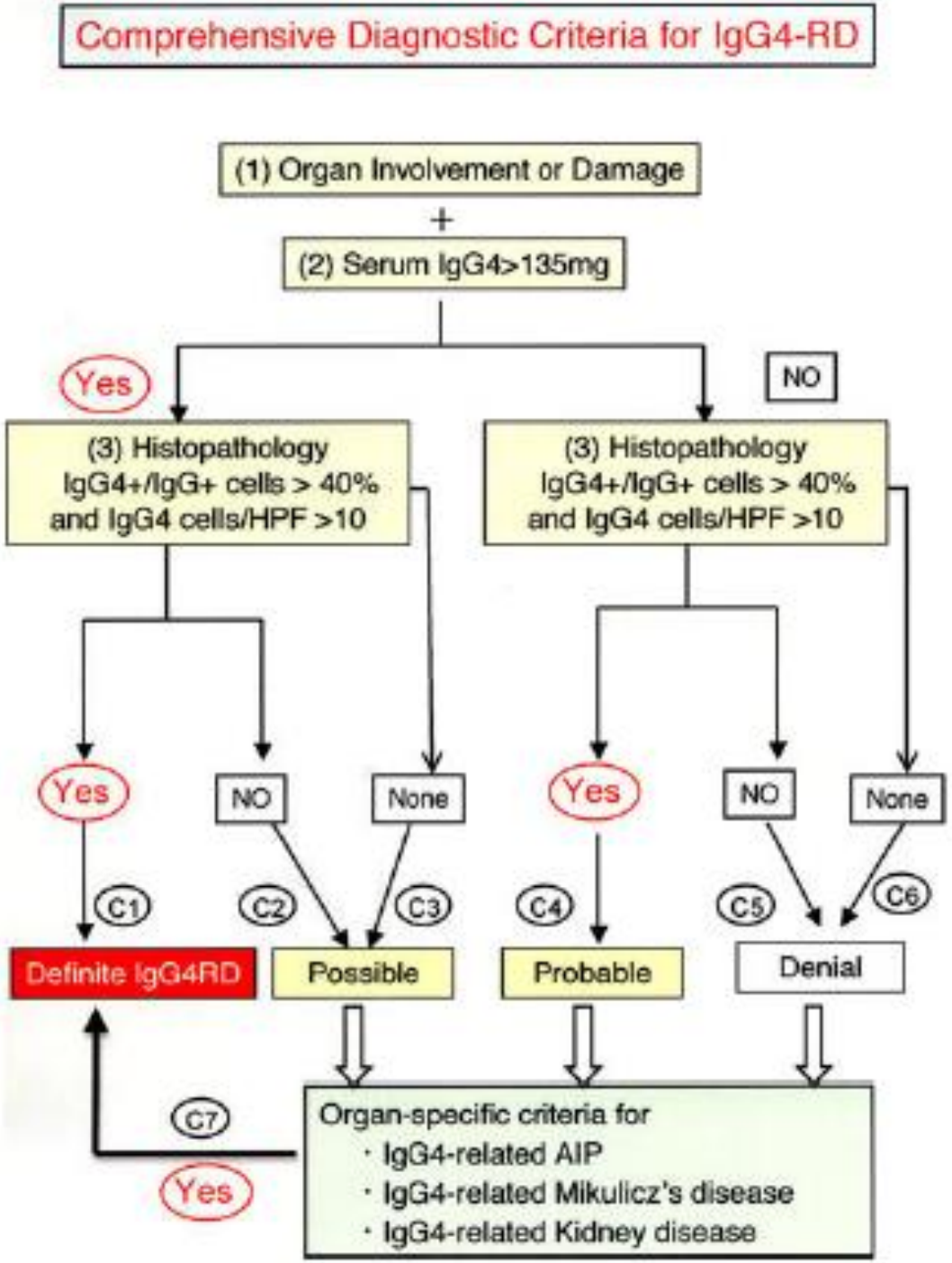
Radiology: Volume 251: Number 1—April 2009

IgG4-related Lung and Pleural Disease: A Clinicopathologic Study of 21 Cases

Zen, Yoh MD[*†]; Inoue, Dai MD[‡]; Kitao, Azusa MD[‡]; Onodera, Manabu MD[†]; Abo, Hitoshi MD[§]; Miyayama, Shiro MD[‖]; Gabata, Toshifumi MD[‡]; Matsui, Osamu MD[‡]; Nakanuma, Yasuni MD[†]

	Pulmonary Lesions				
	Nodular (n = 9)	Bronchovascular (n = 4)	Interstitial (n = 2)	Round GGO (n = 1)	Pleural Lesions (n = 5)
Average age (range)	60 (43-72)	57 (42-70)	66 (59-73)	43	62 (49-76)
Sex (M/F)	6/3	3/1	2/0	1/0	5/0
Pathological specimen (surgical/VATS/biopsy)	7/1/1	1/2/1	0/1/1	0/1/0	1/3/1
Allergic disorders	3 (33%)	4 (100%)	1 (50%)	0	1 (20%)
Extrapulmonary lesions	2 (22%)	3 (75%)	1 (50%)	0	3 (60%)
High-serum IgG concentration	3/4 (75%)	4/4 (100%)	1/1 (100%)	1/1 (100%)	3/3 (100%)
High-serum IgG4 concentration	1/1 (100%)	3/3 (100%)	2/2 (100%)	1/1 (100%)	2/4 (50%)
Association with premalignant or malignant lesions within IgG4-related lesions	0	1 (AAH)	1 (adenoca)	0	0

Am J Surg Pathol 2009;33



1. Clinical examination showing 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+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF

Mod Rheumatol (2012) 22:21–30

Proposed diagnostic criteria for IgG4-related respiratory disease ☆

Shoko Matsui[a,*], Hiroshi Yamamoto[b], Seijiro Minamoto[c], Yuko Waseda[d], Michiaki Mishima[e], Keishi Kubo[f]

I. chest radiograrphy	hilar/mediastinal lymphadenopathy bronchialwall/bronchovascular bundle thickening interlobular septal wallthickening, nodular shadow infiltrative shadow pleuralthickening and/or effusion
II. Serology	Elevated serum IgG4 concentration of more than 135 mg/d
III. Histology a :3 items b :2 items	(1) Marked lymphoplasmacytic cell infiltration (2) IgG4/IgG-positive cell ratio>40% and/or >10 IgG4-positive cells/high powerfield. (3) Obliterative phlebitis or obliterative arteritis. (4) Storiformfibrosis or fibrosis consisting of proliferating spindle-shaped cells around infiltrating lymphoc
IV. Other organ involvement	
V. Reference finding	Hypocomplementemia

Respir Investig. 2016 Mar;54(2):130-2. Epub 2015 Oct 20.

Proposed diagnostic criteria for IgG4-related respiratory disease ☆

Shoko Matsui[a,*], *Hiroshi Yamamoto*[b], *Seijiro Minamoto*[c], *Yuko Waseda*[d], *Michiaki Mishima*[e], *Keishi Kubo*[f]

I. chest radiograrphy	hilar/mediastinal lymphadenopathy bronchialwall/bronchovascular bundle thickening interlobular septal wallthickening, nodular shadow infiltrative shadow pleuralthickening and/or effusion
II. Serology	Elevated s
III. Histology a :3 items b :2 items	(1) Marke (2) IgG4/I (3) Oblite (4) Storifo infiltra
IV. Other organ involvement	
V. Reference finding	Hypocomplementemia

B. Diagnosis

1. Definite diagnosis (definite): I+II+IIIa, or I+II+IIIb+IV
   Histological definite diagnosis [definite (histological)]: I+all four items of III
2. Probable diagnosis (probable): I+II+IV, or I+II +IIIb+V
3. Possible diagnosis (possible): I+II+IIIb

Respir Investig. 2016 Mar;54(2):130-2. Epub 2015 Oct 20.

Pattern of pulmonary involvement

Pulmonary malignancy

Interstitum

Mediastinum

Airway disease

Pleural disease

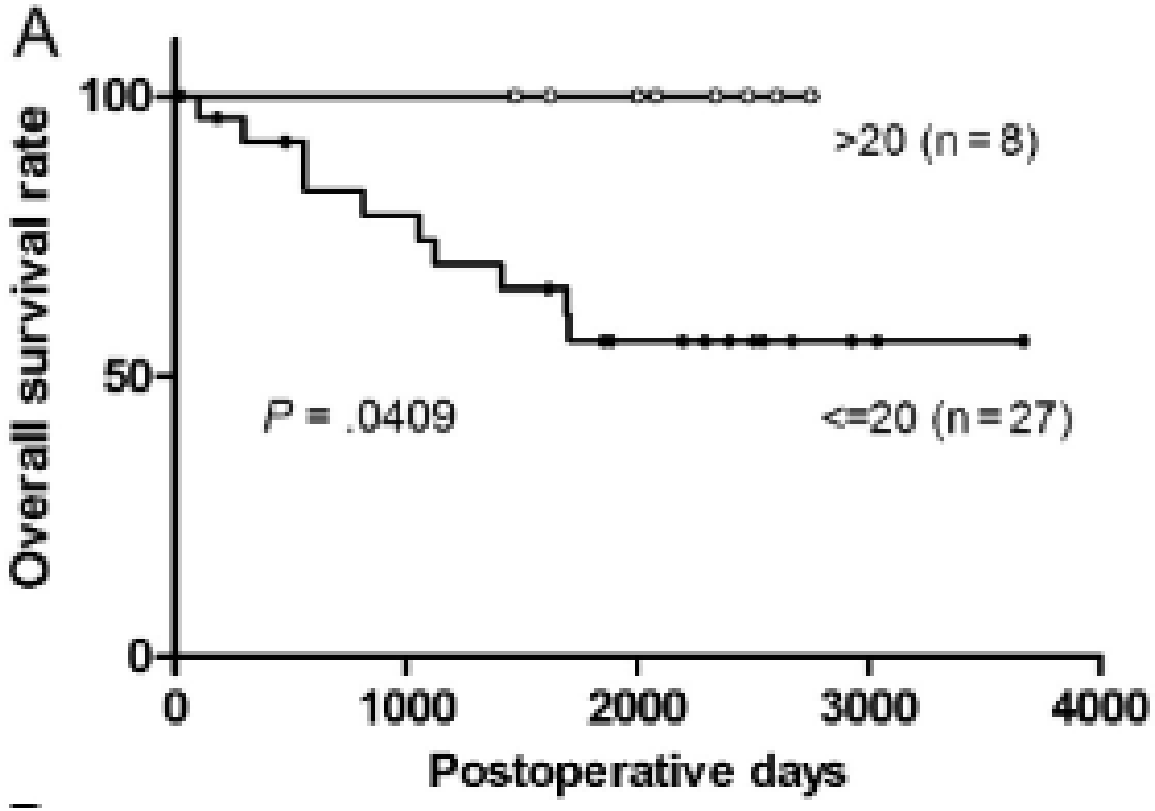
Lung cancer in IgG4-RD

Type of malignancy	Before diagnosis of IgG4-RD	After diagnosis of IgG4-RD
Total	30	36
Time before or after diagnosis of IgG4-RD (years)	6.1	2.7
Lung cancer	6	6
Colon cancer	4	5
Renal cancer	4	1
Prostate cancer	3	4
Gastric cancer	2	5
Breast cancer	2	0
Malignant lymphoma	2	5

Arthritis Research & Therapy (2017) 19:262

Stromal plasam cells expressing IgG4 in Non-Small Cel lung ca

Stage I lung cancer in 2001 – 2007



Human Pathology (2013)44, 1569–1576

Interstinum involvement of IgG4-RLD

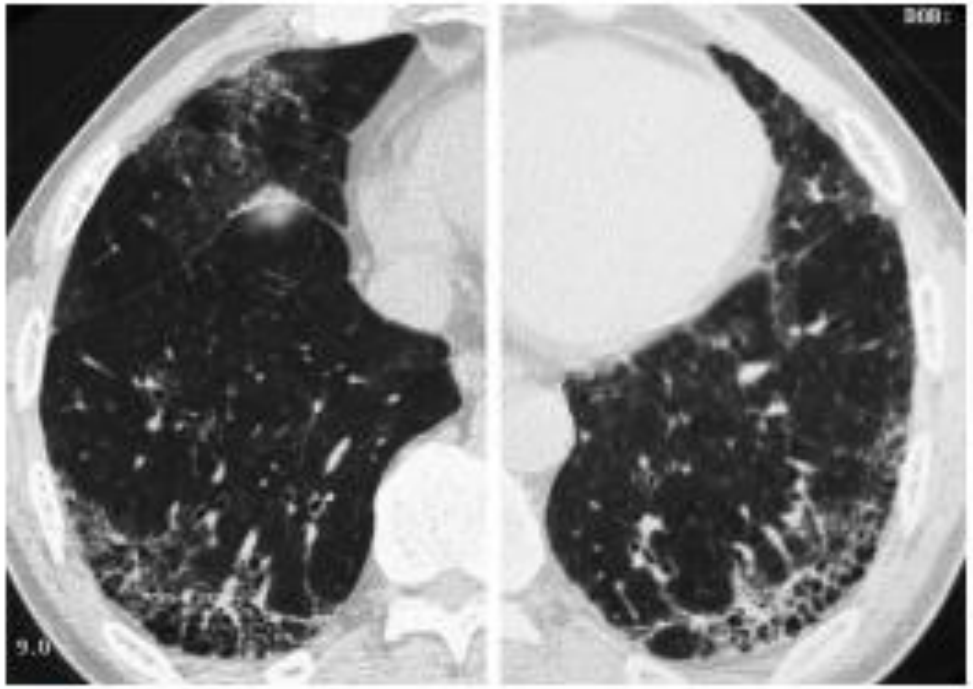


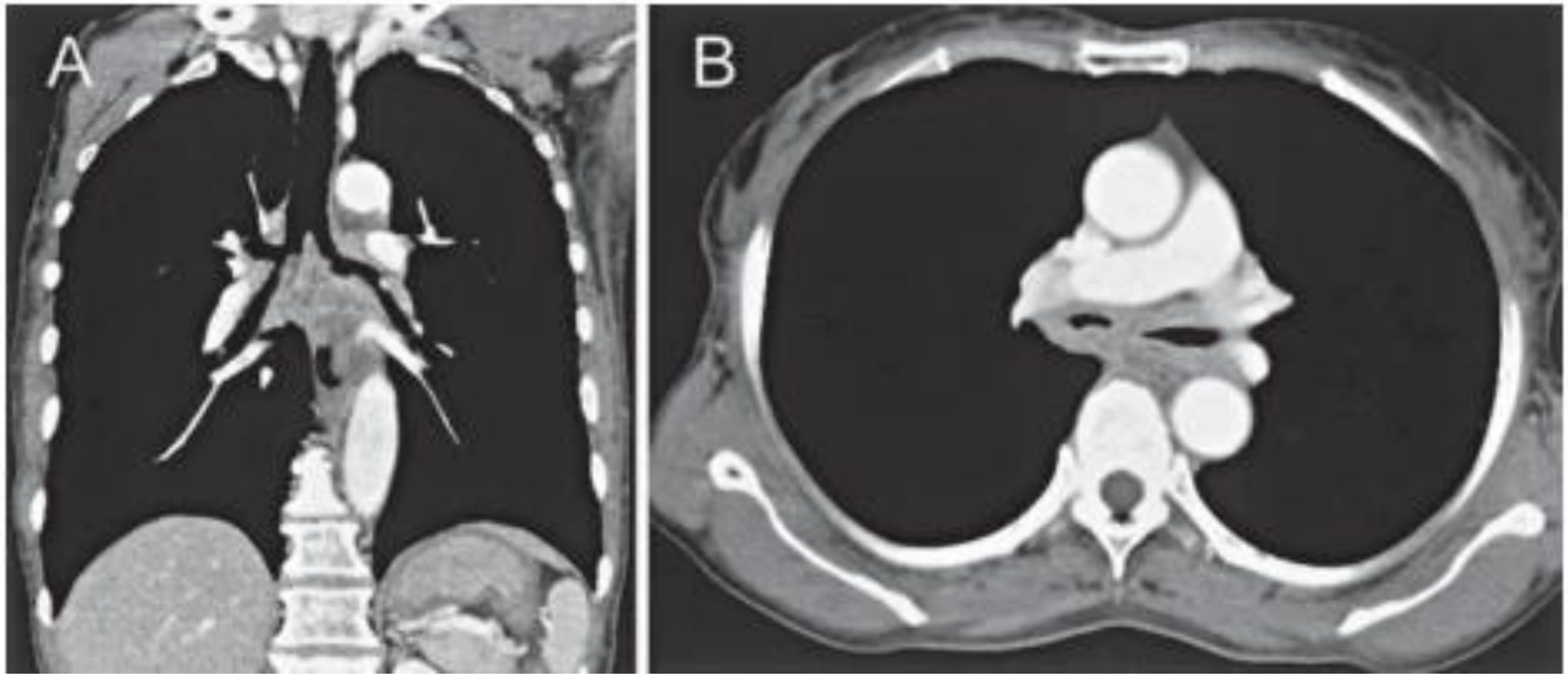
Figure 2. Chest CT scan shows ground-glass opacities and reticular shadows with honeycomb-like changes and traction bronchiectasia especially in the two lower lobes.

Intern Med 2008;47:291–294

Fig. 2. Chest CT on admission. There is consolidation adjacent to the pleura in the right upper lobe.

Endocr J 2006;53: 563–566

Mediastinum



Sclerosing mediastinitis

Thorac Cardiovasc Surg 2007;55:431–433

Three Cases of Bronchial Asthma Preceding IgG4-Related Autoimmune Pancreatitis

ABSTRACT

Background: Autoimmune pancreatitis is characterized by diffuse swelling of the pancreas and a high serum immunoglobulin (Ig) G4 concentration. Histopathologically, dense infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis are seen in the pancreas. Although allergic diseases complicating autoimmune pancreatitis have been reported, the clinical features of bronchial asthma complicated by autoimmune pancreatitis remain unclear.

Case Summary: We report three cases of bronchial asthma preceding the onset of type 1 autoimmune pancreatitis by 3 months to 30 years. All three cases were males with high serum IgG, IgG4, and IgE concentrations. The radioallergosorbent tests were positive for common allergens such as mites and house dust. One case had a pulmonary manifestation that proved to be an inflammatory pseudotumor of the lung with an accumulation of IgG4-positive plasma cells. The asthma symptom was ameliorated by oral prednisolone therapy for autoimmune pancreatitis, and when the corticosteroid doses were reduced, asthma became worse in all three cases.

Discussion: It is possible that atopy and increased Th2 cell activity are related to a higher coincidence of IgG4-related diseases such as type 1 autoimmune pancreatitis. Because the present cases are few in number, further studies are necessary.

Table 1 Clinical and laboratory findings in three cases of asthma with autoimmune pancreatitis

Case No.	Age, y/Sex	Asthma onset	Steroid therapy	IgG (mg/dL)	IgG4 (mg/dL)	IgE (IU/mL)	Eosinophil (/μL)	RAST	Auto-antibody	Biopsy
1	32/M	Pre	Yes	1574	776	280	399	Positive	ANA	ND
2	61/M	Pre	Yes	1740	1090	7220	288	Positive	Negative	Lung
3	60/M	Pre	Yes	4480	1550	233	552	Positive	RF	Pancreas

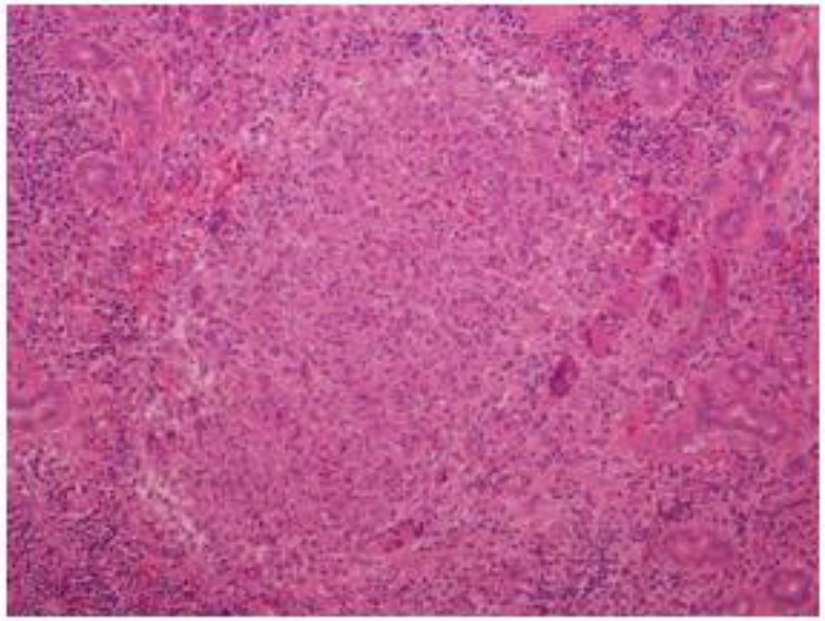
RAST, radioallergosorbent test; ANA, positive anti-nuclear antibody; RF, positive rheumatoid factor.

Allergology International Vol 61, No1, 2012

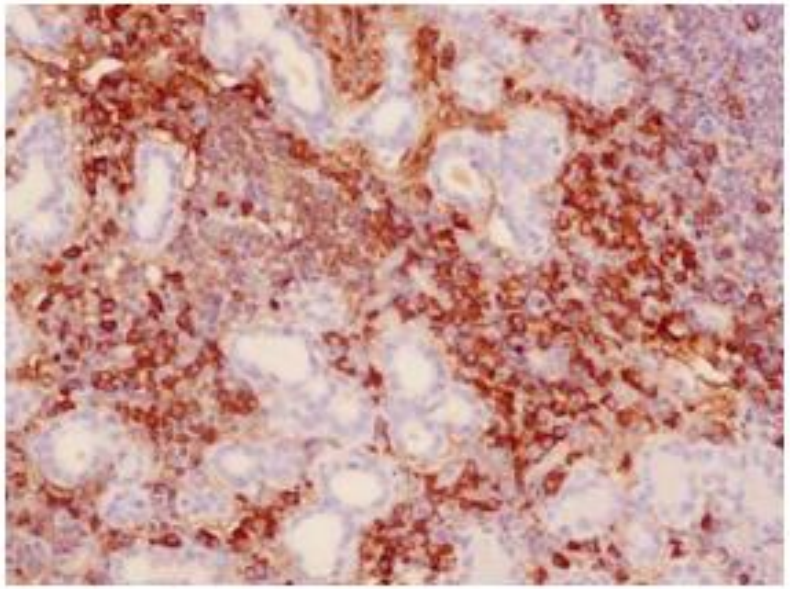
A case of immunoglobulin G4-related chronic sclerosing sialadenitis and dacryoadenitis associated with tuberculosis

Mitsuhiro Kawano · Kazunori Yamada · Yasushi Kakuchi · Kiyoaki Ito · Ryoko Hamano · Hiroshi Fujii · Ryo Inoue · Masami Matsumura · Masayuki Takahira · Yoh Zen · Akihiro Yachie · Akikatsu Nakashima · Masakazu Yamagishi

A 64-year-old
A swelling in her right lacrimal gland



Granuloma without caseous necrosis



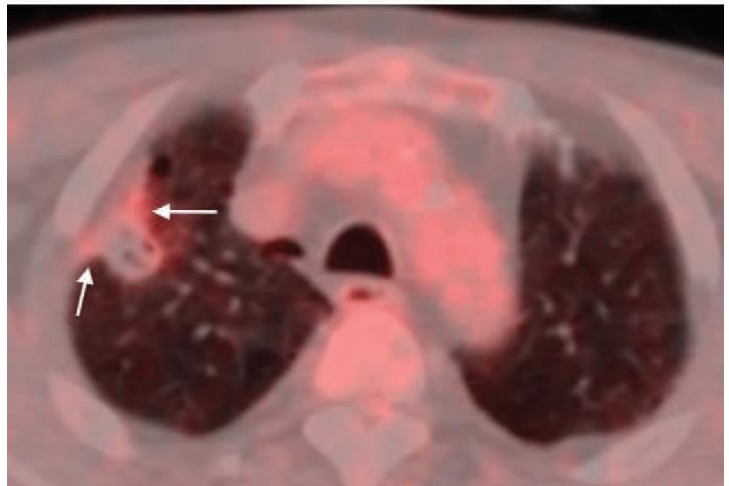
Abundant IgG4-positive plasma cells

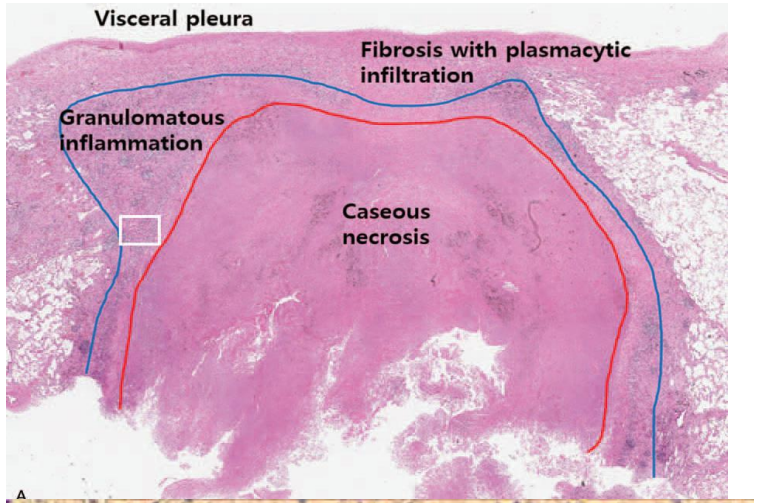
Mod Rheumatol (2009) 19:87–90

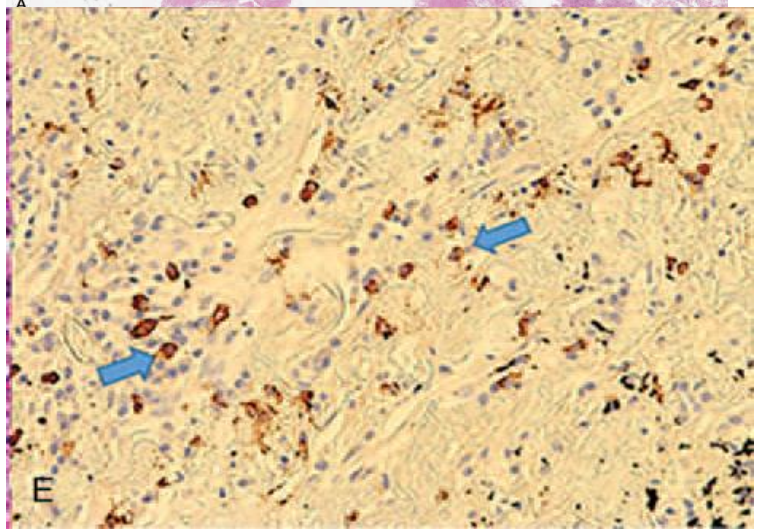
Coexistence of nontuberculous mycobacterium and IgG4-related disease in a solitary pulmonary nodule

A case report

Kyungsoo Bae, MD, PhD[a,b], Hyo Jung An, MD[c], Kyung Nyeo Jeon, MD, PhD[a,b,*], Dae Hyun Song, MD[d], Sung Hwan Kim, MD[e], Ho Cheol Kim, MD[f]







A 76-year-old male

presented cough and sputum.

Bae et al. Medicine (2019) 98:48

IgG4-related disease of pulmonary artery causing pulmonary hypertension

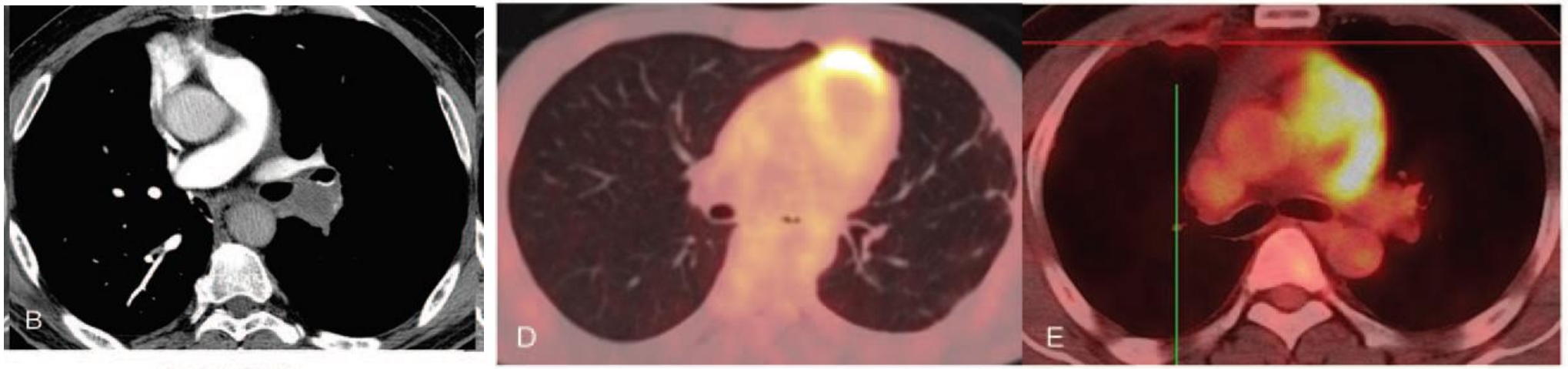
Hui Deng, MD[a], Sheng Zhao, MD[b], Yunlong Yue, MD[c], Yong Liu, MD[d], Yali Xu, MD[a], Jin Qian, MD[a], Xiaorong Ma, MD[a], Peiliang Gao, MD[a], Xiaoyan Yao, MD[a], Xin Jiang, MD[e], Xiqi Xu, MD[e], Zhicheng Jing, MD[e], Yong Wang, MD[a,*], Lei Pan, MD[a,*], Xinying Xue, MD[a,*]

	Patient 1	Patient 2	Patient 3
Age/sex	47/M	52/M	32/M
History (medical/travel/ contact/family)	No history	Pneumonectomy of right middle and below lung	Tuberculosis (recovery)
Symptoms	Short breath after activity	Cough, sputum, blood in phlegm, hemoptysis	Short breath after activity
MRI	Not done	Not done	PE in main PA and right PA, PH
Ultrasonic cardiogram	PE in main PA, PH	Left PA wall thickening and obliteration, PE in right PA, PH	PE in main PA and right PA, PH
Pulmonary perfusion imaging	Not done	Not done	Chronic PE
PET/CT (Suv)	3.1 (not PE)	3.2 (benign lesion)	2.4 (not PE)
RHC (PAP mmHg)	Main pulmonary artery: 97/13/48 Distal segment of right PA stenosis: 18/	Not done	Main pulmonary artery: 118/23/59 Distal segment of right PA stenosi: 21/13/16
Serum IgG, g/L	↑(17.9)	↑(19.4)	↑(19.4)
Serum IgG4 before/after treatment, mg/L	↑(2214→662)	Normal(637)	↑ormal→833)
Serum IgE, IU/mL	↑264.4	Not done	↑ot done/
IHC	CD138(+),IgG(+),IgG4(+),IgG4/IgG(58.2%)	AE1/AE3(+),CD3(+),CD20(+),CD38(+),IgG4/ IgG20%,IgG4(30/HPF)	CD20(+),CD37(+),CD38(+), IgG4/IgG(46.38%)
Treatment	Methylprednisolone and rituximab	Methylprednisolone	Methylprednisolone and cyclophosphamide
Improvement (following up days)	Lesions shrunk remarkably (31 mo)	Dead	Lesions shrunk remarkably (3 mo)

Deng et al. Medicine (2018) 97:20

IgG4-related disease of pulmonary artery causing pulmonary hypertension

Hui Deng, MD[a], Sheng Zhao, MD[b], Yunlong Yue, MD[c], Yong Liu, MD[d], Yali Xu, MD[a], Jin Qian, MD[a], Xiaorong Ma, MD[a], Peiliang Gao, MD[a], Xiaoyan Yao, MD[a], Xin Jiang, MD[e], Xiqi Xu, MD[e], Zhicheng Jing, MD[e], Yong Wang, MD[a,*], Lei Pan, MD[a,*], Xinying Xue, MD[a,*]



IgG4-RD

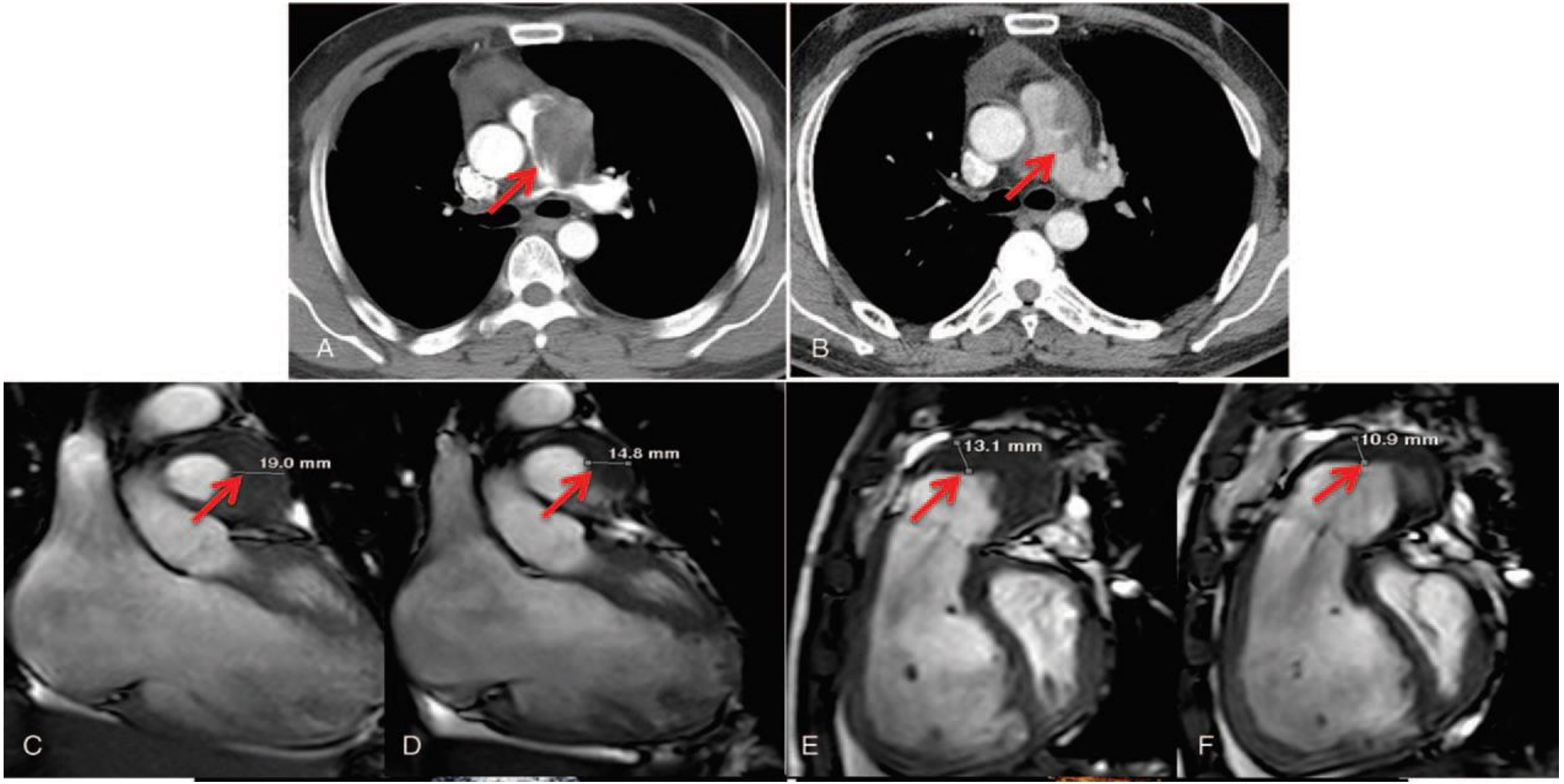
IgG4-RD

Tumor

) 97:20

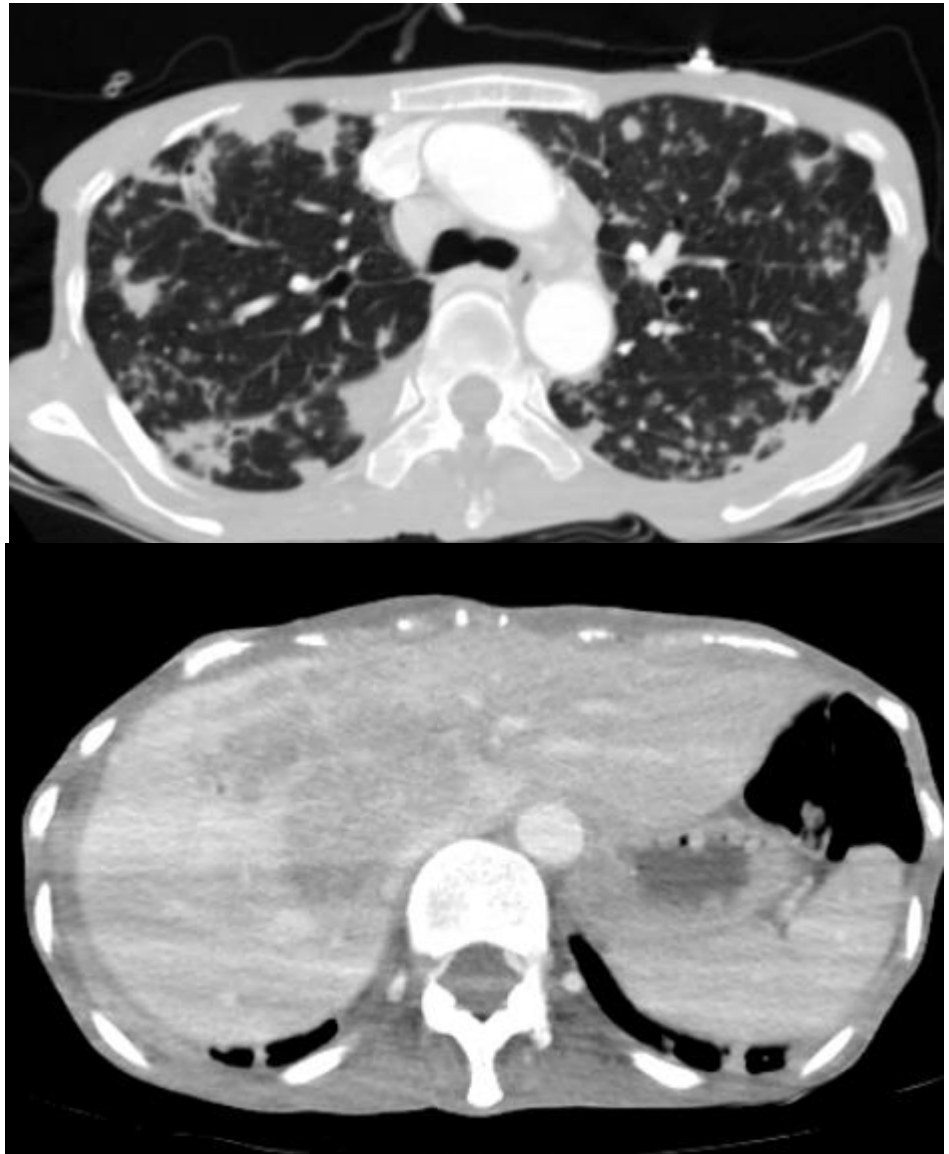
IgG4-related disease of pulmonary artery causing pulmonary hypertension

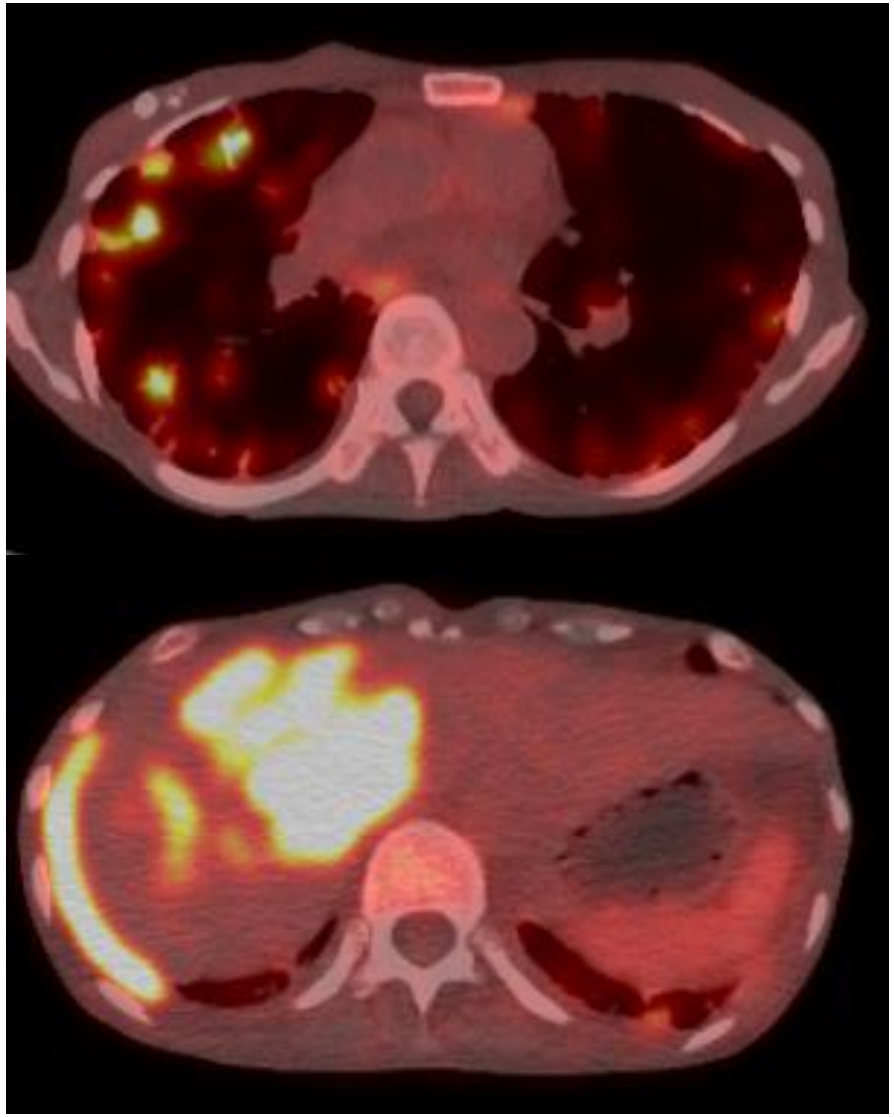
Hui Deng, MD[a], Sheng Zhao, MD[b], Yunlong Yue, MD[c], Yong Liu, MD[d], Yali Xu, MD[a], Jin Qian, MD[a], Xiaorong Ma, MD[a], Peiliang Gao, MD[a], Xiaoyan Yao, MD[a], Xin Jiang, MD[e], Xiqi Xu, MD[e], Zhicheng Jing, MD[e], Yong Wang, MD[a,*], Lei Pan, MD[a,*], Xinying Xue, MD[a,*]



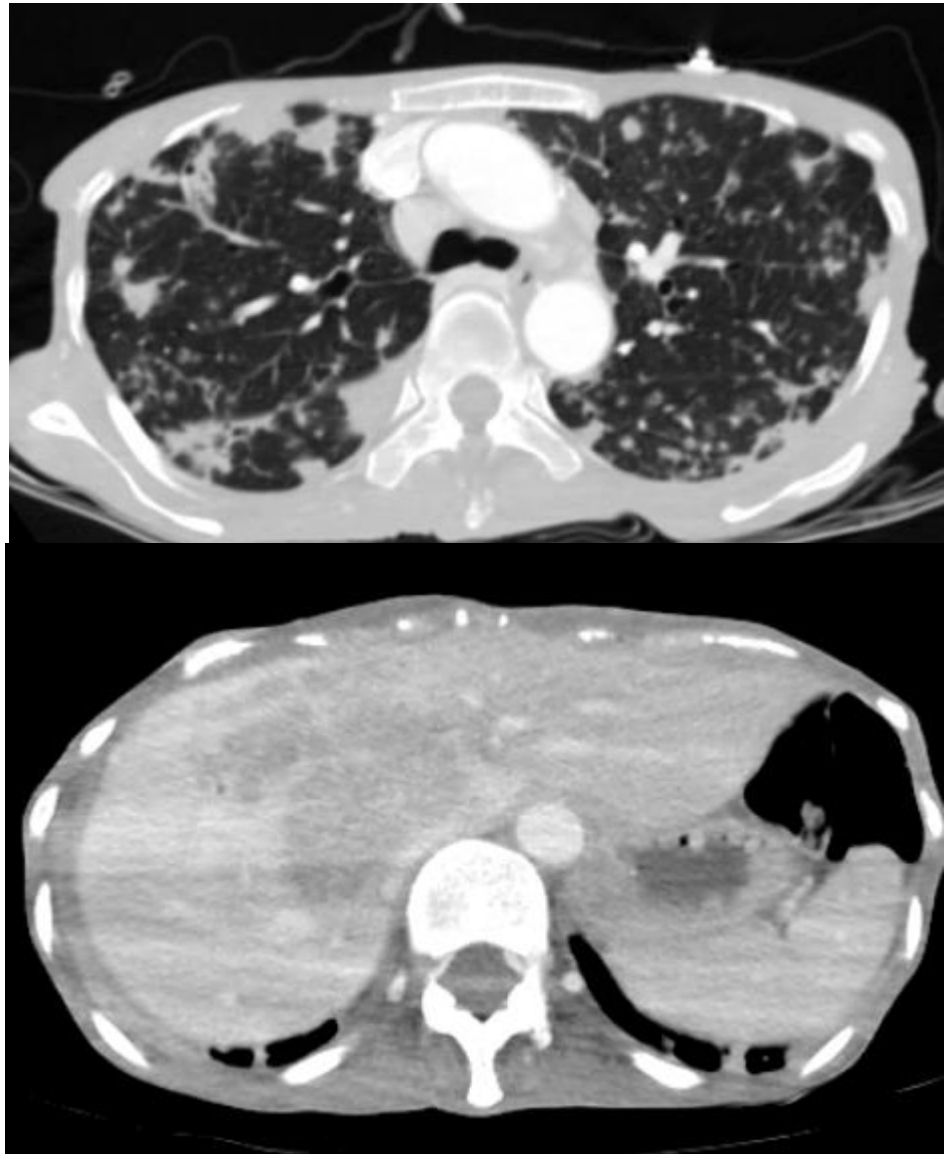
Deng et al. Medicine (2018) 97:20

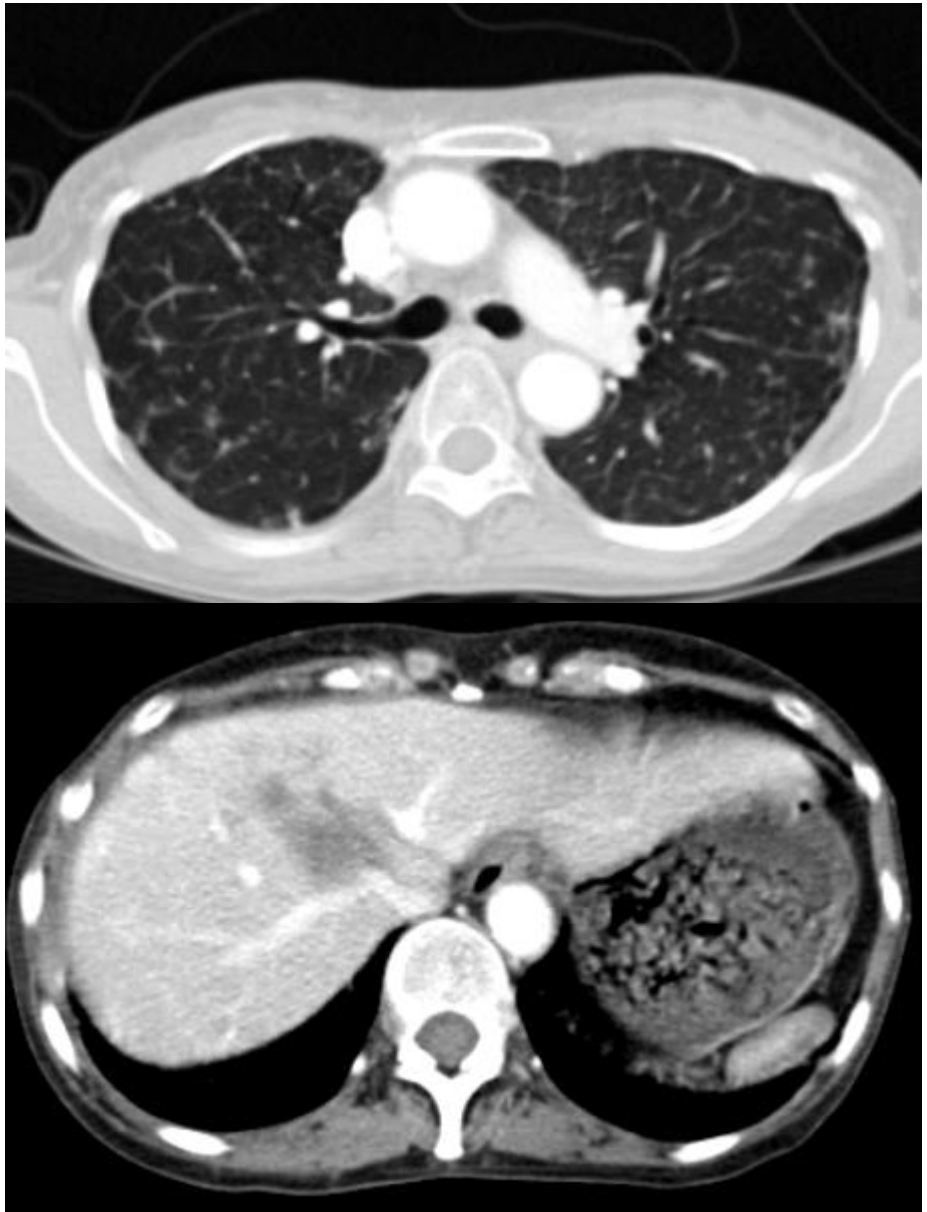
Case F/ 50 :dyspnea





Case F/ 50 :dyspnea





Take Home message

Clinical Features	Laboratory	Imaging	Diagnostic Criteria IgG4-RD (45)
Symptoms Cough Chest pain Dyspnea Hemoptysis Asymptomatic	↑ serum IgG4 (most patients) KL-6 may be ↑ in serum and/or BAL ANA, RF, CRP, ESR levels are unreliable	Involvement Airways Interstium Mediastinum Pleura CT patterns Solid nodular lesion Round-shaped GGOs Alveolar interstitial type with honeycombing, bronchietasis and diffuse GGOs Bronchovascular type with thickening of the bronchovascular bundles and interlobular septa PET Lesions may have varying degrees of avidity	Highly suggestive of disease Requires at least two histopathologic features (except dacryoadentitis): Dense lymphoplasmacytic infiltrate Fibrosis (storiform) Obliterative phlebitis Elevated $IgG4^+$:IgG^+ cell ratio $>$ 40% Probable histopathologic features Single histologic feature Requires additional evidence to confirm diagnosis (for example): Other organ involvement Serum IgG4 level $>$ 135 mg/dl Insufficient histopathological evidence Does not meet either above category