Paris, 27.04.2017

Chronic Periaortitis and IgG4-Related Disease

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JOAQUÍN ALBARRÁN (1860-1912)

HÔPITAL COCHIN

Albarrán J. Retention renale par peri-ureterite: liberation externe de l'uretere. *Assoc Fr Urol* 1905

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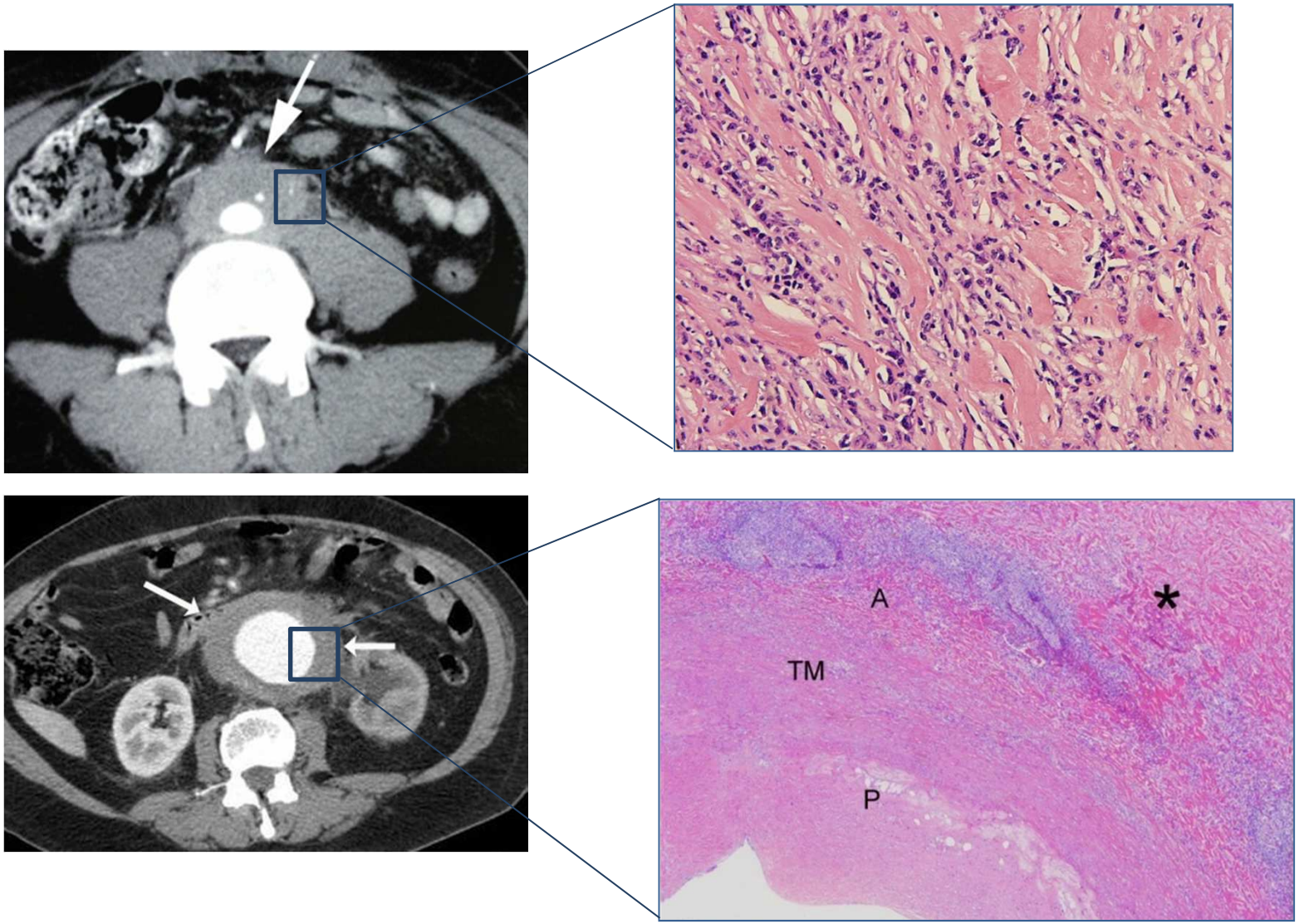
Albarrán J. Retention renale par peri-ureterite: liberation externe de l'uretere. *Assoc Fr Urol* 1905

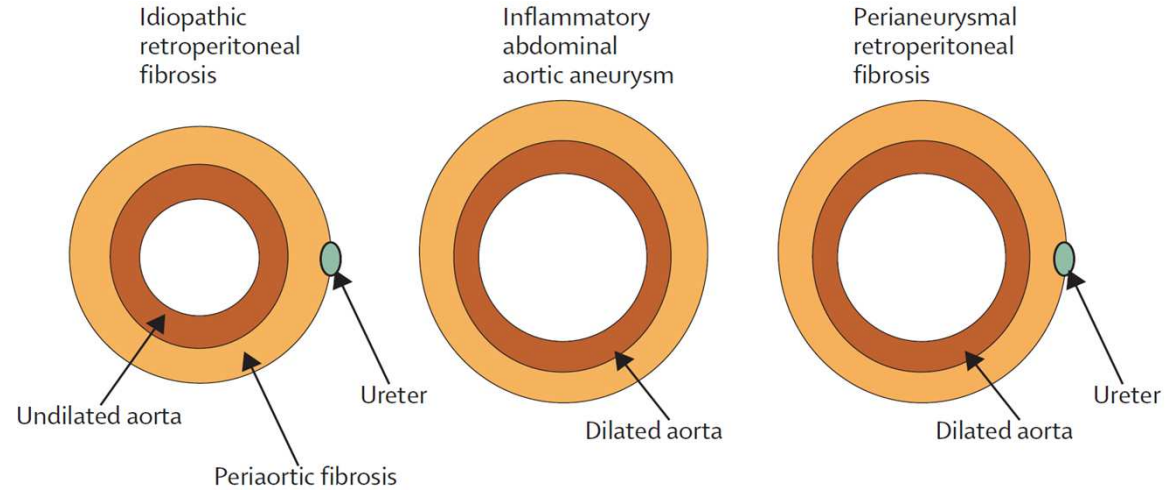
JOHN K. ORMOND (1886–1978)

Ormond JK. Bilateral ureteral obstruction due to envelopment and compression by an inflammatory process. *J Urol* 1948

FROM RETROPERITONEAL FIBROSIS TO CHRONIC PERIAORTITIS



THE SPECTRUM OF CHRONIC PERIAORTITIS

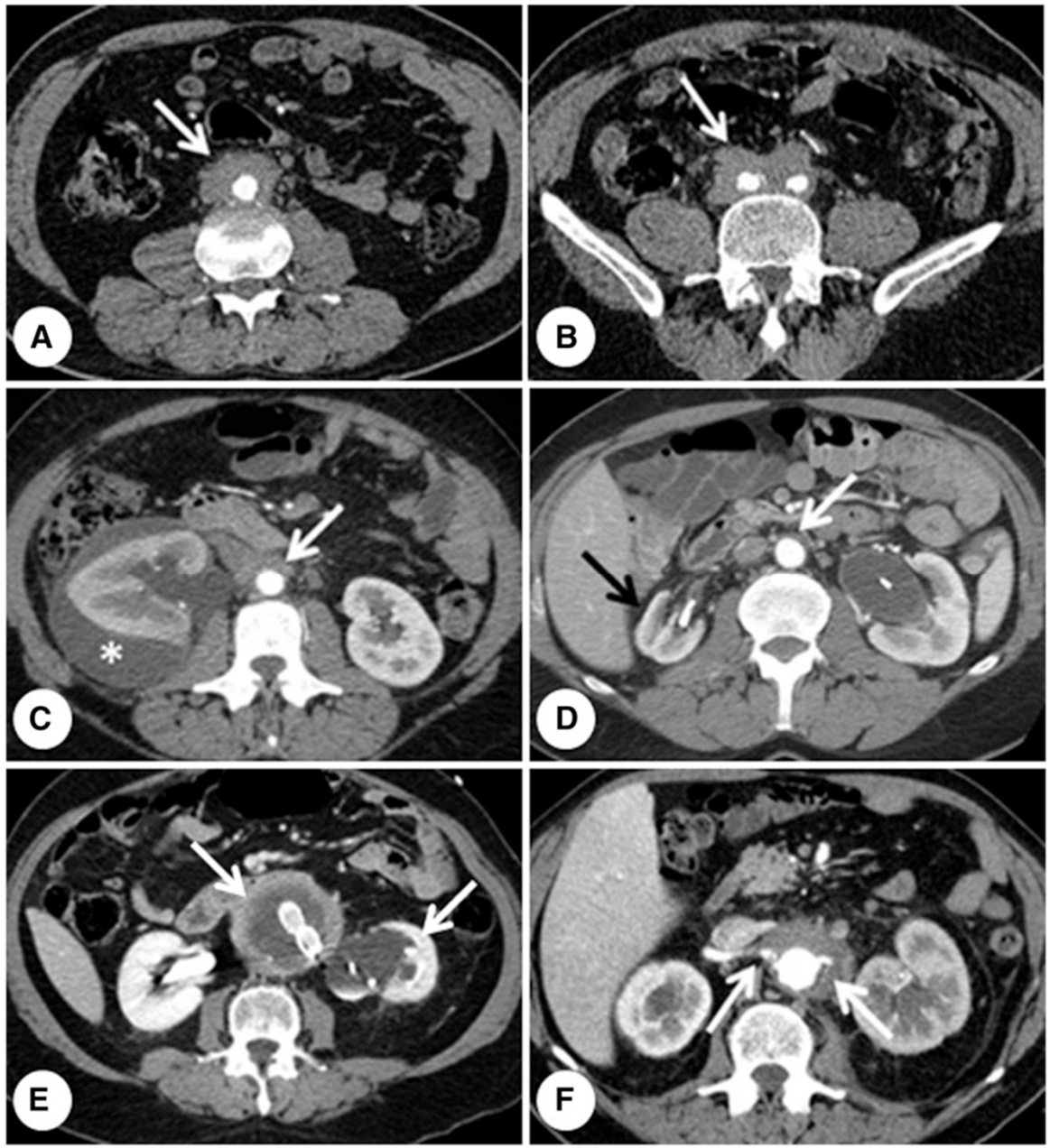


IDIOPATHIC RPF/NON-ANEURYSMAL CP

ANEURYSMAL CP

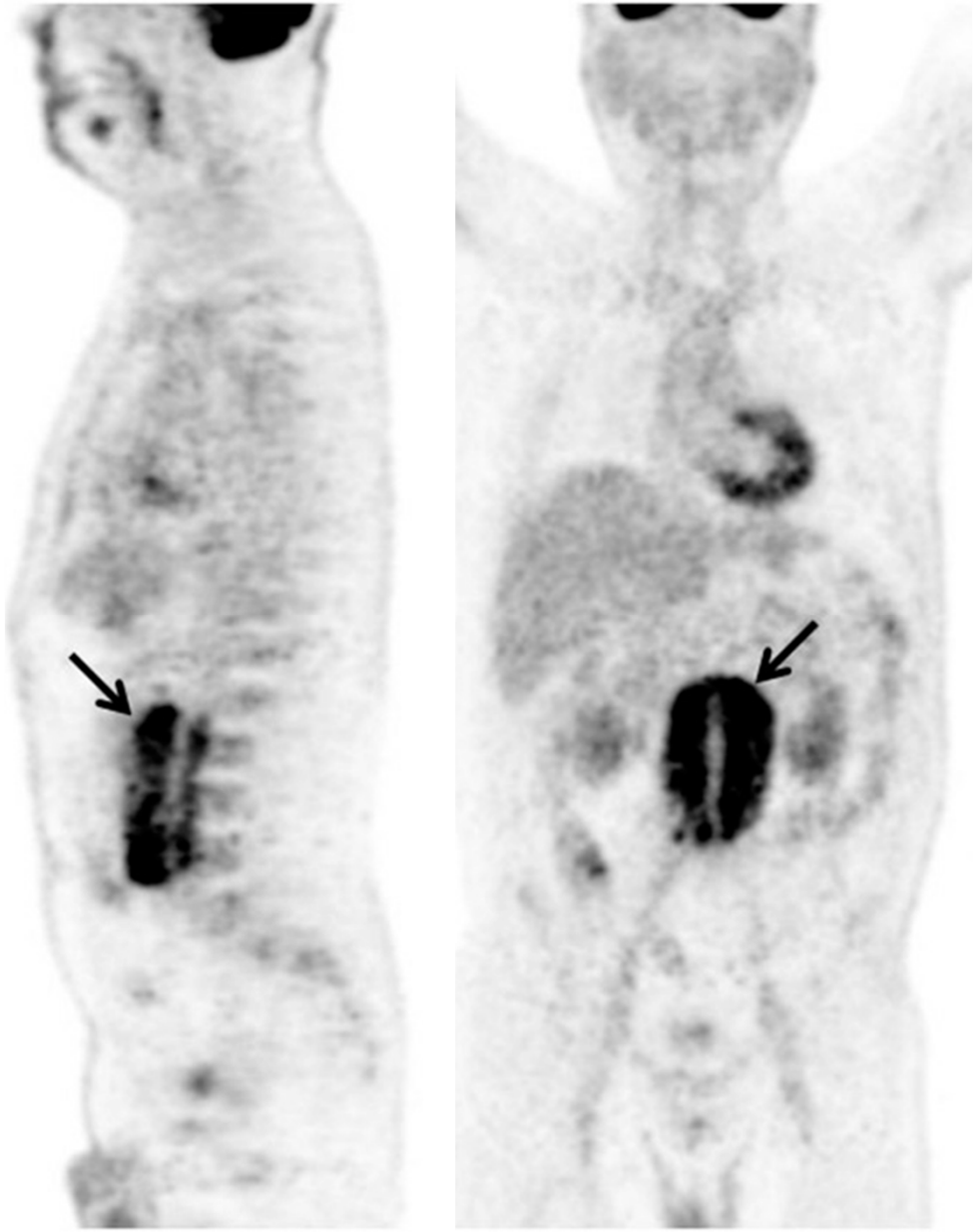
Vaglio A, *Lancet* 2006

TYPICAL CT APPEARANCE OF CHRONIC PERIAORTITIS



Vaglio A, *J Am Soc Nephrol* 2016

^{18}F-FDG-PET APPEARANCE of CHRONIC PERIAORTITIS



Vaglio A, *J Am Soc Nephrol* 2016

Epidemiology and clinical presentation

EPIDEMIOLOGY

Non aneurysmal forms (idiopathic retroperitoneal fibrosis)

Incidence: 0.1/100,000 inhabitants/year (Uibu T et al. *Lancet* 2004)
1.3/100,000 inhabitants/year (van Bommel E et al. *Medicine(Baltimore)* 2009)

Prevalence: 1.4/100,000 inhabitants (Uibu T et al. *Lancet* 2004)

M/F ratio: 2:1-3:1

Aneurysmal forms (inflammatory abdominal aortic aneurysms)

4-9% of all abdominal aortic aneurysms
M/F ratio 4:1-9:1

Incidence peaks between 50 and 60 years

Uibu T, *Lancet* 2004; van Bommel E, *Medicine (Baltimore)* 2009

CLINICAL MANIFESTATIONS

	Mayo Clinic, Rochester (*n*=185)[4]	Johns Hopkins University, Baltimore (*n*=48)[19]	A. Schweitzer Hospital, Dordrecht (*n*=53)[2]	University Hospital, Parma (*n*=210)
Mean age at diagnosis, years	58	54	64	58
Male gender, %	61	54	77	70
Systemic symptoms, %[a]	27	60	92	66
Pain (flank, abdominal), %	38	94	92	81
Testicular manifestations (pain, varicocele, hydrocele), %	13	27	46	51
Constipation, %	12	NA	30	28
Lower extremity edema, %	13	23	8	15
Lower extremity claudication, %	2	NA	11	12
Hydronephrosis, %	57	67	55	72
Unilateral, %	25	21	40	29
Bilateral, %	32	46	15	43
Renal atrophy, %	8	NA	21	30
Impaired renal function, %[b]	42	NA	66	57
Mean ESR, mm/h	32	40	45	63
Mean CRP, mg/L	20.7	NA	23	32
Mean serum creatinine, mg/dL	1.3	NA	1.4	3.9[c]
Mean Hb, g/dL	12.6	11.6	12.4	12.5
Increased ESR, %	53	NA	74	85
Increased CRP, %	47	NA	62	78

Vaglio A, *J Am Soc Nephrol* 2016

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Vaglio A, *J Am Soc Nephrol* 2016

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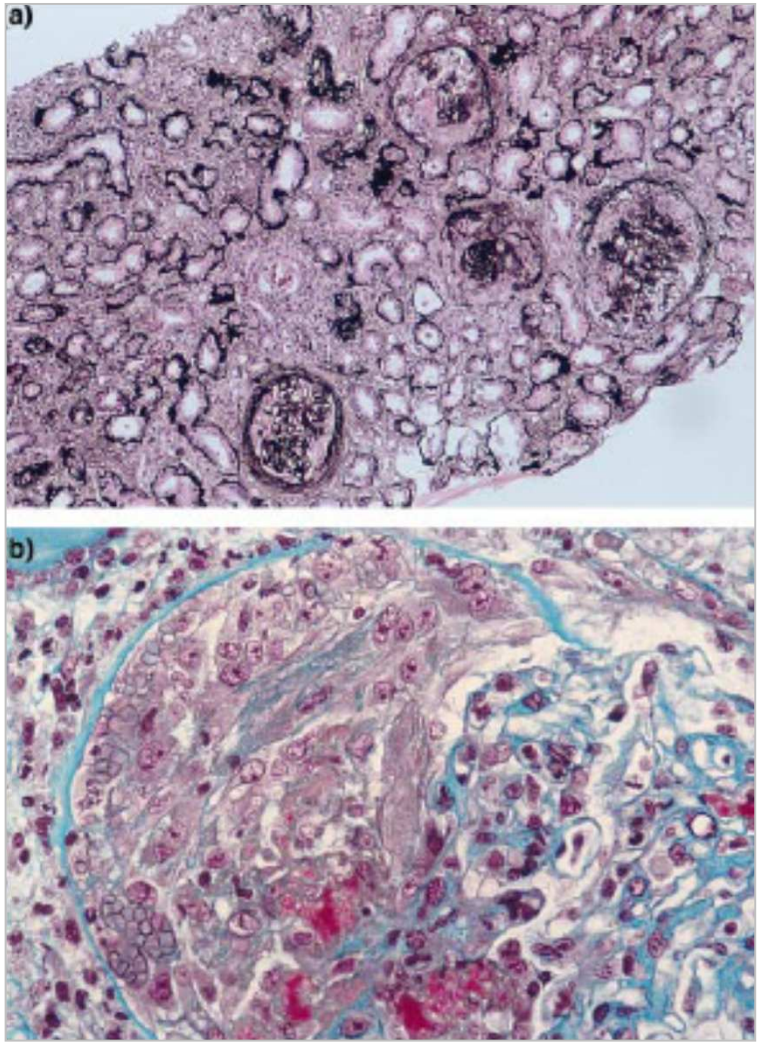
Vaglio A, *J Am Soc Nephrol* 2016

Disease associations

COMPLEXITY OF AN APPARENTLY SIMPLE CLINICAL PHENOTYPE

- Association with systemic autoimmune diseases
- Association with organ-limited autoimmune diseases
- “Diffuse” (thoraco-abdominal) periaortitis
- Association with fibro-inflammatory lesions affecting other organs

ASSOCIATION WITH SYSTEMIC AUTOIMMUNE DISEASES



***Panel 2*: Main associations between retroperitoneal fibrosis and autoimmune or inflammatory diseases**

Autoimmune thyroid disease
Hashimoto's thyroiditis[11,12]
Riedel's thyroiditis[52,64–66]
Graves' disease[66]

Small and medium-sized vessel vasculitis
Wegener's granumolatosis[67,68]
Polyarteritis nodosa[44]
Microscopic polyangiitis[60]
Hepatitis C virus-related cryoglobulinaemia[69]

Ankylosing spondylitis[70,71]

Systemic lupus erythematosus[14,50,65]

Rheumatoid arthritis[11,14,72]

Glomerulonephritis
ANCA-positive rapidly progressive glomerulonephritis[11,60]
Membranous nephropathy[73]

Sclerosing cholangitis[74,75]

Primary biliary cirrhosis[76,77]

Sclerosing pancreatitis[30,78]

Uveitis[79]

ANCA: anti-neutrophil cytoplasmic antibodies.

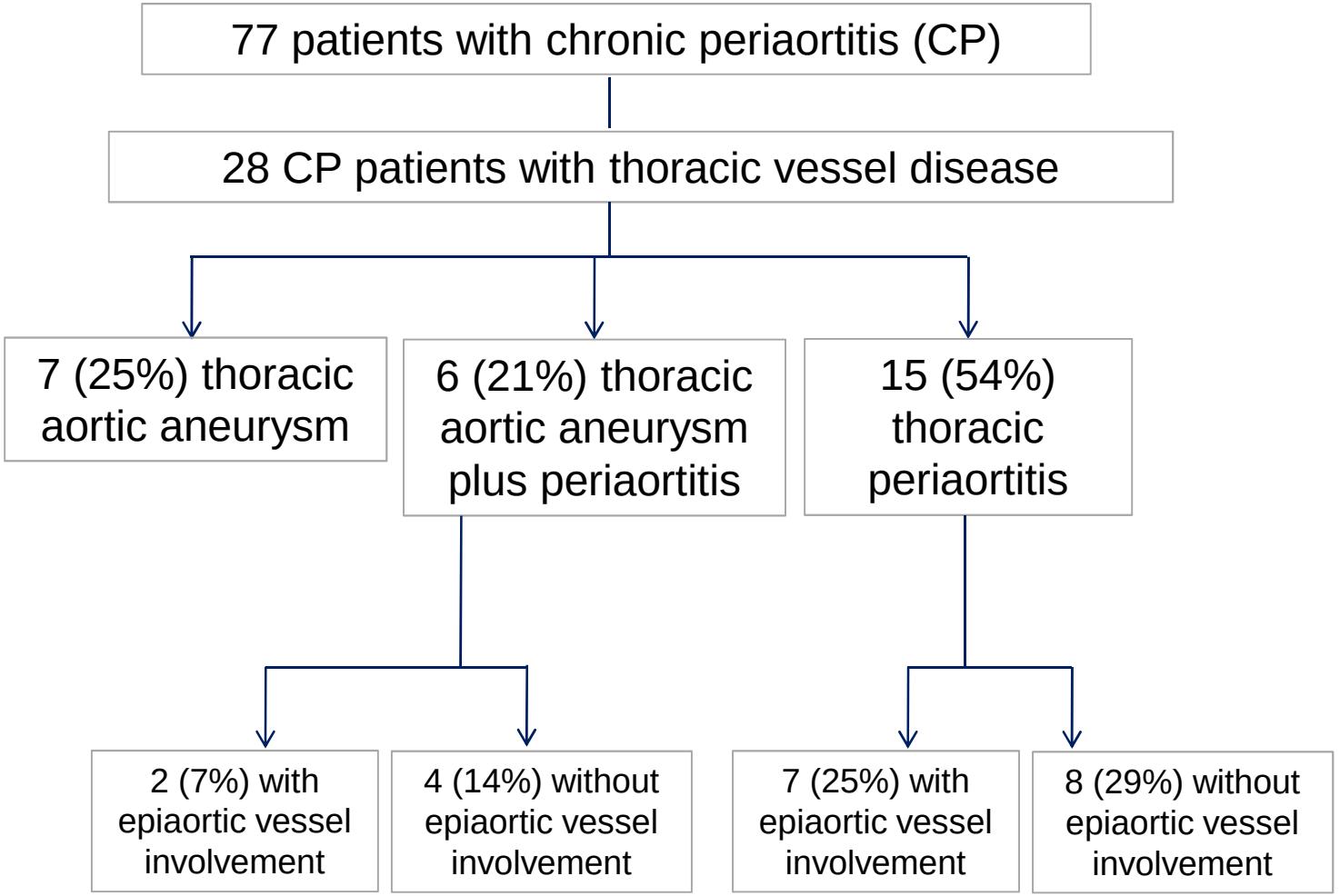
Vaglio A, *J Intern Med* 2002; *Lancet* 2006

ASSOCIATION WITH ORGAN-SPECIFIC AUTOIMMUNE DISEASES

	CP patients (n=73)	**Controls (n=71)**	P value
Age (years)	55.4 (10.6)	55.0 (9.6)	0.85
Male n (%)	46 (63)	41 (58)	0.52
TSH mIU/L	1.23 (0.79-1.70)	1.50 (1.07-2.59)	0.86
FT4 ng/dL	1.22 (0.20)	0.93 (0.18)	<.0001
AbTPO positivity n (%)	**18 (24.7)**	**7 (10.6)**	**0.03**
AbTg positivity n (%)	12 (16.4)	5 (7.0)	0.11
Ultrasonographic evidence of HT n(%)	**50 (69.4)**	**23 (32.4)**	**<.0001**
Thyroid volume (mL)	11.42 (5.31)	10.00 (4.43)	0.12
Thyroid nodules n (%)	18 (25.3)	24 (33.8)	0.27
Thyroid nodules diameter (mm)	14 (8-15)	10 (8-15)	0.77
Boby Mass Index (kg/m2)	26.90 (3.71)	27.44 (2.70)	0.38
Smoking (pack-years)	34.20 (26.20)	8.84 (10.32)	<.0001
CIRS score	3 (2-5)	0 (0-1)	<.0001

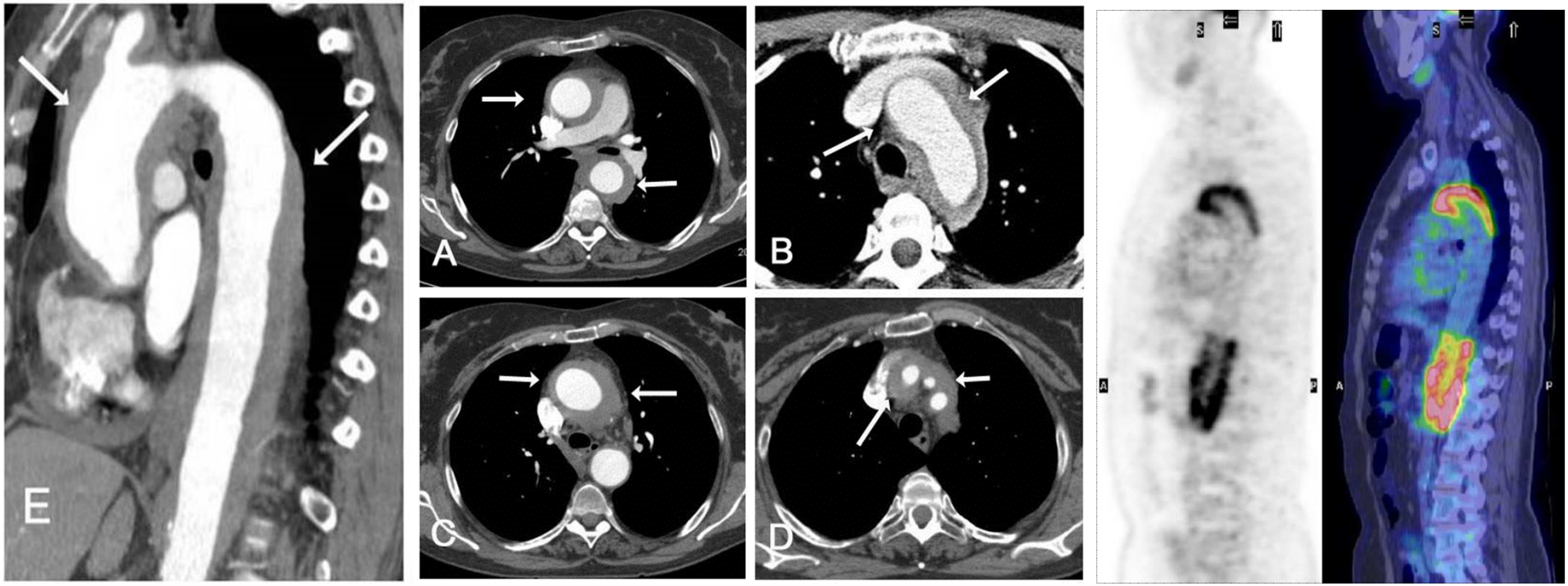
Ceresini G, *Autoimmun Rev* 2015

“DIFFUSE” (THORACO-ABDOMINAL) PERIAORTITIS



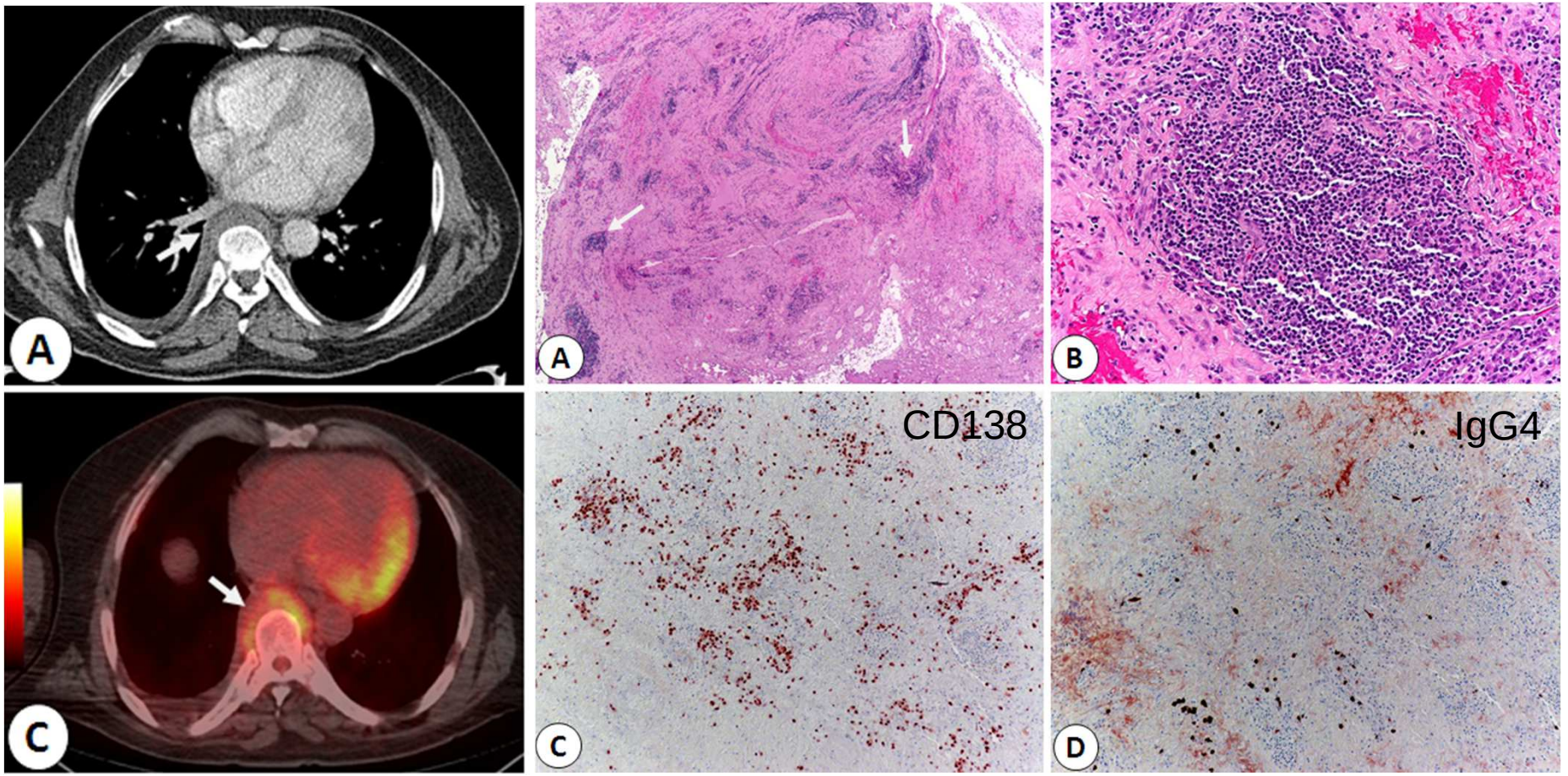
Palmisano A, *Rheumatology (Oxford)* 2015

“DIFFUSE” (THORACO-ABDOMINAL) PERIAORTITIS



Palmisano A, *Rheumatology (Oxford)* 2015

ASSOCIATION WITH OTHER FIBRO-INFLAMMATORY DISORDERS



IDIOPATHIC MEDIASTINAL FIBROSIS: 3 out of 9 cases in our series were associated with CP

Rossi GM, *Clin Rev Allergy Immunol* 2016

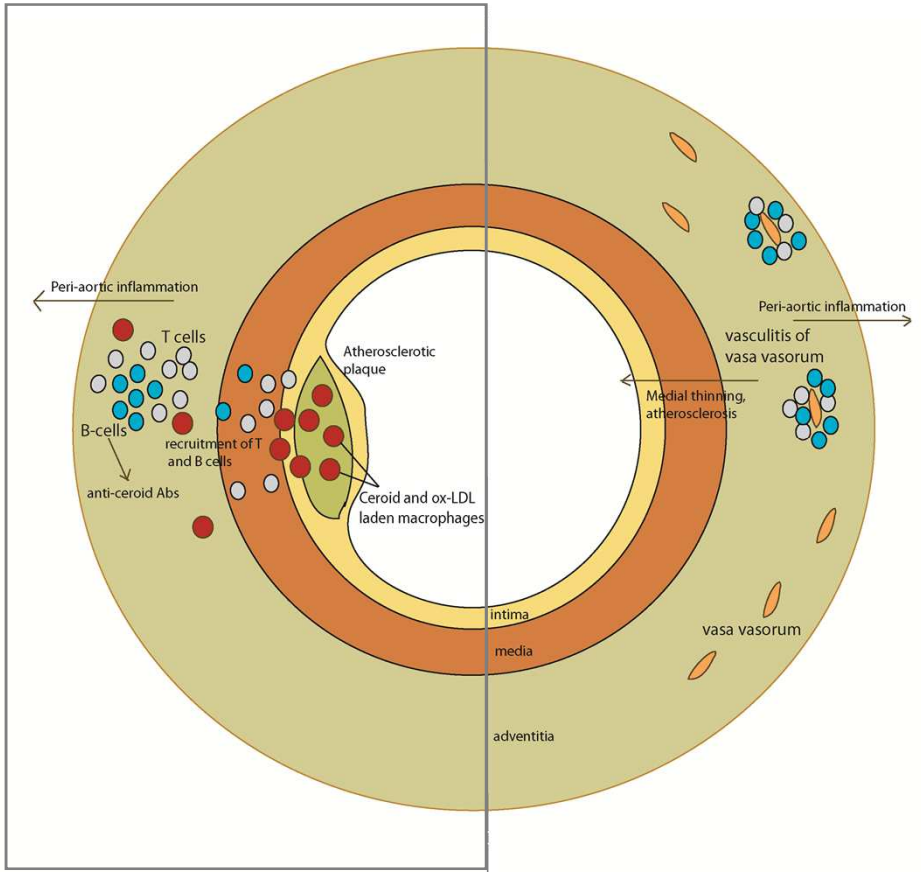
Immunopathogenetic model

PATHOGENESIS: DOES ATHEROSCLEROSIS LEAD TO PERIAORTITIS?

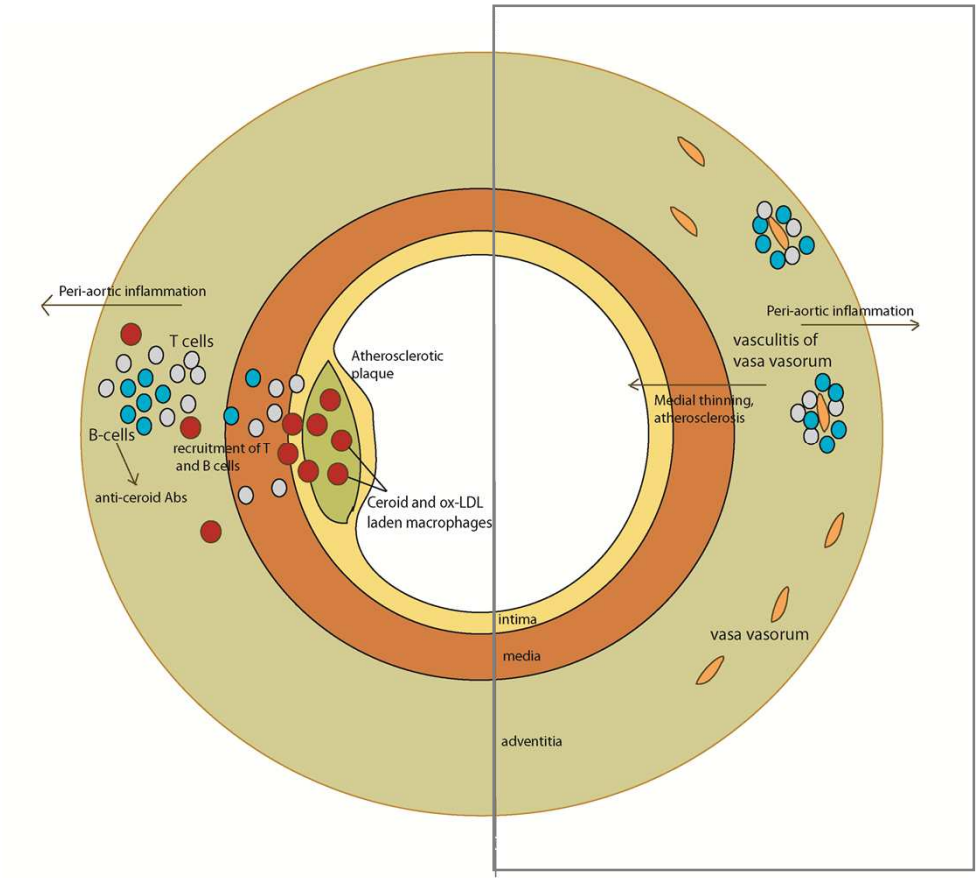
Atherosclerosis hypothesis

Local inflammatory reaction against antigens (oxidised LDL and ceroid) of the atherosclerotic plaques

- Serum Abs to oxLDL and ceroid
- IgG in close apposition to extracellular ceroid
- lipid-laden macrophages in nearby lymph nodes



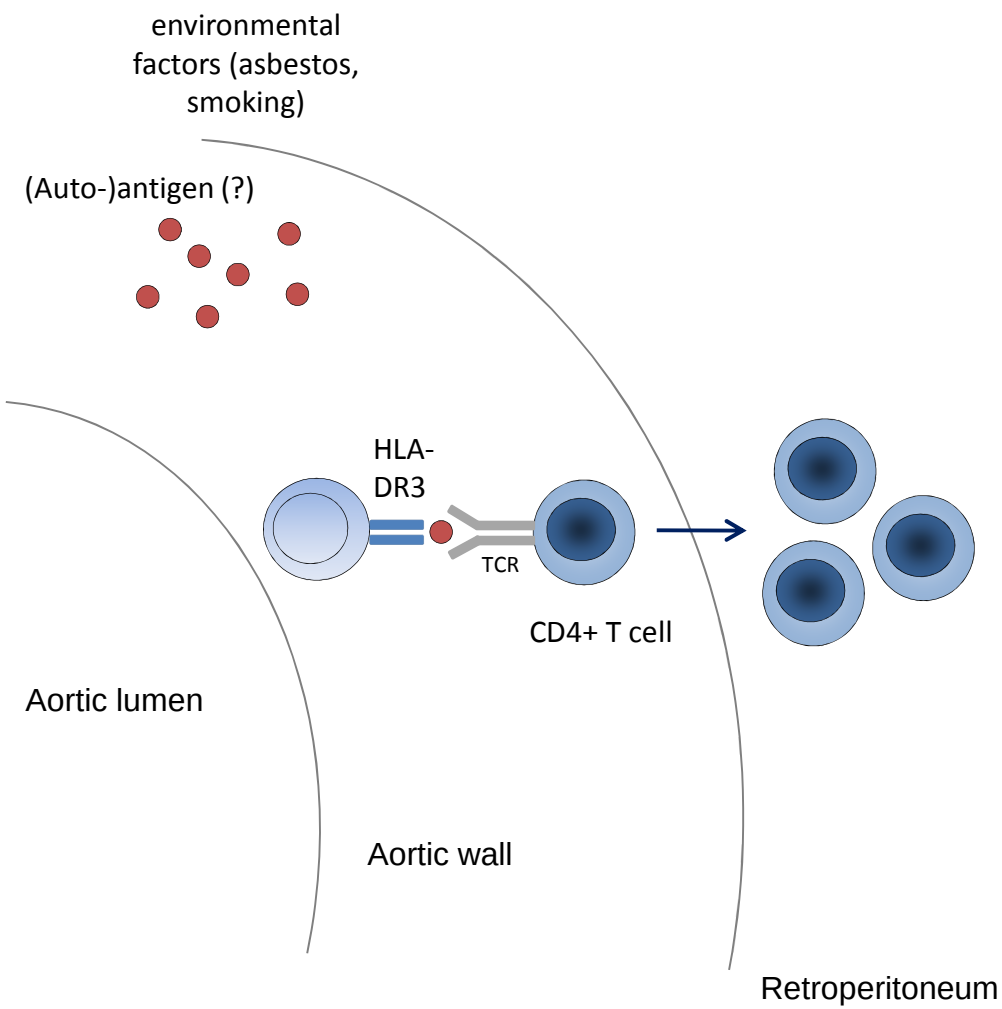
PATHOGENESIS: PRIMARY AORTITIS?



Aortitis hypothesis

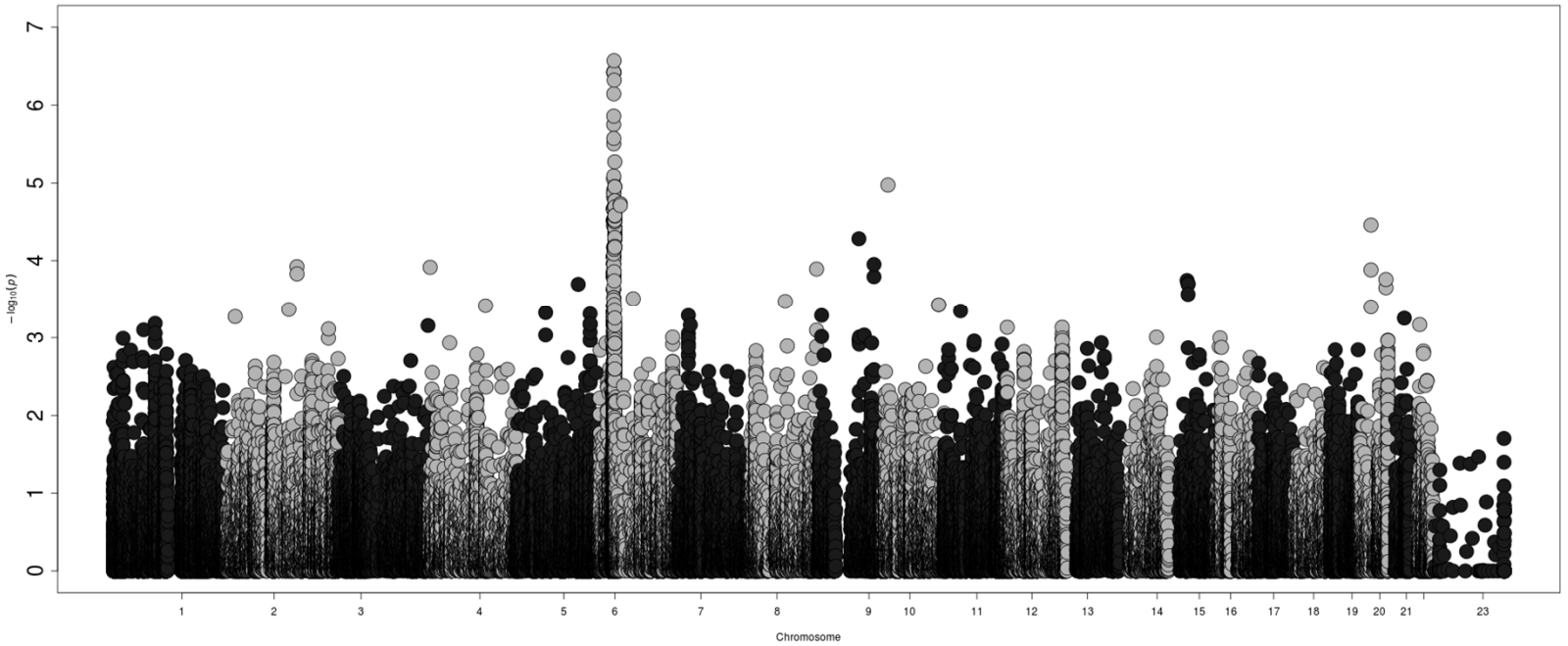
- Inflammation predominates in the adventitia (as in LVV)
- Adventitial germinal centres
- *Vasa vasorum* vasculitis
- Diffuse involvement of the aorta and its branches
- Periaortitis in arterial segments not involved by atherosclerosis

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS



PATHOGENESIS: GENETIC ASSOCIATIONS

- **HLA DRB1*03**
- CCR5 delta 32
- CCL11 haplotype
- FcGR2A

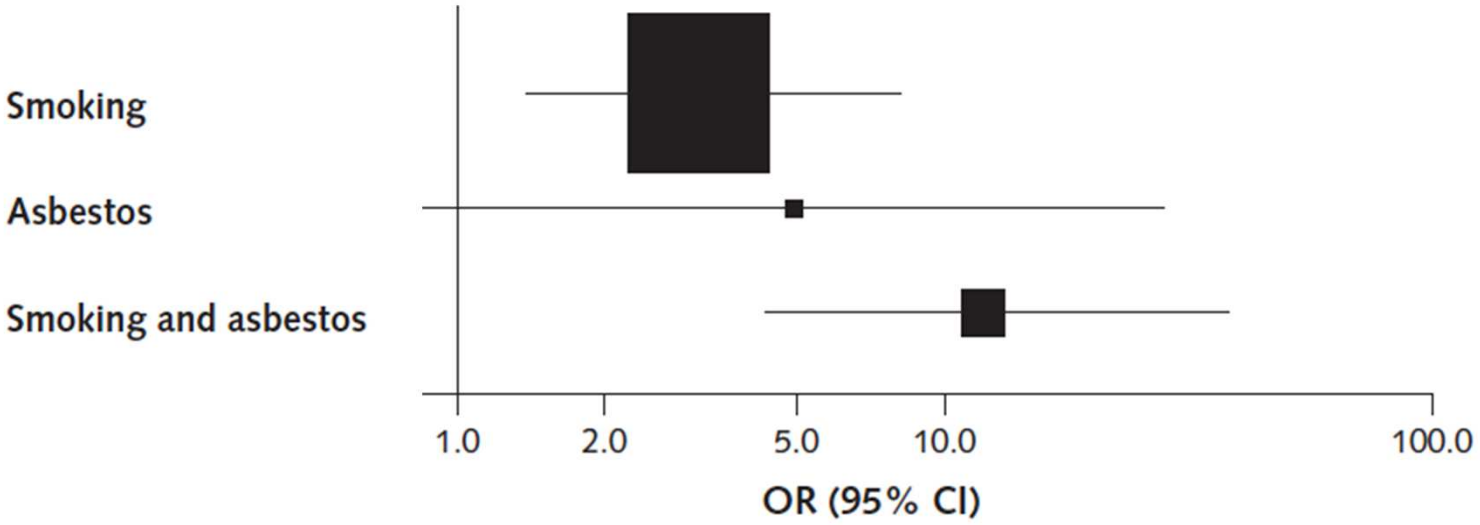


Immunochip platform; 270 cases/500 controls (in collaboration with J. Martin, Granada)

Martorana D, *Arthritis Rheum* 2006; Boiardi L, *Rheumatology* 2011; Mangieri D, *Nephrol Dial Transplant* 2012

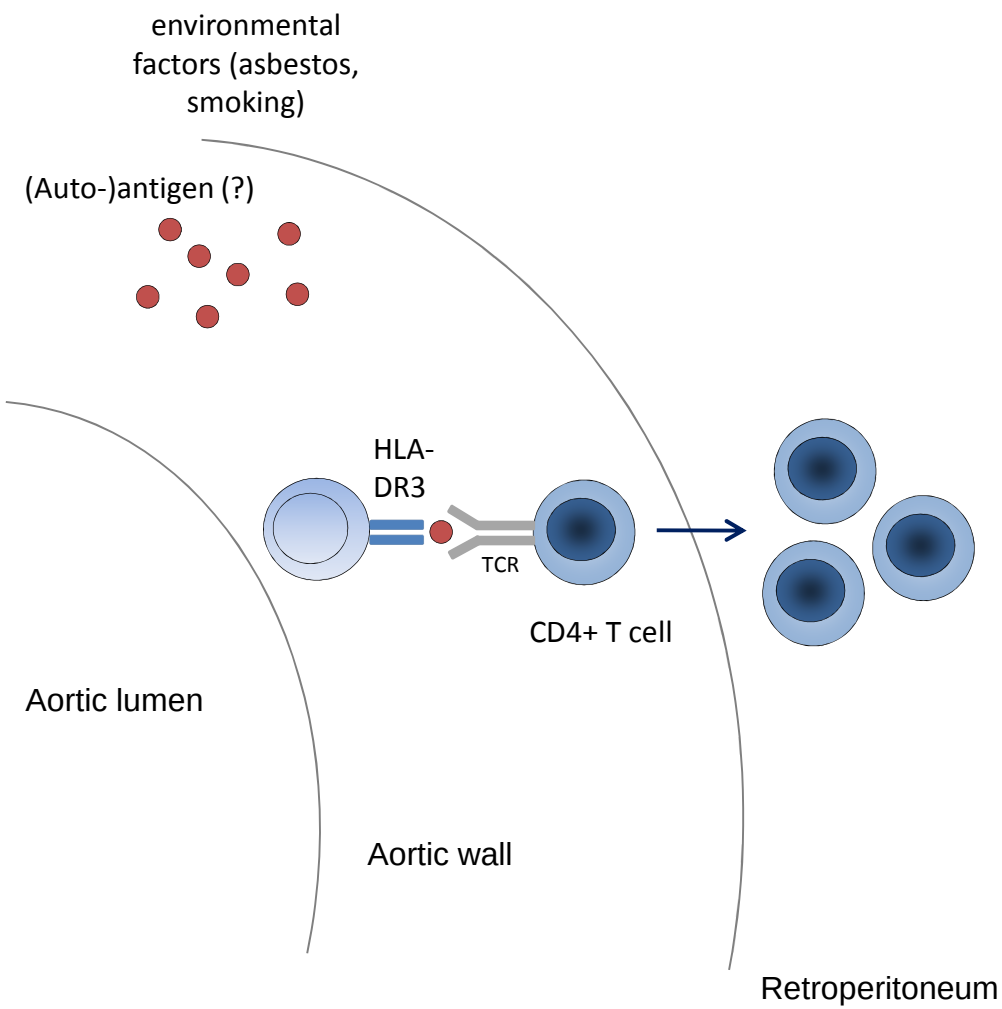
PATHOGENESIS: ASBESTOS AND SMOKING

Exposure	Participants, *n*		OR (95% CI)	*P* Value
	Control Group	Case Group		
Smoking	153	49	3.15 (1.40–8.11)	0.004
Asbestos	8	4	4.91 (0.78–28.02)	0.090
Smoking and asbestos	23	27	12.04 (4.32–38.28)	<0.001

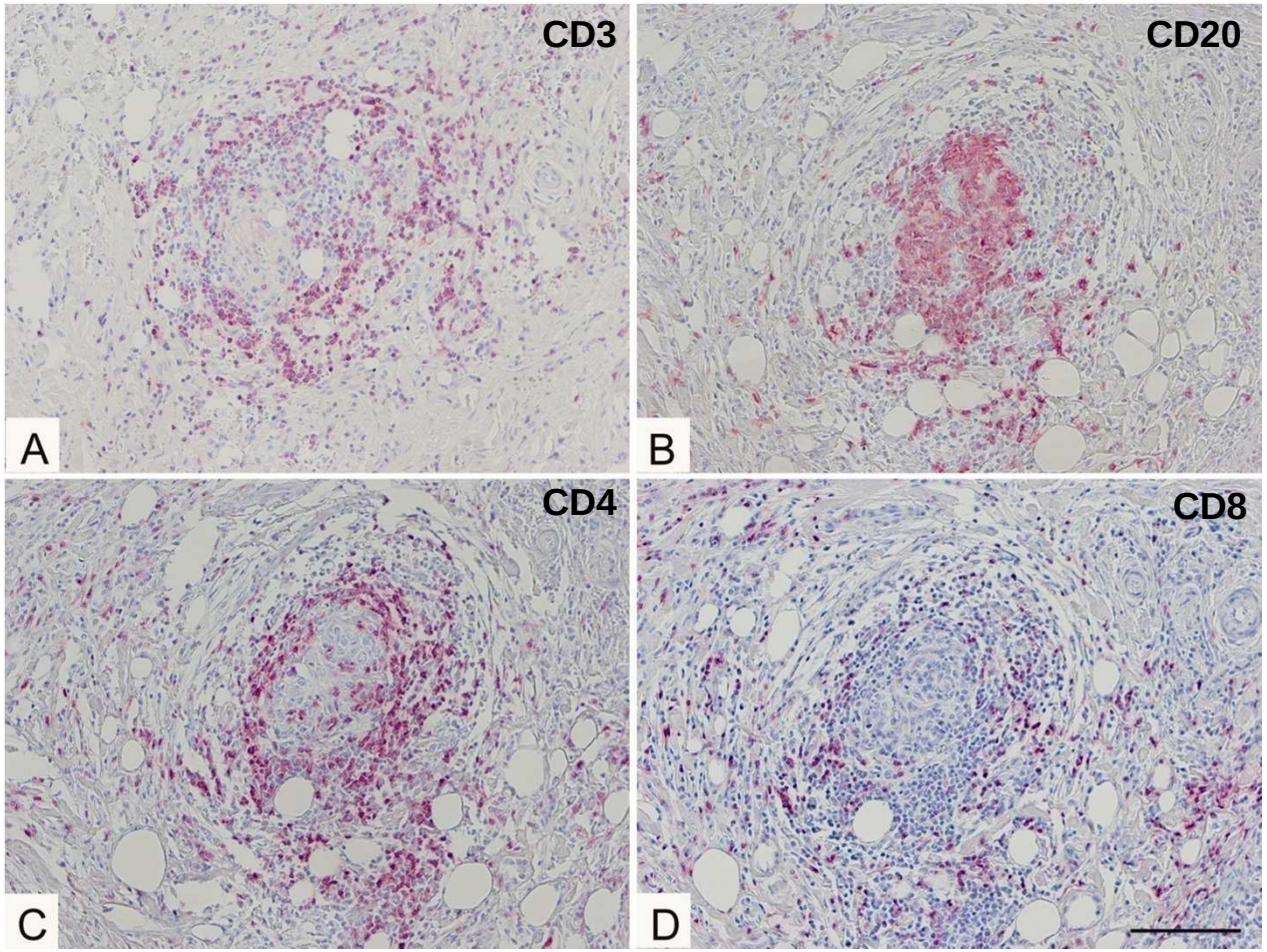


Goldoni M, *Ann Intern Med* 2014

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

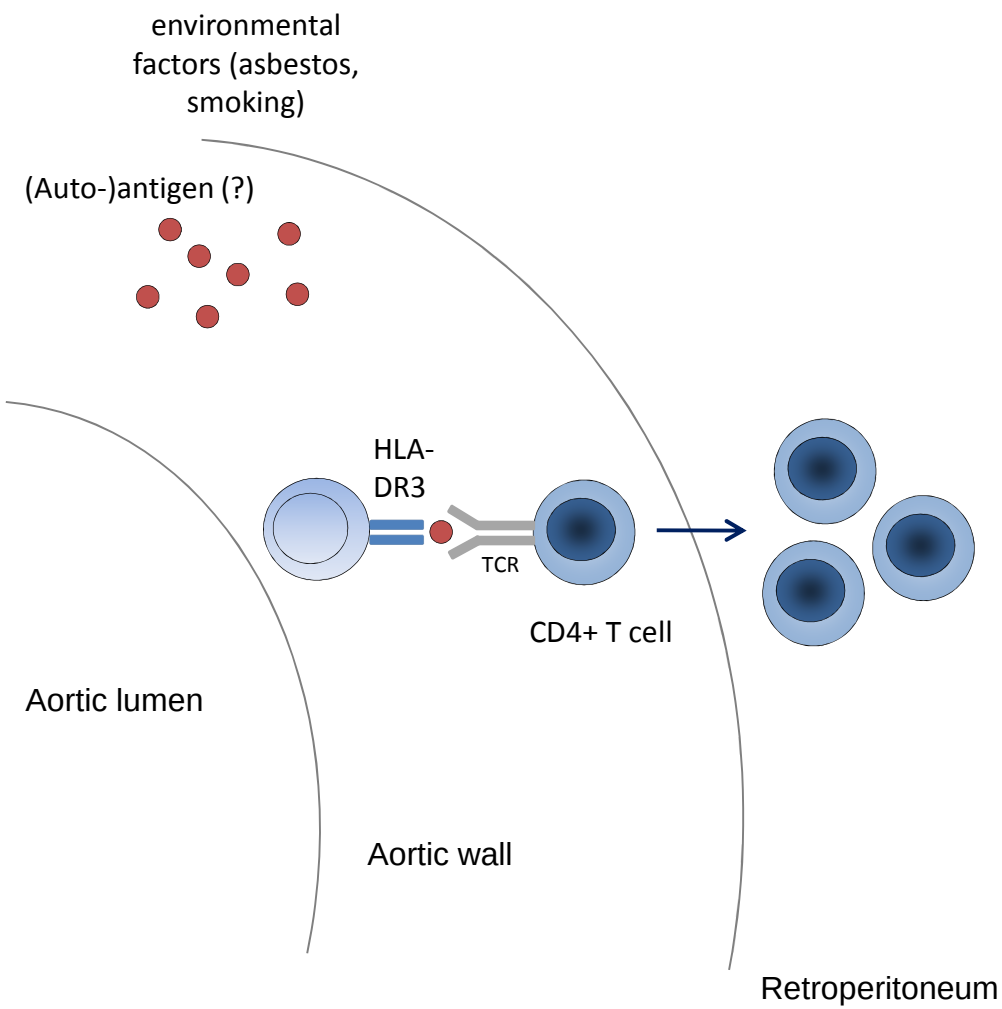


ARCHITECTURAL ORGANISATION OF THE LYMPHOCYTE SUBSETS



Corradi D, *Kidney Int* 2007

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS



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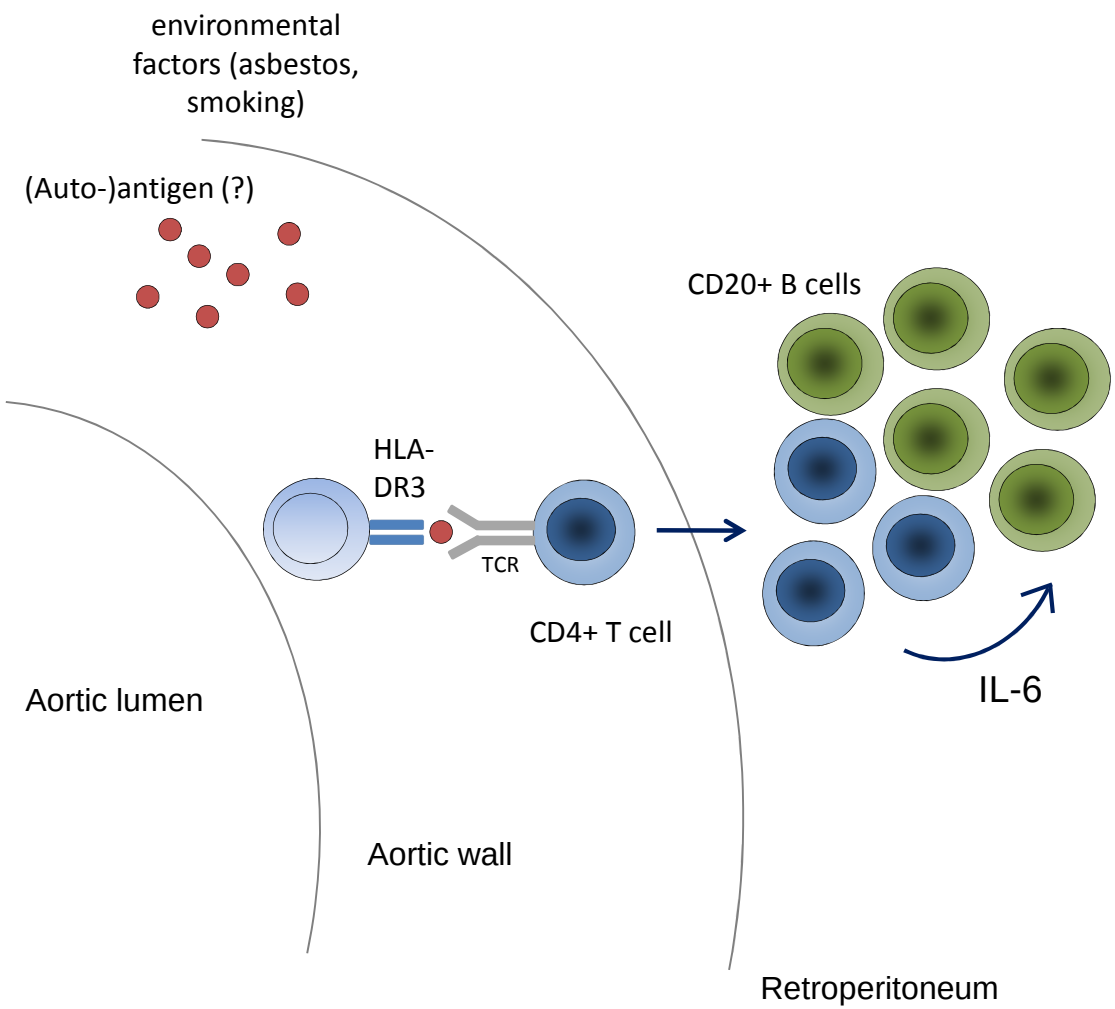
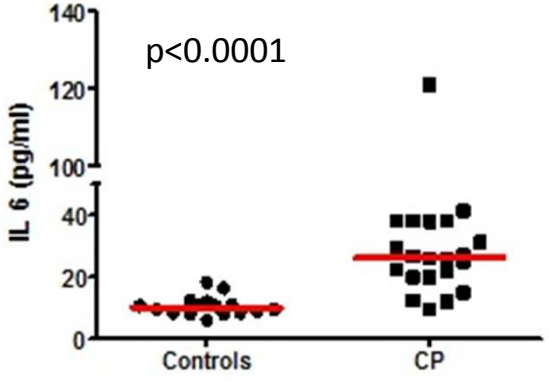
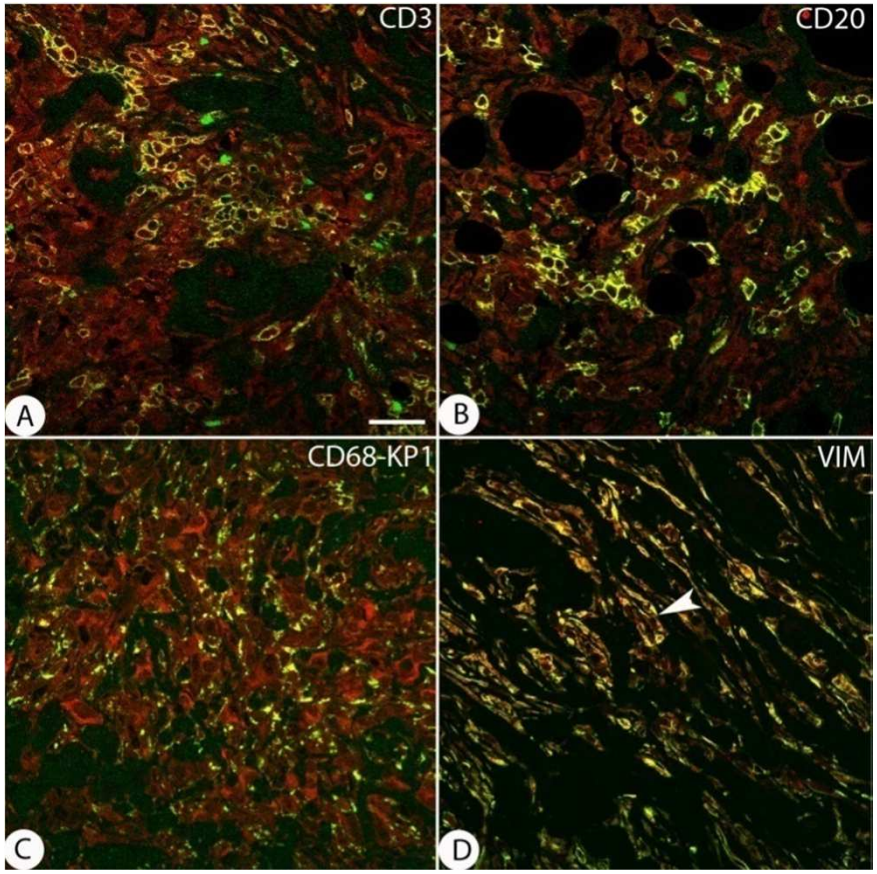


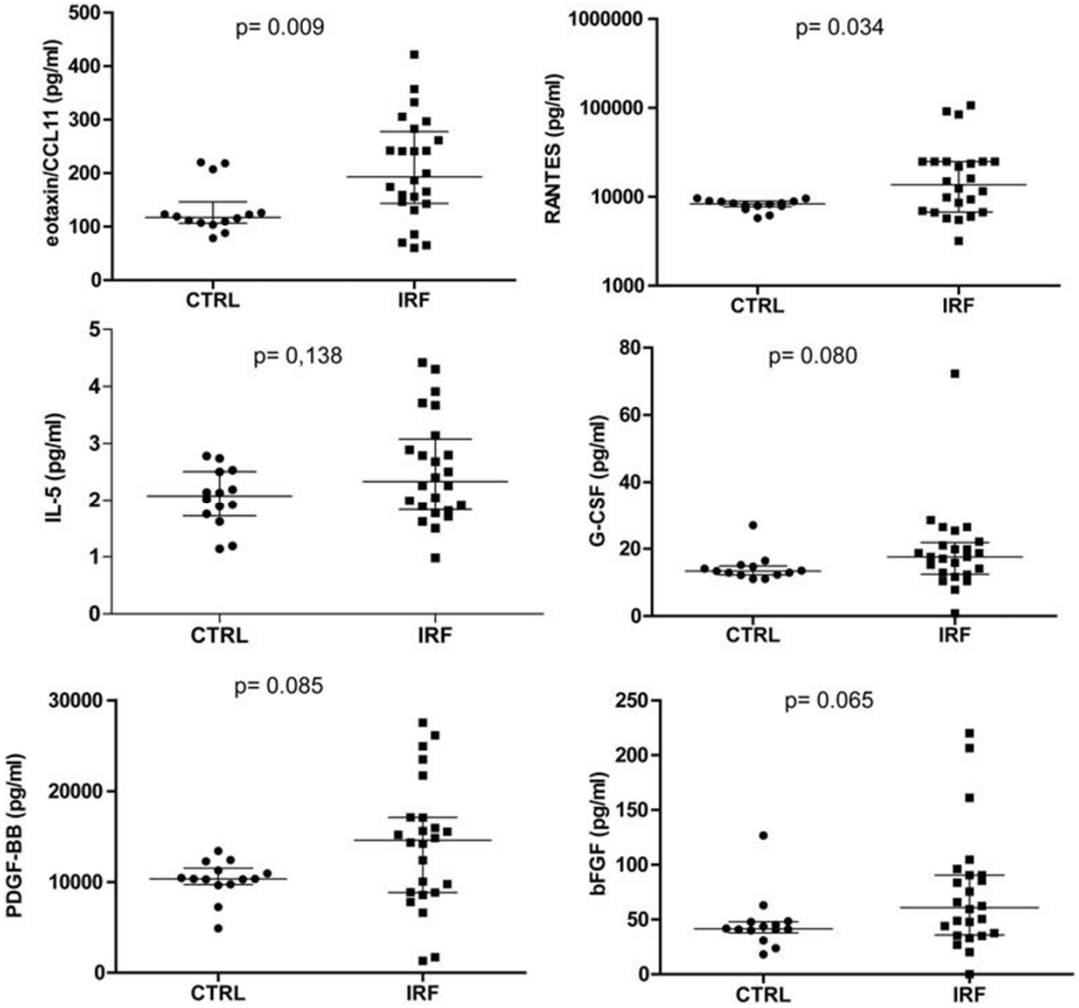
INTERLEUKIN-6 IN CP





Vaglio A, *Arthritis Rheum* 2013

CP PATHOGENESIS: EOTAXIN-1

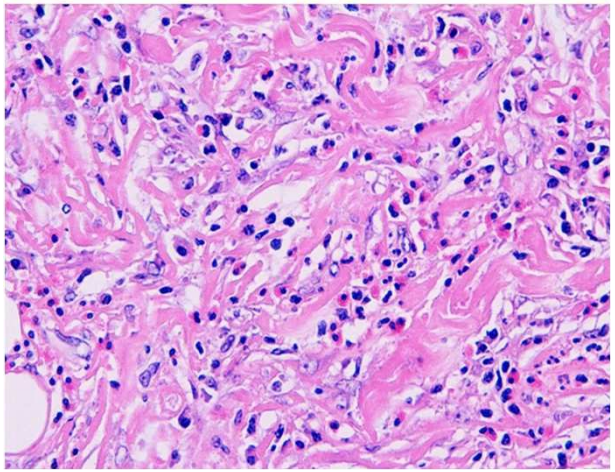


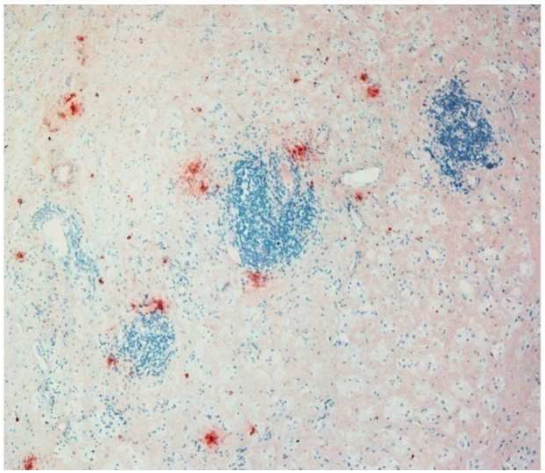
Mangieri D, *Nephrol Dial Transplant* 2012

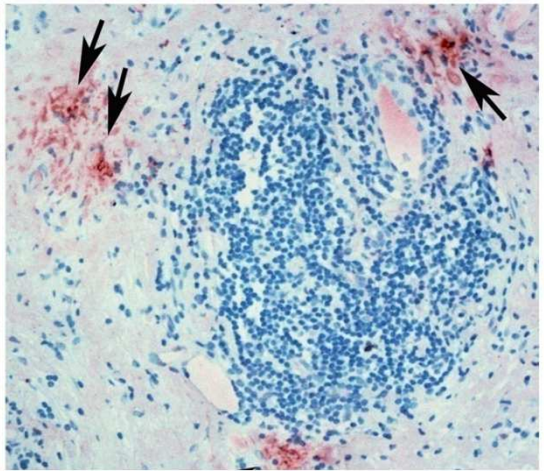
CP PATHOGENESIS: EOSINOPHILS, MAST CELLS AND EOTAXIN-1

Eosinophils

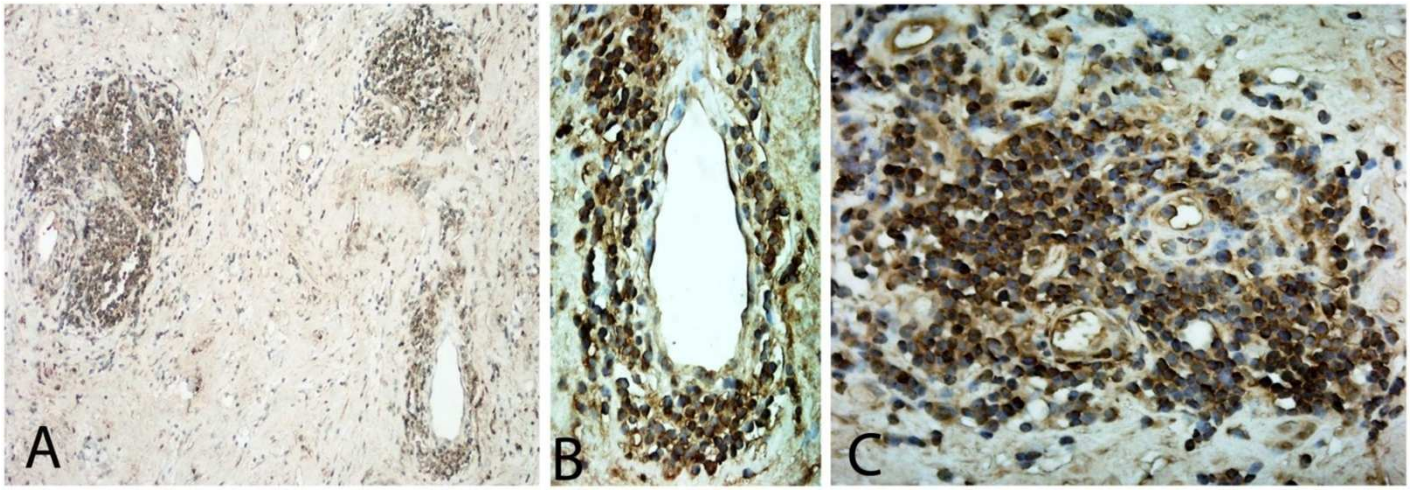
Tryptase+ degranulating mast cells





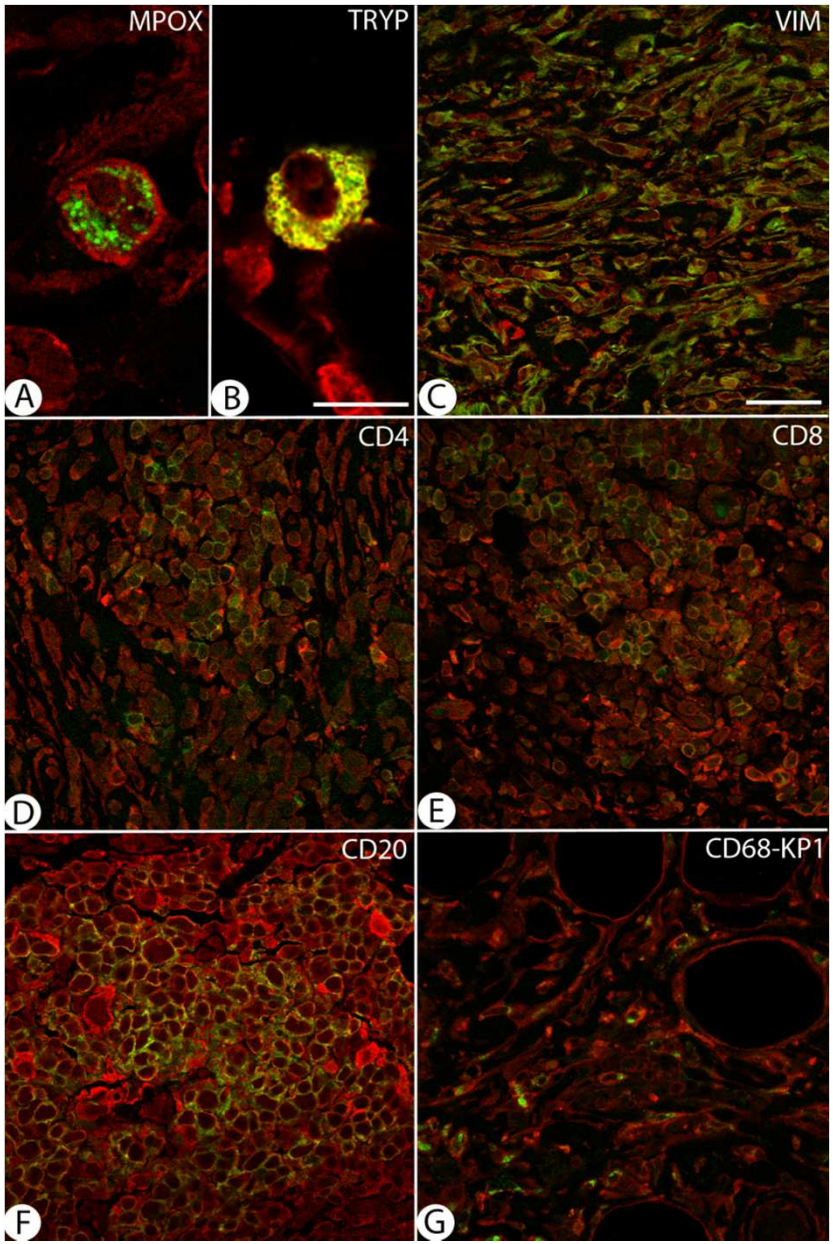


Eotaxin/CCL11 expression in retroperitoneal biopsies



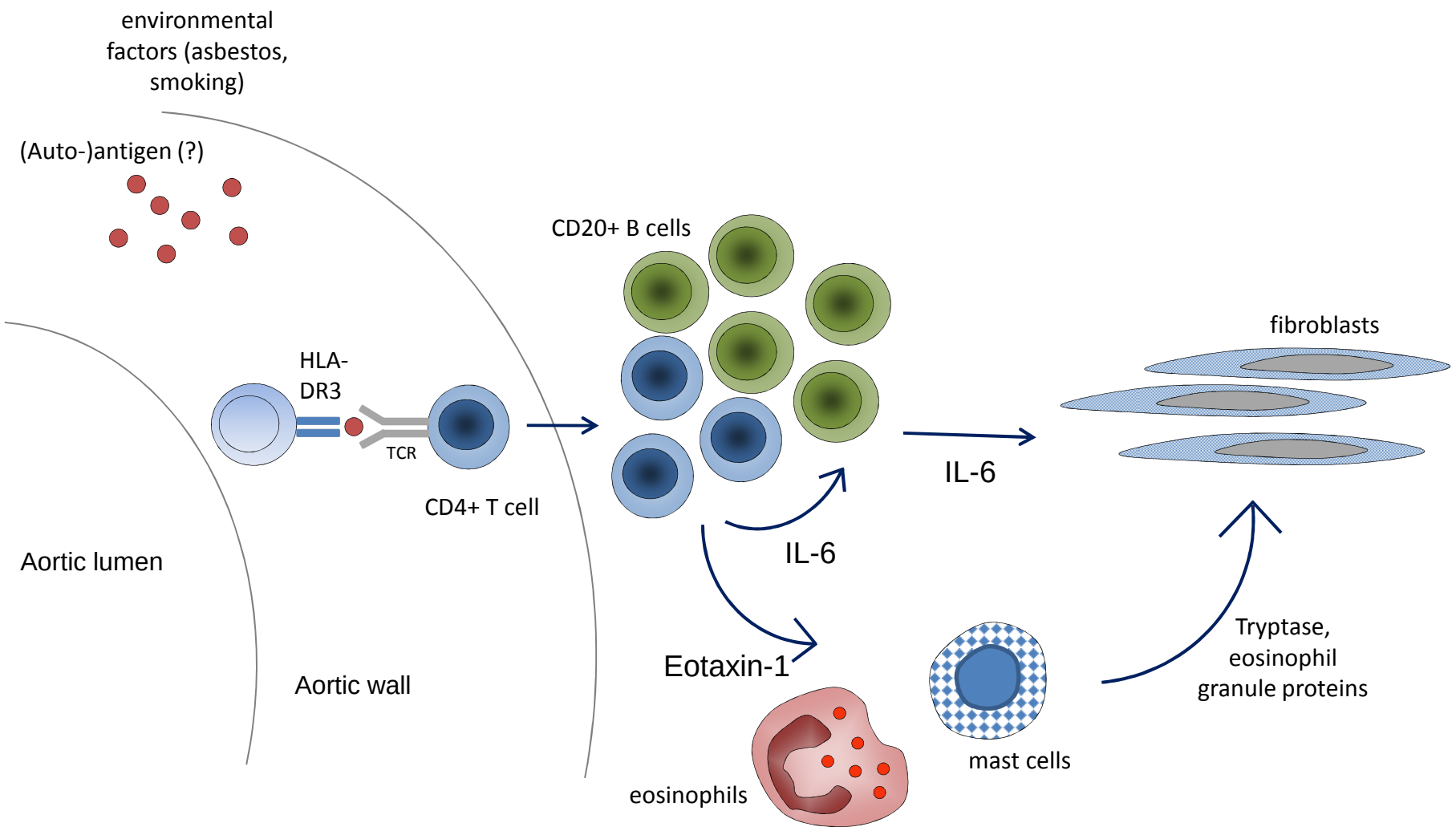
Mangieri D, *Nephrol Dial Transplant* 2012

CP PATHOGENESIS: EOSINOPHILS, MAST CELLS AND EOTAXIN-1



Mangieri D, *Nephrol Dial Transplant* 2012

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS



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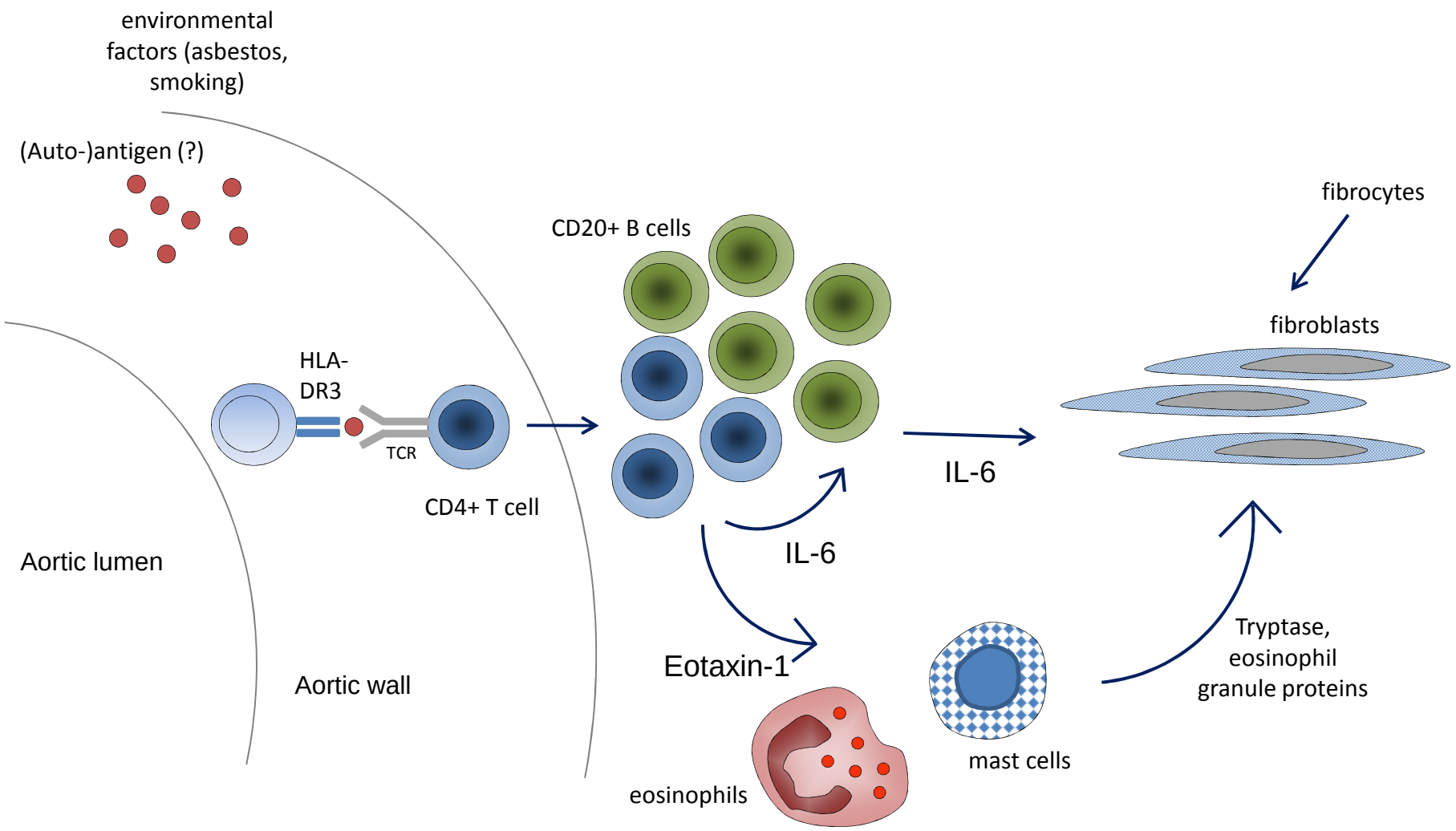
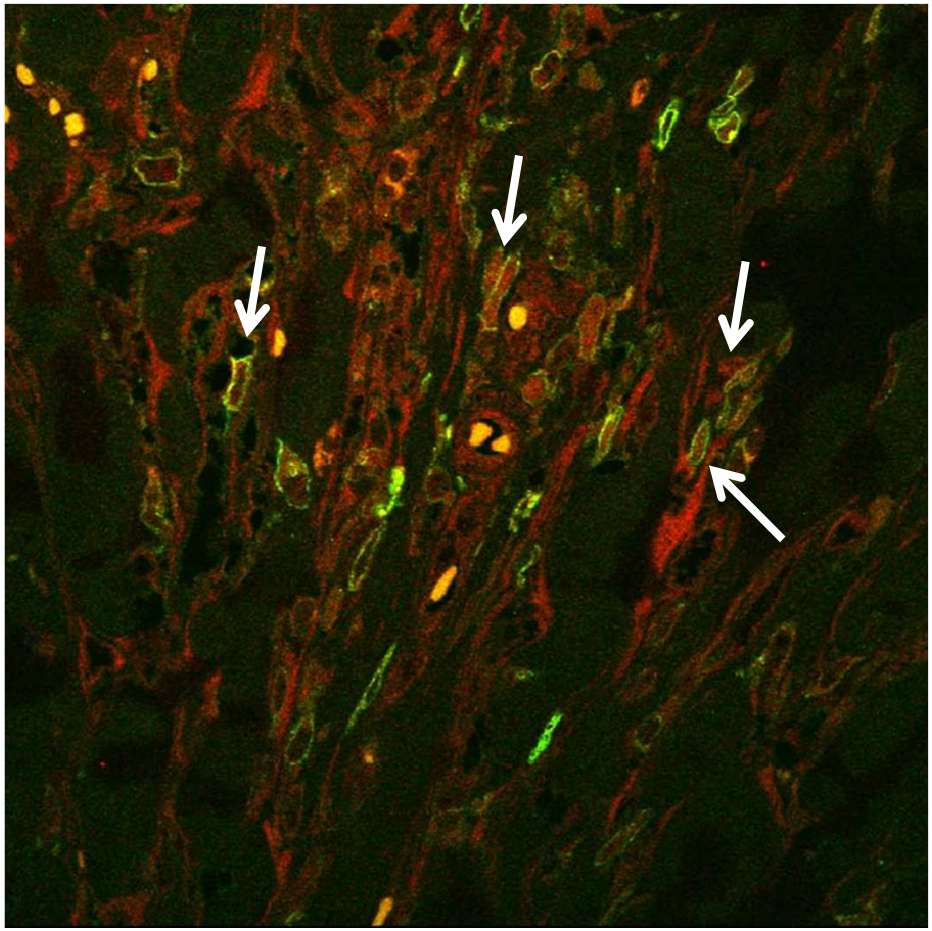


FIBROCYTES

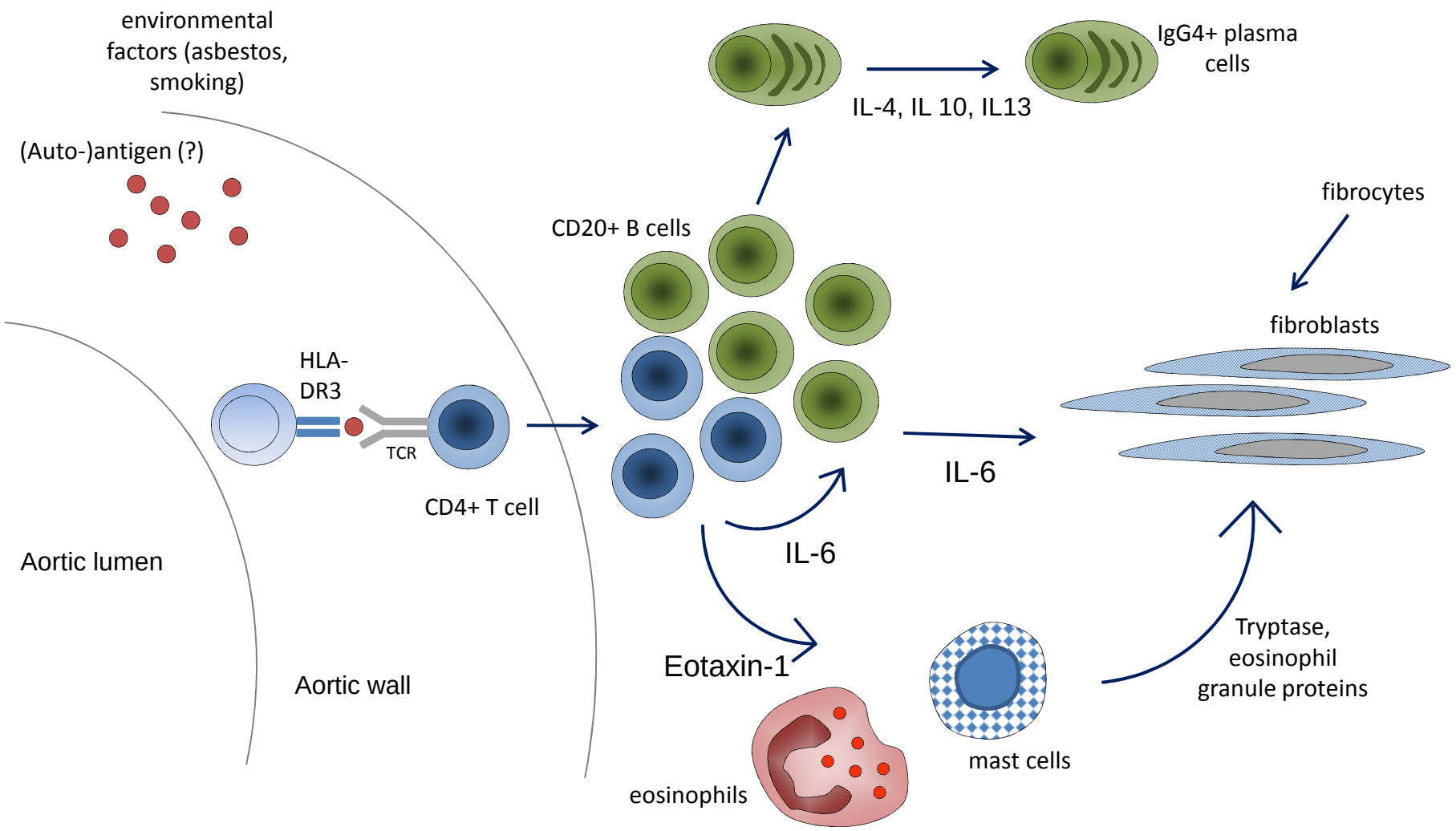
Fibrocytes are a rare population of (circulating) precursors of tissue fibroblasts, which stain positive for CD45 and type I Col



Type I col
CD45

$CD45^+$ $ColI^+$ cells in a CP biopsy

IMMUNOPATHOGENESIS OF CHRONIC PERIAORTITIS

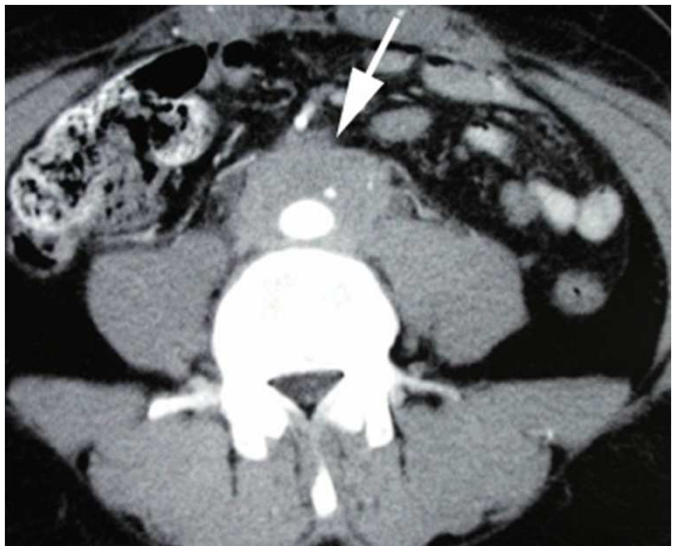


adapted from Vaglio A, *J Am Soc Nephrol* 2016

Chronic periaortitis and the spectrum of IgG4-RD

ASSOCIATION WITH IgG4-RELATED (SYSTEMIC) DISEASE

Kuttner's tumour of the parotid gland



RPF

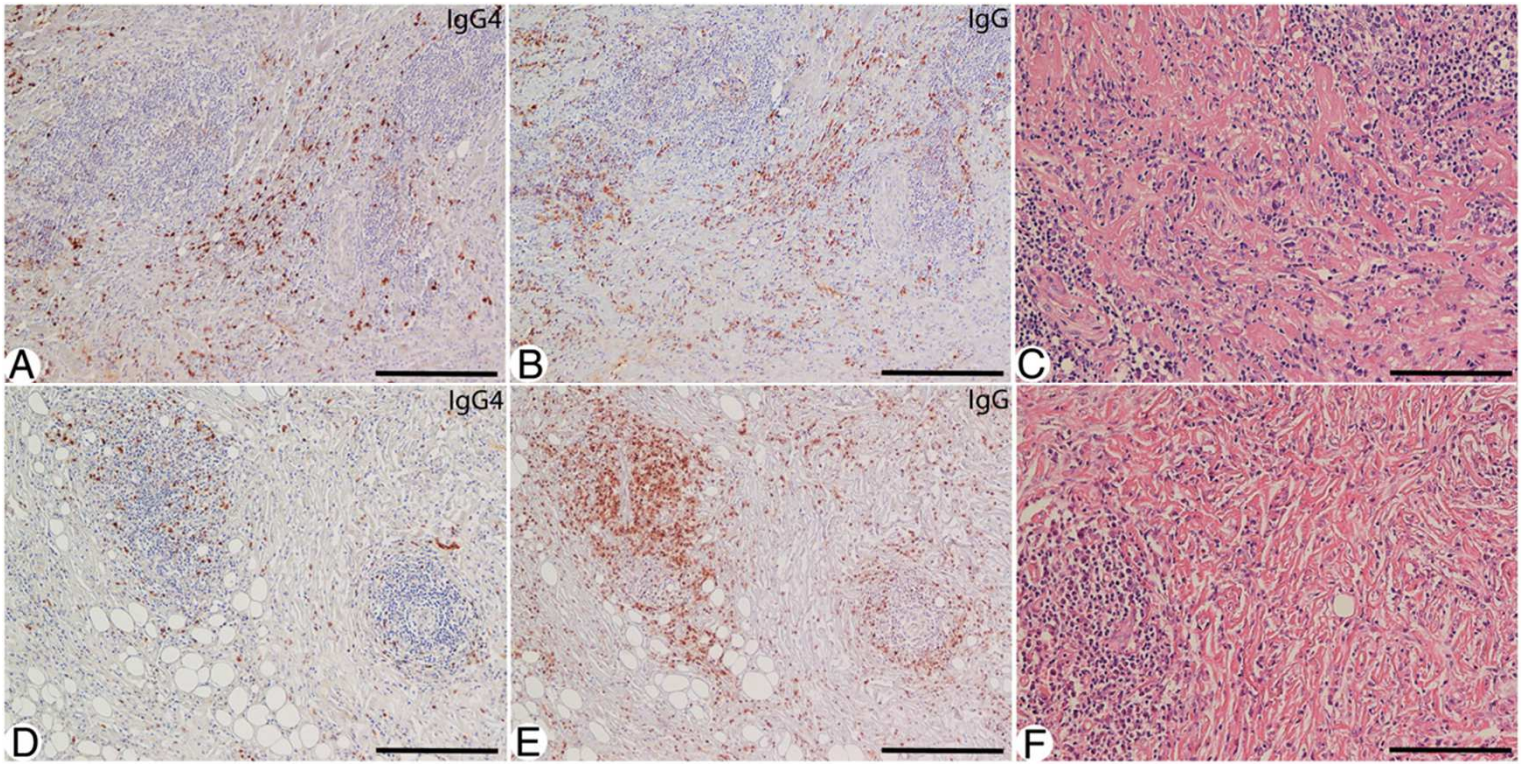
Tubulo-interstitial nephritis

Sclerosing pancreatitis

Palmisano A, *Clin Nephrol* 2010; Vaglio A, *Rheum Dis Clin NA* 2007; Saeki T, *Kidney Int* 2010

IgG4-RELATED DISEASE

1. Typical organ involvement (often tumour-like)
2. IgG4 >135 mg/dL
3. Tissue IgG4+ plasma cells >40% of IgG+ plasma cells and >10/hpf

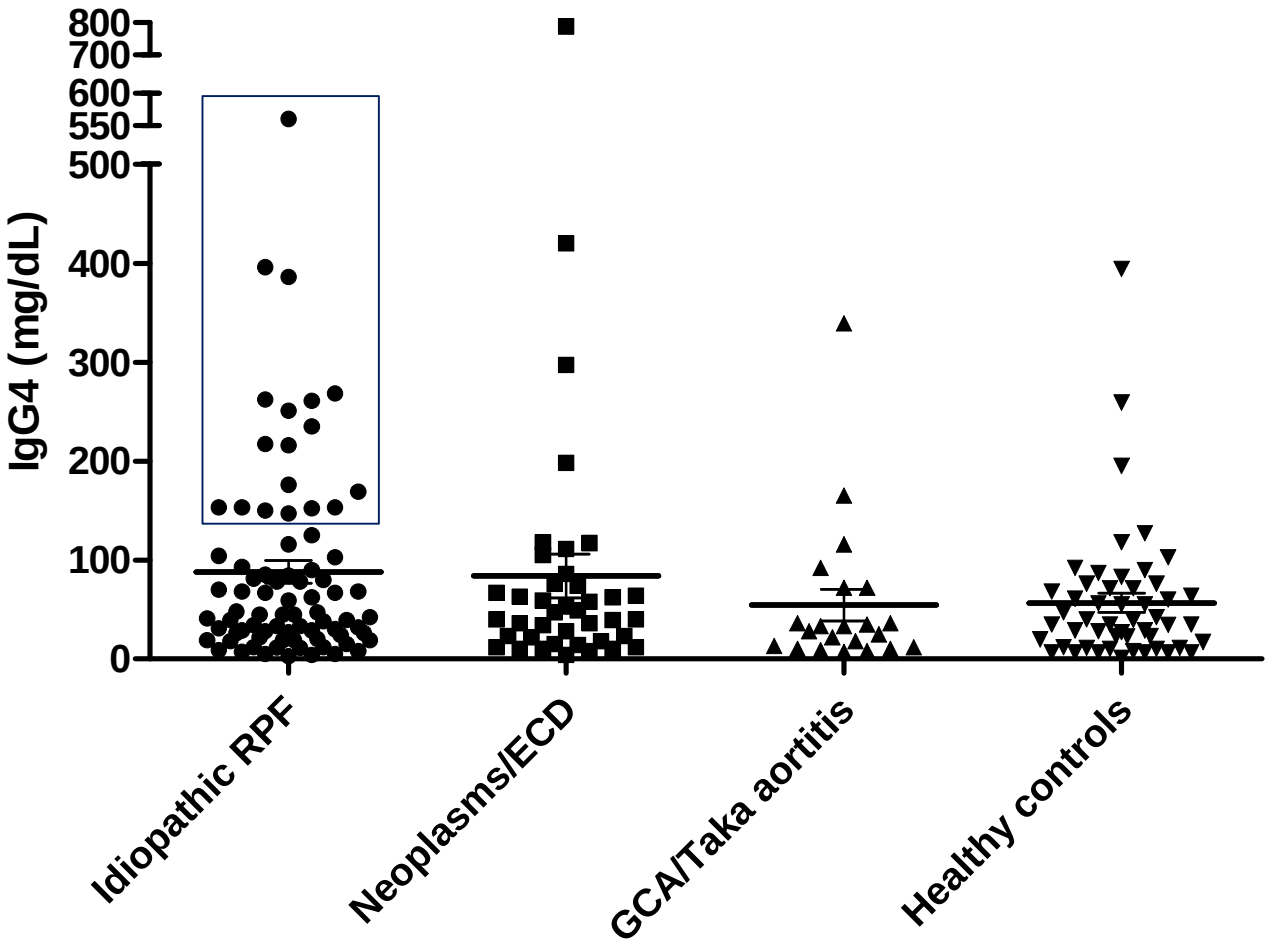


IgG4-related CP

IgG4-unrelated CP

Umehara H, *Mod Rheumatol* 2012; Corradi D, *Cardiovasc Pathol* 2016

SERUM IgG4 in CHRONIC PERIAORTITIS



Vaglio A, *manuscript in preparation*

IgG4-RELATED vs -UNRELATED CP

TABLE 3. Radiologic Features of the IgG4-Related RPF and Non-IgG4-Related RPF Groups

RPF Characteristic	IgG4-Related RPF Group No. (%)	Non-IgG4-Related RPF Group No. (%)	P
Location mass			
Periaortic	10/12 (83)	8/9 (89)	1.0
Periiliac	8/12 (67)	7/9 (78)	0.7
Pericaval	2/12 (17)	0/10 (0)	1
Presacral	1/12 (8)	1/9 (11)	1
Retrovesicular	1/12 (8)	0/9 (0)	1
Perirectal	1/12 (8)	1/9 (11)	1
Pelvic side-wall	1/12 (8)	3/9 (33)	0.3
Periureteral			
Unilateral	5/12 (33)	2/9 (22)	0.6
Bilateral	1/12 (8)	3/9 (33)	0.3
Mass maximal thickness, cm	0.9 ± 0.5	1.0 ± 0.6	
Abdominal aortic dilation	2/12 (17)	0/9	1
Hydronephrosis			
Unilateral	3/12 (25)	2/9 (22)	1
Bilateral	1/12 (8)	3/9 (33)	0.3
Renal atrophy	2/12 (17)	1/9 (11)	1
Localized lymphadenopathy	1/12 (8)	1/9 (11)	1
Diffuse lymphadenopathy	0/12	1/9 (11)	1
Mesenteric mass	0/12	2/9 (22)	0.2
Imaging type	12 CT	7 CT: 2 MRI	

Khosroshahi A, *Medicine (Baltimore)* 2012

IgG4-RELATED vs -UNRELATED CP

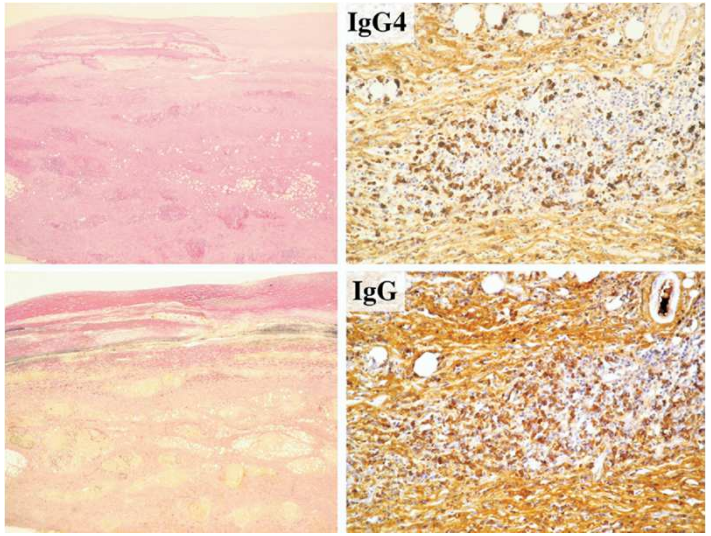
	All patients	Serum IgG4 level at presentation		*P* value
		Normal range	Elevated[a]	
No. of patients, *n*	59	35	24	
First presentation/recurrence	53/6	30/5	23/1	0.38
Age, years	61.0 (57.0–69.0)	62.0 (54.5–69.0)	61.0 (58.0–66.8)	0.71
Male gender, *n* (%)	39 (66.1)	21 (60.0)	18 (75.0)	0.27
Duration of symptoms, months	4.5 (2.0–11.0)	4.0 (2.0–11.0)	5.0 (3.0–10.0)	0.58
Visual analog scale score, mm				
Pain	70.0 (44.8–85.0)	70.0 (43.0–80.0)	70.0 (42.5–90.0)	0.47
Discomfort	60.0 (39.5–77.5)	55.0 (33.0–70.0)	60.0 (50.0–85.0)	0.40
Weight loss, kg	4.0 (0.0–7.0)	4.0 (0.0–8.0)	1.0 (0.0–7.0)	0.84
Acute-phase reactant levels				
ESR, mm/h	39.5 (20.8–62.5)	34.5 (16.0–56.3)	46.0 (32.3–64.0)	0.08
CRP, mg/L	7.0 (5.0–23.5)	6.0 (5.0–23.5)	9.0 (5.0–26.0)	0.44
Renal function				
Creatinine, μmol/L	92.0 (74.0–122)	86.0 (73.0–114.0)	99.5 (77.8–137.0)	0.16
Hydro-ureteronephrosis, *n* (%)	31 (54.2)	18 (51.4)	14 (58.3)	0.79
D-J splint or PNS, *n* (%)	16 (27.1)	9 (25.7)	7 (29.1)	0.77
Abdominal CT findings				
Thickness RPF mass, mm	29.5 (20.3–48.0)	32.0 (17.0–49.5)	29.0 (22.0–45.0)	0.73
Abdominal infrarenal aortic diameter, mm	22.0 (19.3–29.8)	24.5 (18.0–33.8)	21.5 (20.0–24.5)	0.19
Atypical retroperitoneal localization, *n* (%)	11 (18.6)	6 (17.1)	5 (20.8)	0.74
Locoregional lymphadenopathy, *n* (%)	17 (28.8)	7 (20.0)	10 (41.7)	0.08
Extra-retroperitoneal localization, *n* (%)	10 (16.9)	4 (11.4)	6 (25.0)	0.28
Success tamoxifen therapy[b], *n* (%)	27/47 (57.4)	19/31 (61.3)	8/16 (50.0)	0.54

Pelkmans LG, *Clin Rheumatol* 2017

IgG4-RELATED vs –UNRELATED *ANEURYSMAL* CP (IAAA)

	Inflammatory AAA		
	IgG4-related (n = 13)	*Non-IgG4-related (n = 10)*	P *value*
Age (years)	70 (59-76)	69 (59-81)	.863
Gender (male/female)	11/2	9/1	.704
Aneurysmal diameter (mm)	58 (33-87)	52 (28-100)	.550
Symptoms			
Low grade fever	5 (38%)	4 (40%)	.942
Abdominal or back pain	1 (8%)	5 (50%)	**.025**
Rupture	0	3 (30%)	**.038**
Death immediately after surgery	2 (15%)	0	.194

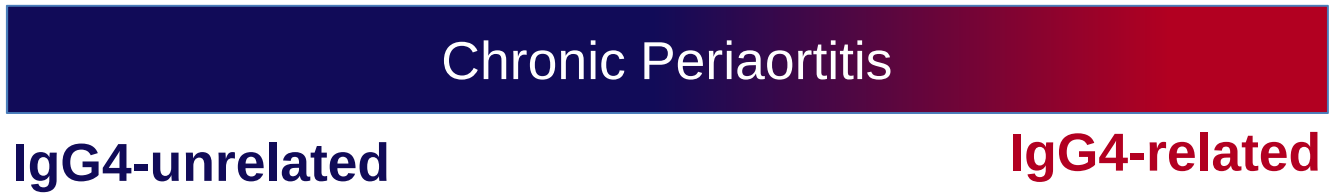
	Inflammatory AAA		
	IgG4-related (n = 13)	*Non-IgG4-related (n = 10)*	P *value*
Smoking habit	7 (54%)	7 (70%)	.442
Hypertension	2 (15%)	4 (40%)	.192
Ischemic heart diseases	3 (23%)	5 (50%)	.189
Diabetes	1 (8%)	1 (10%)	.849
Hyperlipidemia	3 (23%)	1 (10%)	.412
Autoimmune diseases	7 (54%)	1 (10%)	**.025**
Drug allergy	5 (38%)	1 (10%)	.123
Bronchial asthma	4 (31%)	1 (10%)	.232



Kasashima S, *J Vasc Surg* 2009

IgG4-RELATED vs -UNRELATED CP

	No. pts	IgG4+ cases, n(%)	Criteria to differentiate IgG4+ vs IgG4- CP	Main findings (in the IgG4+ subset)
Castelein T, 2015	17	9 (53)	Serum IgG4 level	Multifocal involvement, male predominance
Kasashima S, 2008	23	13 (56)	Histology and IHC	Higher incidence of autoimmune diseases
Khosroshahi A, 2013	23	13 (56)	Histology and IHC	Multifocal involvement
Koo B, 2014	19	9 (47)	Histology and IHC	Higher relapse rate
Yamashita M, 2008	15	6 (30)	Histology and IHC	Multifocal involvement
Zen Y, 2009	17	10 (59)	Histology and IHC	Multifocal involvement, male predominance



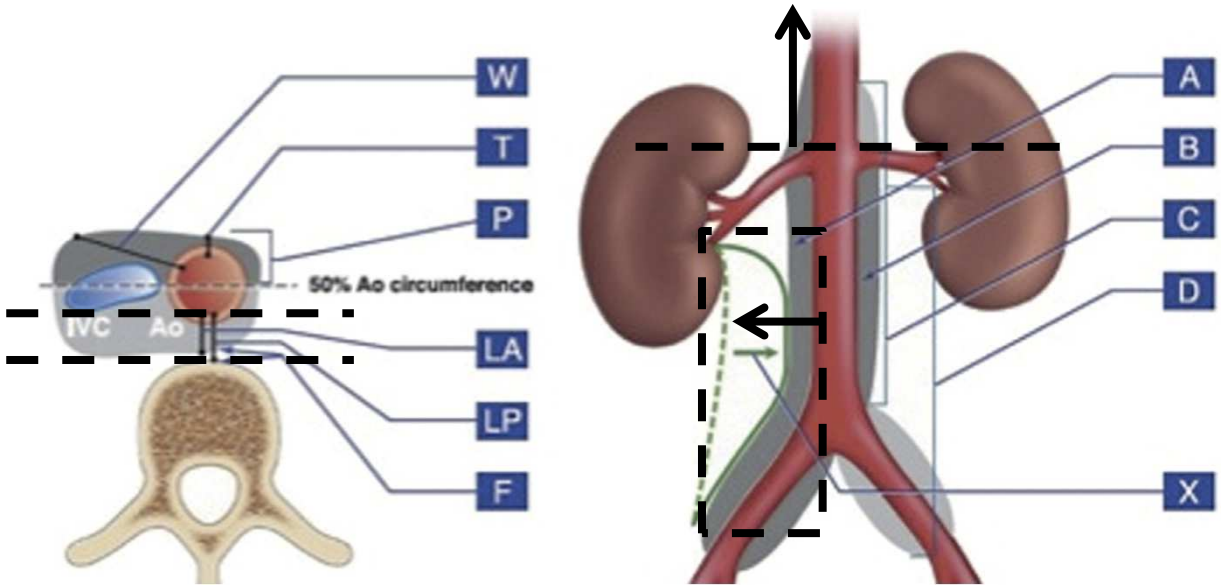
Rossi GM, *Intern Emerg Med* 2017

Differential diagnosis

DIAGNOSIS- EXCLUSION OF SECONDARY FORMS

- Drugs (*eg*, ergotamine, methysergide, pergolide, methyldopa)
- Malignancies (*eg*, carcinoid, lymphomas, sarcoma, carcinoma of the GI tract, breast, prostate)
- Infections (*eg*, TB, actinomycosis, histoplasmosis)
- Radiotherapy
- Surgery (*eg*, colectomy, hysterectomy, lymphadenectomy)
- Others (*eg*, Erdheim-Chester disease, amyloidosis, trauma)

DIAGNOSIS- MALIGNANT VS. IDIOPATHIC CP

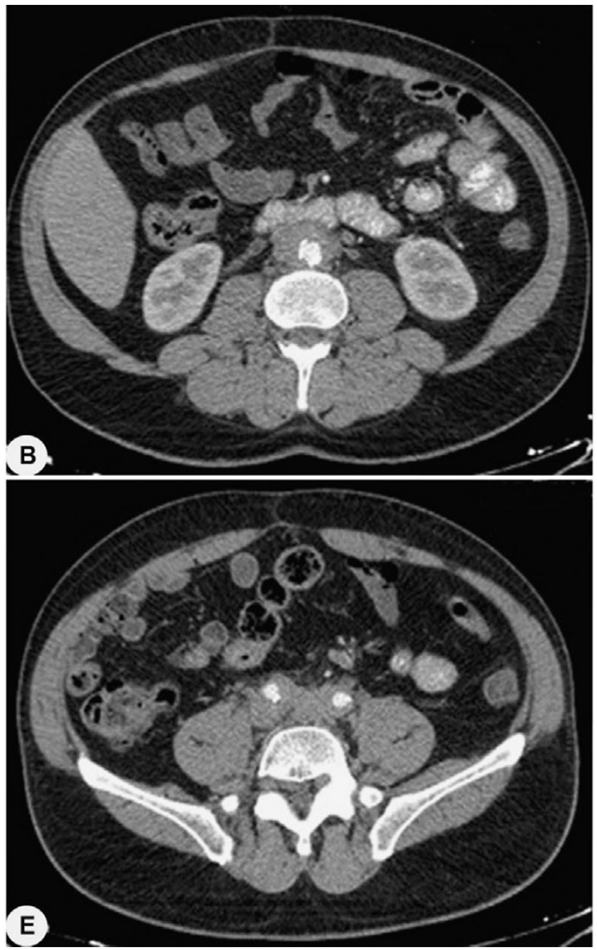


CT/MRI characteristics of IDIOPATHIC forms

- Homogeneous, muscle-isodense tissue surrounding the antero-lateral sides of the abdominal aorta
- Extension from the origin of the renal arteries to below the aorto-iliac bifurcation
- No anterior displacement of the aorta or bone erosions
- Usually less “bulky” than malignant forms

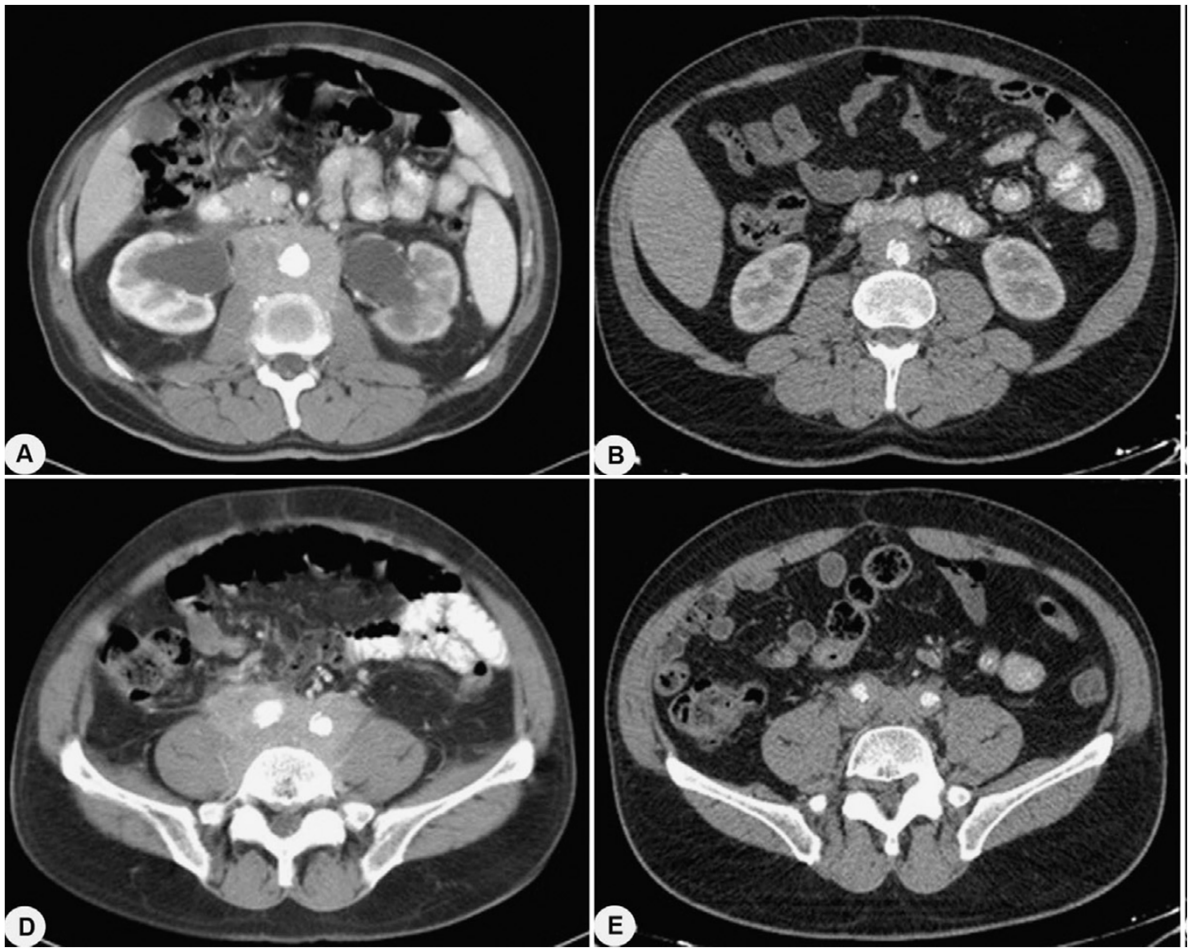
Mirault T, *Medicine (Baltimore)* 2012

DIAGNOSIS- IMAGING STUDIES



Urban ML, *Rev Med Interne* 2015

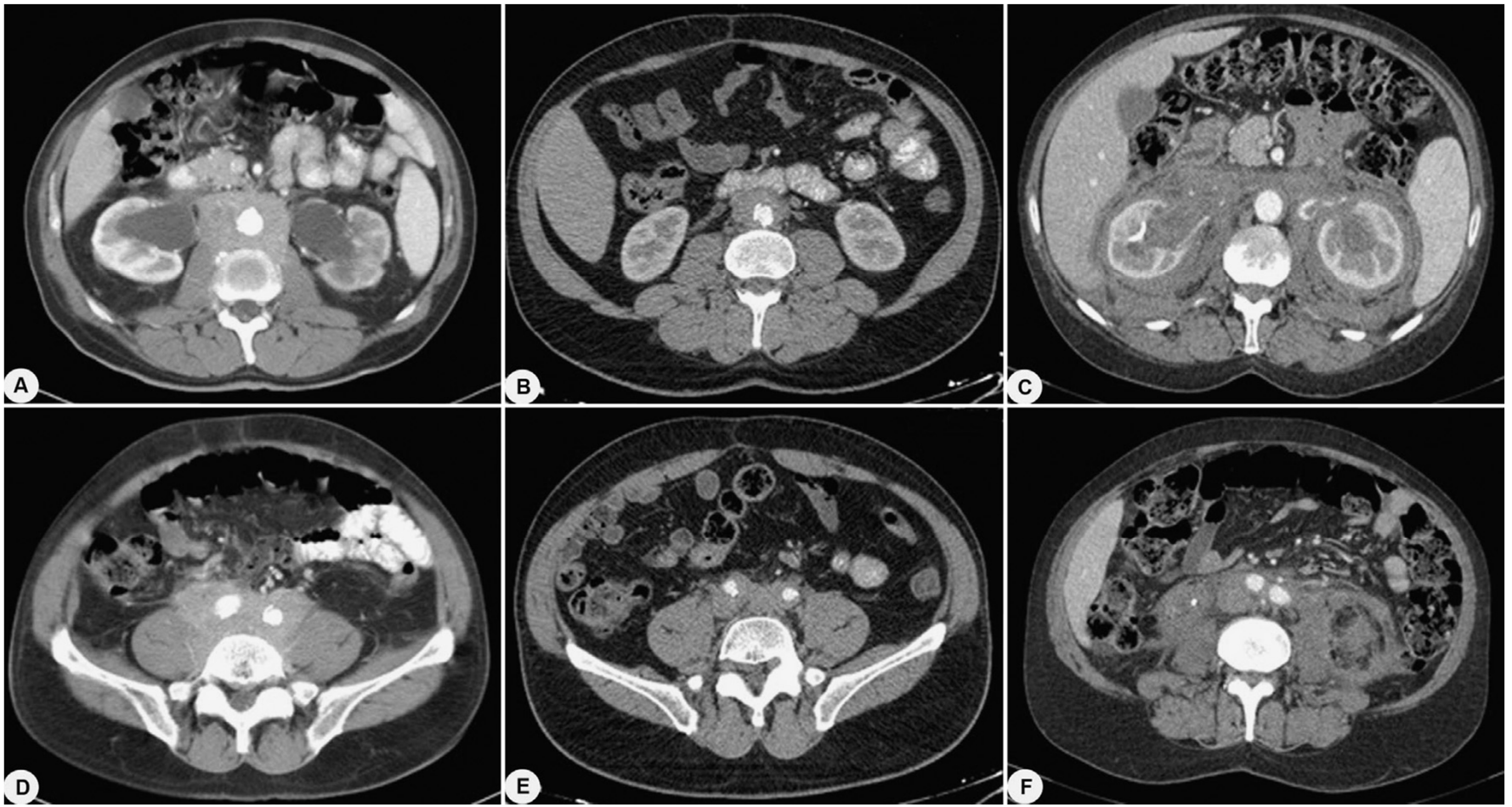
DIAGNOSIS- IMAGING STUDIES



NHL Chronic Periaortitis

Urban ML, *Rev Med Interne* 2015

DIAGNOSIS- IMAGING STUDIES



NHL | Chronic Periaortitis | Erdheim-Chester disease

Urban ML, *Rev Med Interne* 2015

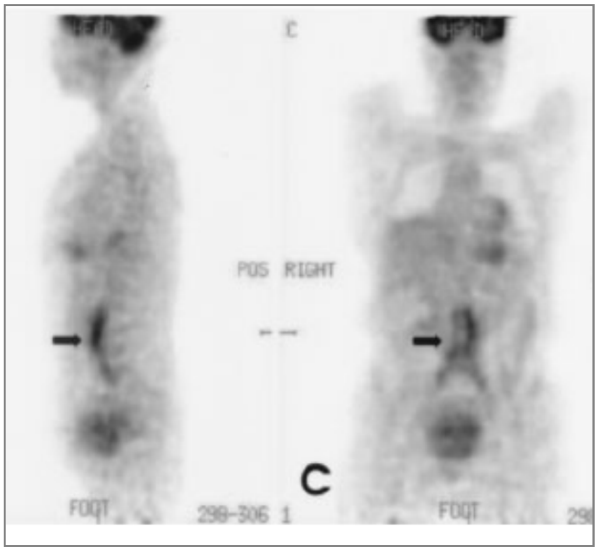
DIAGNOSIS- IMAGING STUDIES

Typical CP (Idiopathic RPF)

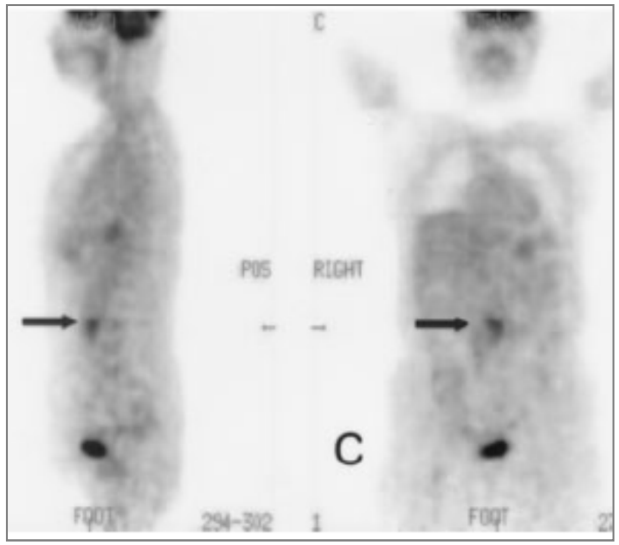
Atypical Idiopathic RPF

Rossi GM, *Intern Emerg Med* 2017

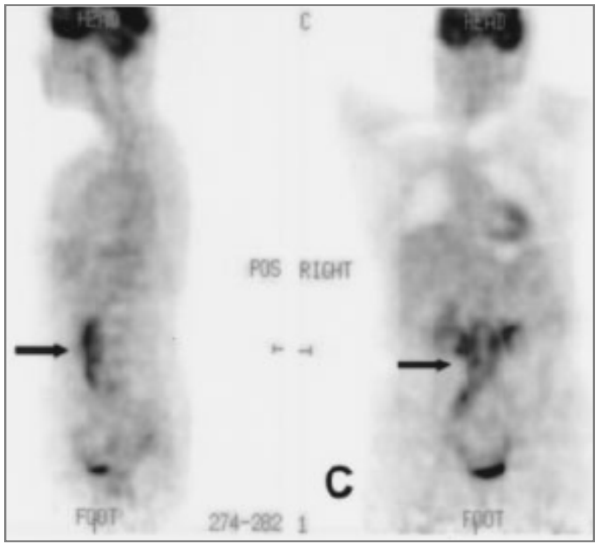
18F-FDG PET IN CP



Disease onset



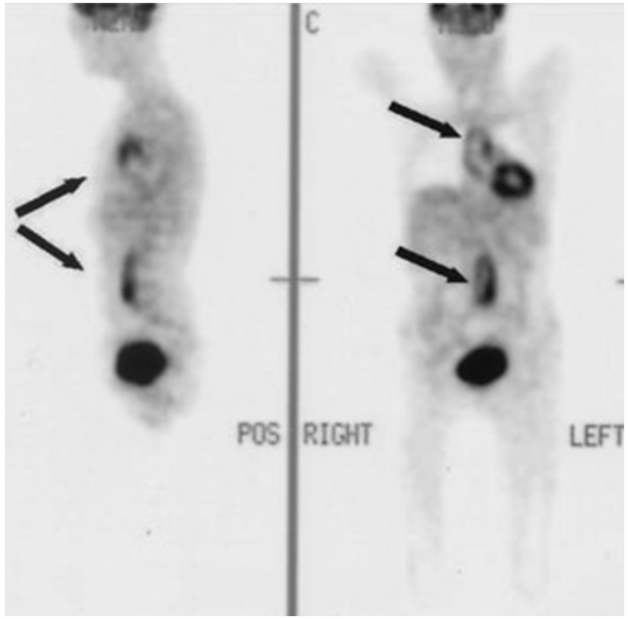
After 4 months of prednisone



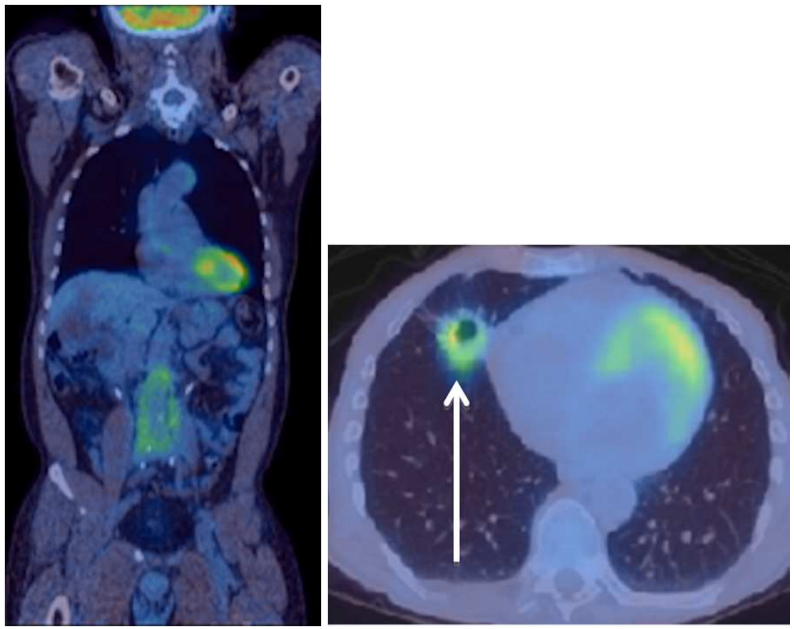
Disease relapse

Vaglio A, *Arthritis Rheum* 2005

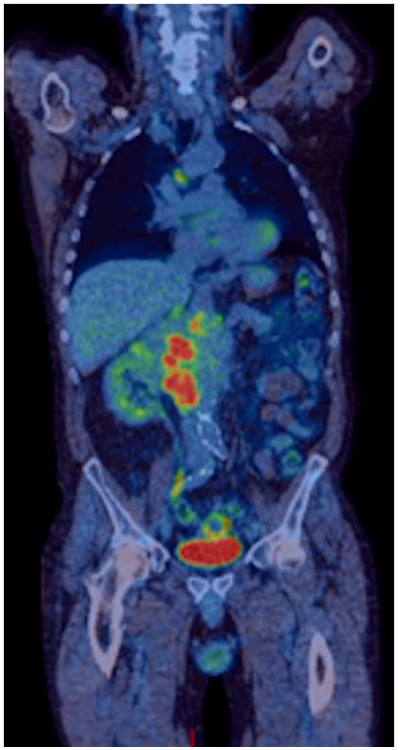
18F-FDG PET IN CP



Thoracic and abdominal CP



CP in a patient with GPA



NHL

Salvarani C, *Arthritis Rheum* 2005; Fernando A, *Eur Urol* 2017

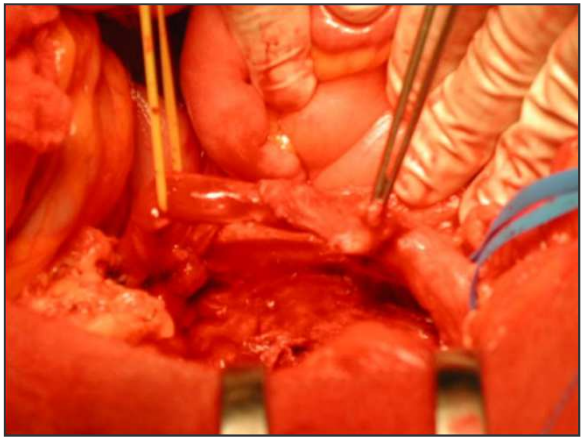
18F-FDG PET IN CP

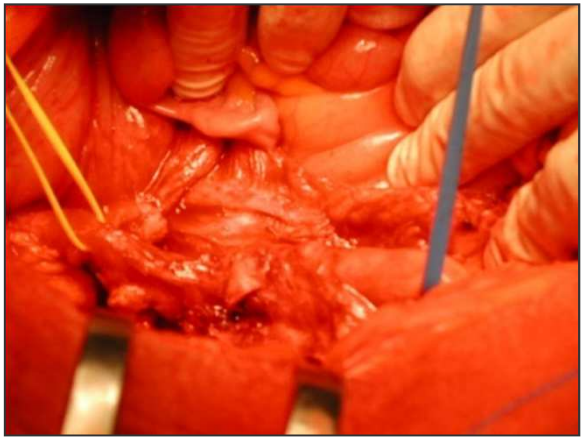
FDG-PET findings	Response to steroids, n (%)	NO response to steroids, n (%)
Negative (n=14)	0 (0)	14 (100)
Low-grade positive (n=24)	3 (12)	21 (88)
High-grade positive (n=11)	9 (82)	2 (18)

Fernando A, *Eur Urol* 2017

Treatment and outcome

TRADITIONAL SURGERY (back to Albarrán…)





courtesy of S. Ferretti, Urology, Parma

Surgical ureterolysis

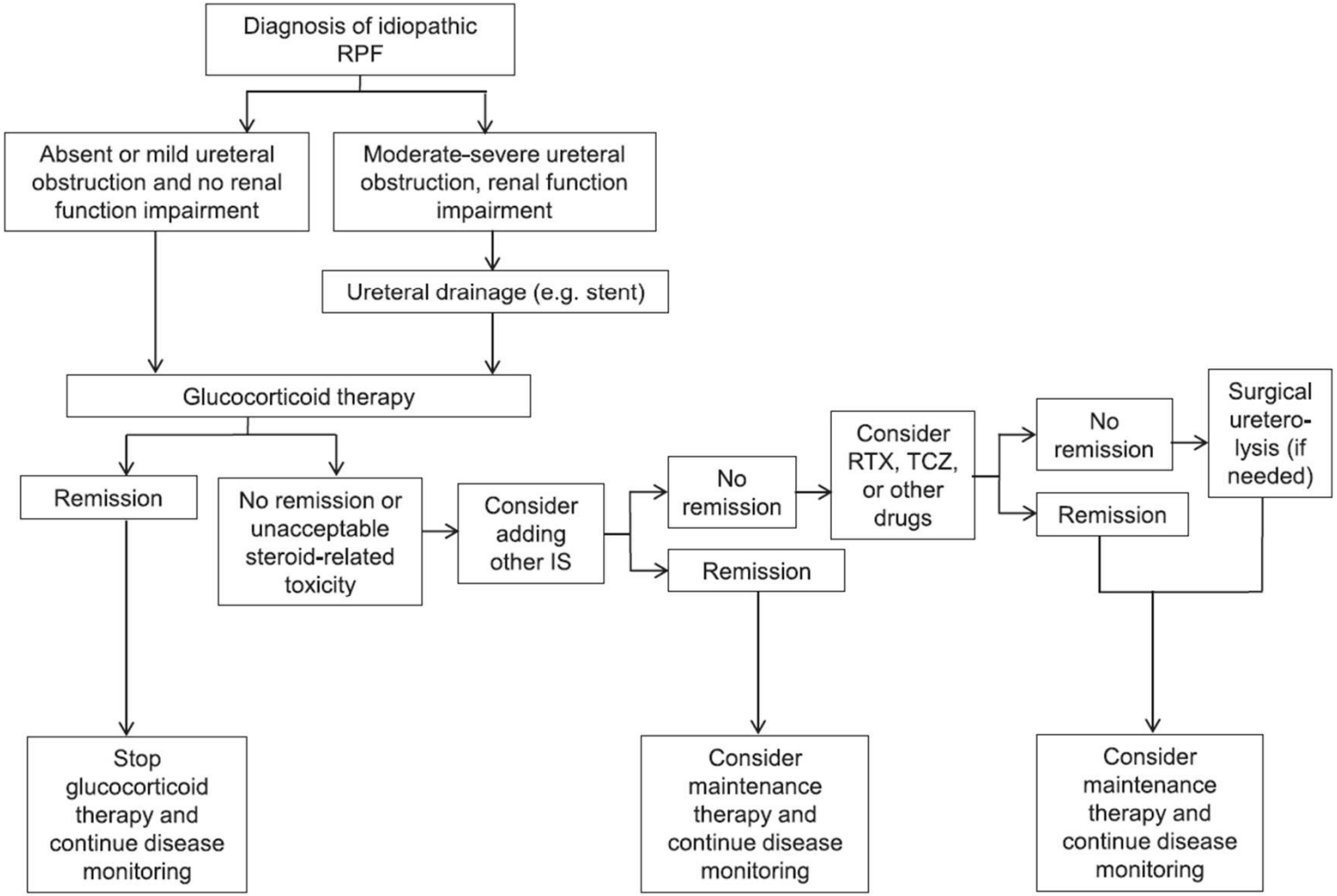
- Ureterolysis (± intraperitonealisation) + omental wrapping
- Allows multiple biopsies
- 50% relapse if treated with surgery alone vs 10-30% with surgery+medical therapies

Laparoscopy vs Open

- Shorter hospital stay and lower transfusion rates
- Conversion rate to open approx 20%

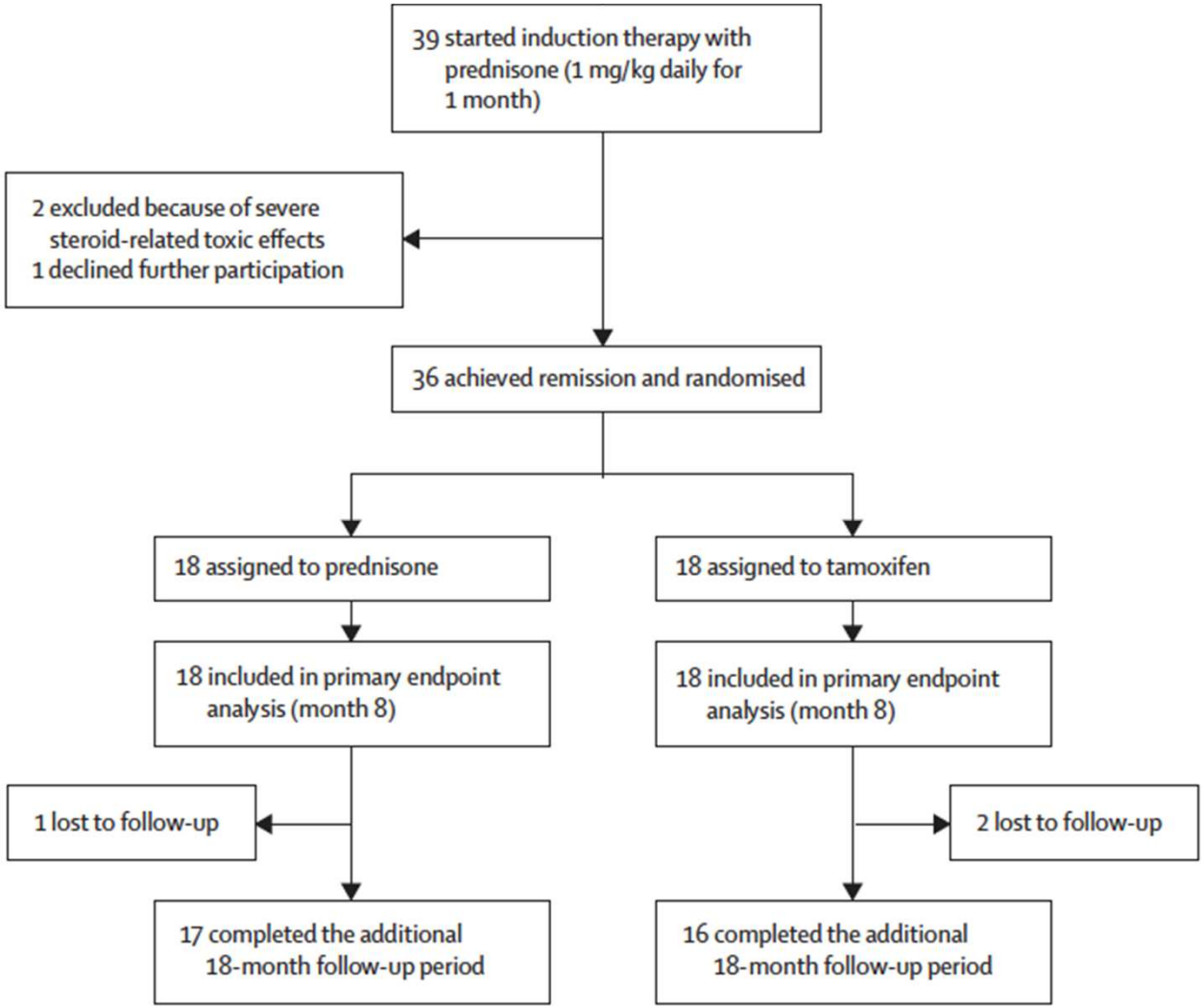
Srinivasan AK, *J Urol* 2008

TREATMENT ALGORITHM



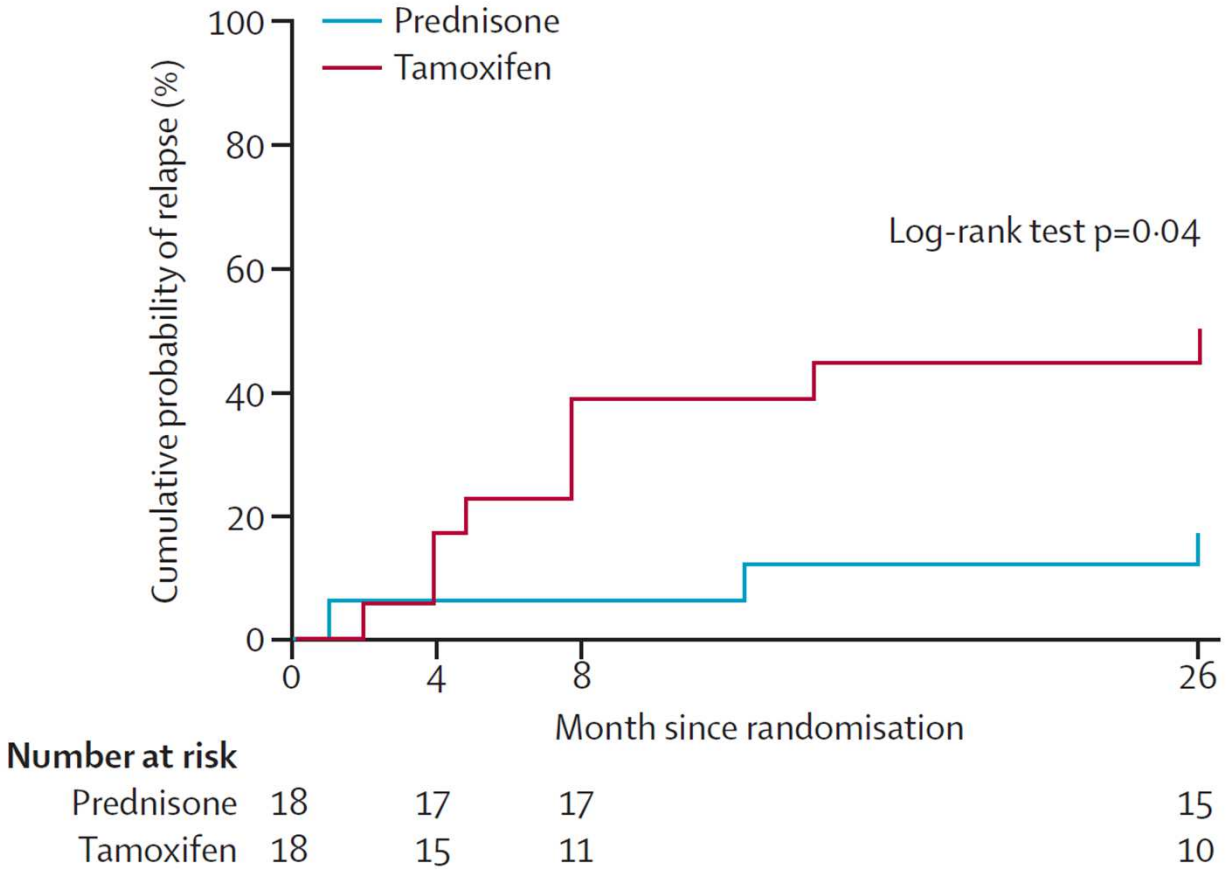
Vaglio A, *J Am Soc Nephrol* 2016

GLUCOCORTICOIDS AS FIRST-LINE THERAPY



Vaglio A, *Lancet* 2011

GLUCOCORTICOIDS AS FIRST-LINE THERAPY

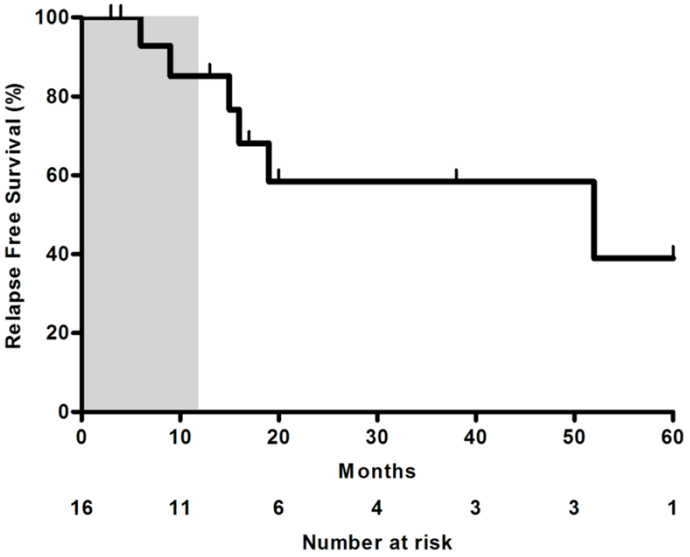


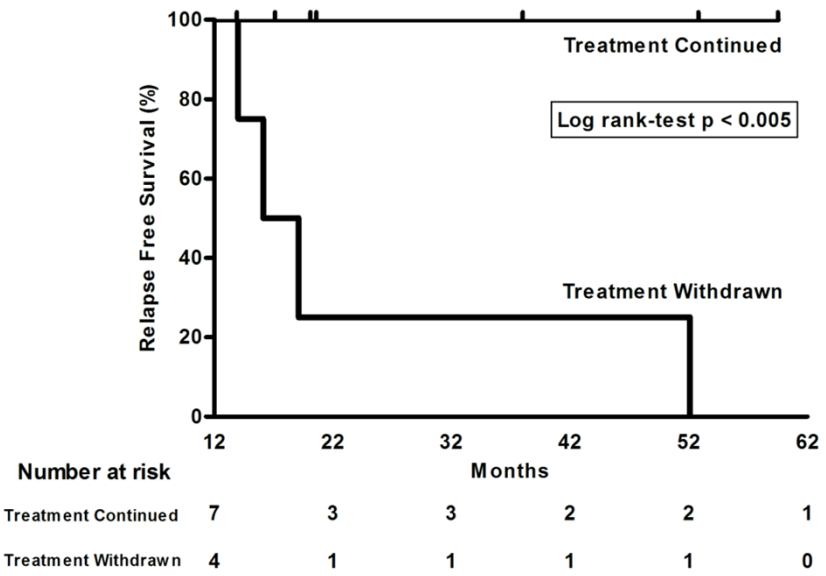
Vaglio A, *Lancet* 2011

TREATMENT OF RELAPSING DISEASE

16 consecutive *relapsing* CP patients

MTX (15-20 mg/week) + PDN for 12 months (followed by observation or treatment continuation)



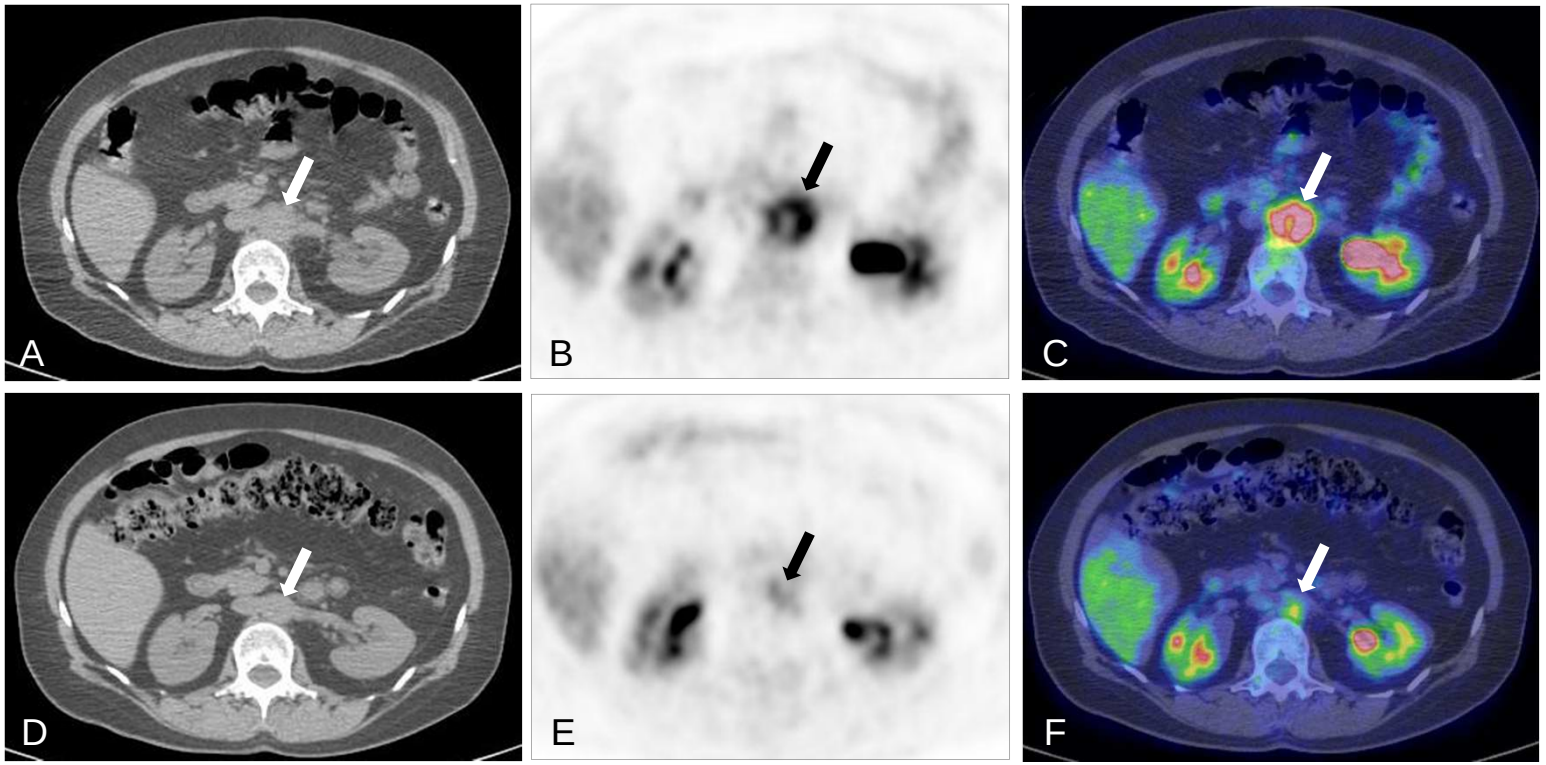


Alberici F, *Ann Rheum Dis* 2013

RITUXIMAB FOR RELAPSING-REFRACTORY DISEASE

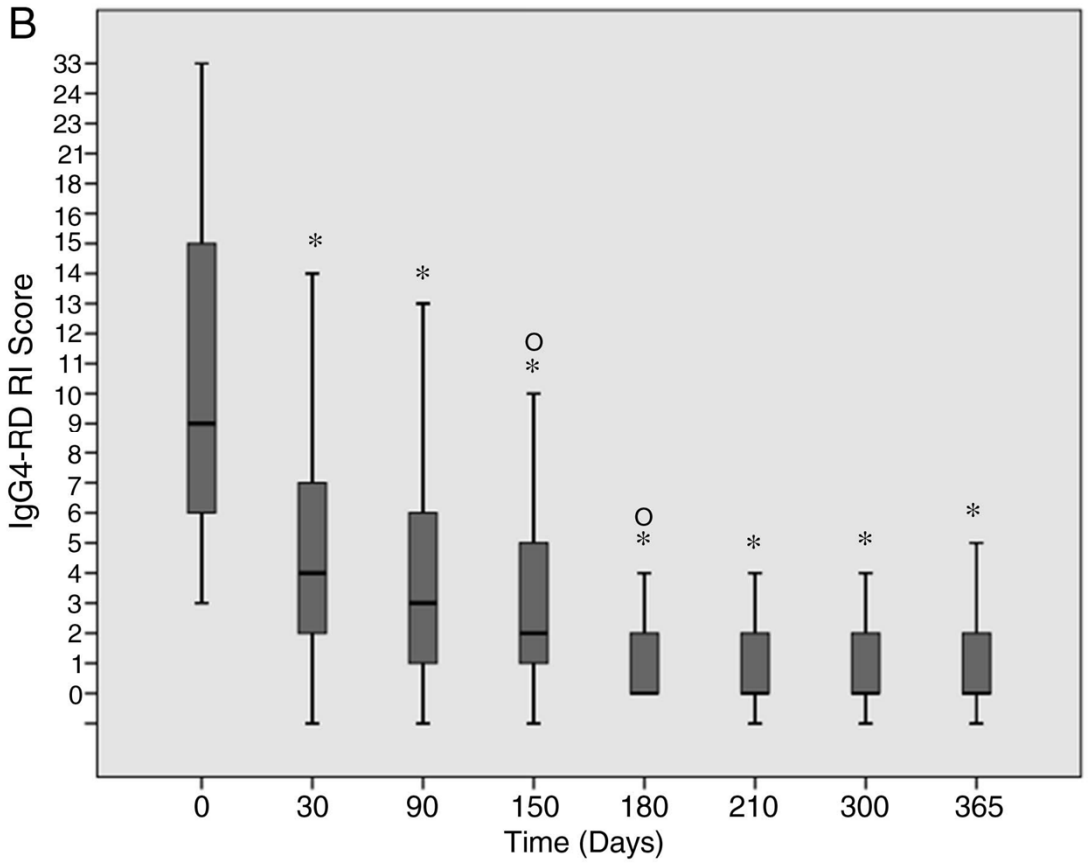
Before Rituximab

After Rituximab



Maritati F, *Ann Rheum Dis* 2012

RITUXIMAB FOR IgG4-RD



Carruthers M, *Ann Rheum Dis* 2015

RITUXIMAB FOR (IgG4-negative) CP

- 16 patients with difficult-to-treat CP
  12 relapsing-refractory
  4 contraindications to standard-dose GCs

- 14/16 had normal serum IgG4
- No one had evidence of (systemic) IgG4RD

- 13 RTX+low-dose GCs (<12.5 mg/d)
- 3 RTX monotherapy
  RTX: 375 mg/m2/w x4 weeks or 1 g x2 two weeks apart

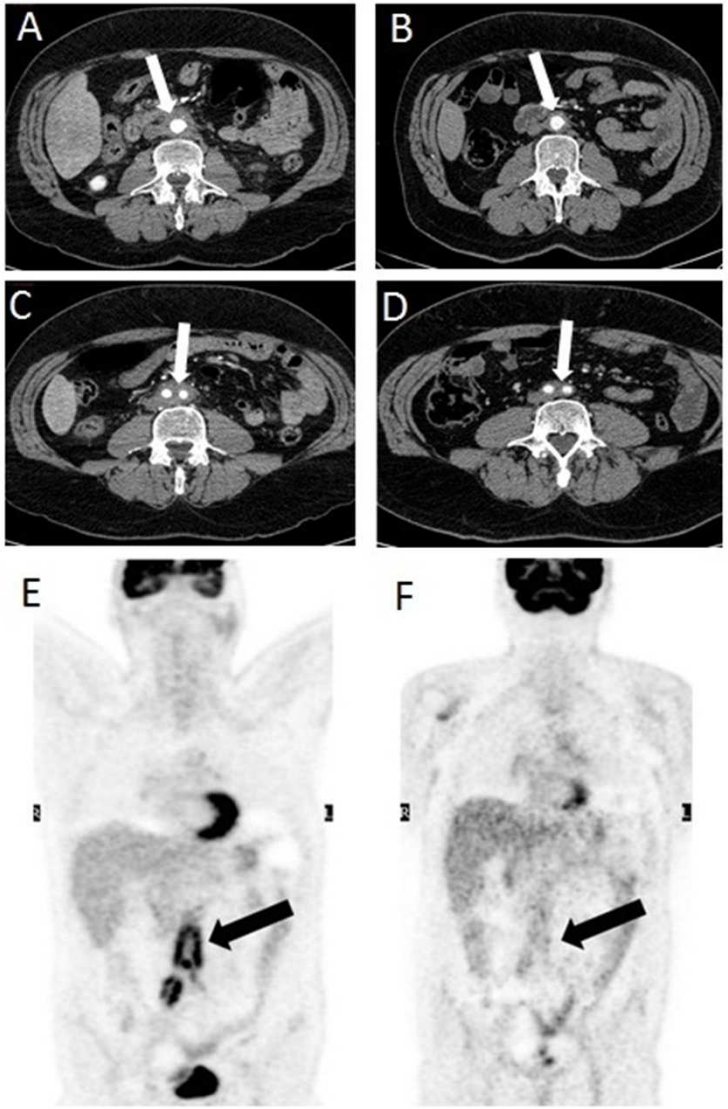
- At m6, **15/15 evaluable patients had PET response** and symptom remission
- CP shrinkage on CT/MRI was less common

- 2/2 patients responded to RTX retreatment for relapse

Urban ML, *unpublished*

TOCILIZUMAB FOR RELAPSING-REFRACTORY DISEASE

Before and after Tocilizumab



Vaglio A, *Arthritis Rheum* 2013

ACKNOWLEDGMENTS

Nephrology, Parma University Hospital
Maria Letizia Urban
Alessandra Palmisano
Federica Maritati
Federico Alberici
Giovanni M Rossi
Rossana Rocco
Maria Nicastro
Lucio Manenti

Pathology, Parma University Hospital
Domenico Corradi

Genetics, Parma University Hospital
Davide Martorana
Francesco Bonatti
Alessia Adorni

Urology, Parma University Hospital
Stefania Ferretti

Endocrinology, Parma University Hospital
Graziano Ceresini

Occupational Medicine, Parma University Hospital
Silvia Bonini
Matteo Goldoni

Nuclear Medicine, Reggio Emilia Hospital
Annibale Versari

Rheumatology, Reggio Emilia Hospital
Carlo Salvarani
Nicolò Pipitone

Nephrology, Policlinico Hospital, Milano
Gabriella Moroni

Internal Medicine, University of Firenze
Giacomo Emmi

CSIC, Granada, Spain
Javier Martin