Diagnostiek en behandeling IgG4 ziekte

“the great mimicker”

Coen Stegeman, internist-nefroloog

UMC Groningen

Naamgeving van het ziektebeeld

- IgG4-related (systemic) disease (IgG4-R(S)D)
- IgG4-associated disease
- IgG4-related (systemic) sclerosing disease
- IgG4-related autoimmune disease
- IgG4 syndrome
- Hyper-IgG4 disease
- Systemic IgG4-related plasmocytic syndrome (SIPS)
- IgG4 positive multi-organ lymphoproliferative syndrome (IgG4-MOLPS)

Stone JH, et a. Arthitis Rheum 2012;64:3061-7

Naamgeving van het ziektebeeld

TABEL 2 Alternatieve benamingen voor IgG4-gerelateerde systemische ziekte

alternatieve benamingen voor IgG4-gerelateerde systemische ziekte
IgG4-gerelateerde plasmocytaire ziekte
IgG4-gerelateerde scleroserende ziekte
IgG4-positief multi-orgaan lymfoproliferatief syndroom (IgG4+ MOLPS)
idiopatische systemische fibrose
pseudotumoren
myofibroblastische tumoren
xanthofibrogranulomatose
multifocale fibrosclerose

Kramer AB, et al. Ned Tijdschr Geneeskd 2011;155:A3603

Consensus meeting 4-7 oktober 2011, Boston

IgG4-related disease (IgG4-RD)

Individuele orgaanmanifestaties:

- IgG4-related ……..

  pancreatitis

  orbital inflammatory pseudotumor

  hypophysitis

  retroperitoneal fibrosis

  lymphadenopathy

  etc.....

Stone JH, et a. Arthitis Rheum 2012;64:3061-7

Table 3. Preferred nomenclature for individual organ manifestations of IgG4-related disease

Organ system/tissue	Preferred name
Pancreas	Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
Eye	IgG4-related ophthalmic disease is the general term for the periocular manifestations of this disease. There are several subsets, outlined below.
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue (orbital inflammatory pseudotumor)	IgG4-related orbital inflammation (or IgG4-related orbital inflammatory pseudotumor)
Extraocular muscle disease	IgG4-related orbital myositis
Orbit with involvement of multiple anatomic structures	IgG4-related pan-orbital inflammation (includes lacrimal gland disease, extraocular muscle involvement, and other potential intraorbital complications)
Salivary glands (parotid and submandibular glands)	IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
Pachymeninges	IgG4-related pachymeningitis
Hypophysis	IgG4-related hypophysitis
Thyroid (Riedel thyroiditis)	IgG4-related thyroid disease
Aorta	IgG4-related aortitis/periaortitis
Arteries	IgG4-related periarteritis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis
Liver	IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
Lung	IgG4-related lung disease
Pleura	IgG4-related pleuritis
Pericardium	IgG4-related pericarditis
Kidney	IgG4-related kidney disease. The specific renal complications should be termed tubulointerstitial nephritis secondary to IgG4-related disease and membranous glomerulonephritis secondary to IgG4-related disease. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis.
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis

Stone JH, et a. Arthitis Rheum 2012;64:3061-7

Historie van het ziektebeeld

- 1995 beschrijving autoimmuun pancreatitis (AIP) [1]
  - diffuse vorm (scleroserend)
  - tumor (massawerking; icterus)
- 2001 (sterk) verhoogde serum IgG4 waarden bij AIP [2]
- 2003 extra-pancreatische lesies bij AIP [3]
  - scleroserende cholangitis / cholecystitis
  - pseudotumoren (lever, long)
  - sialadenitis
  - retroperitoneale fibrose

(1) Yoshida K, et al. Dig Dis Sci 1995;40:1561-8
(2) Hamano H, et al. N Engl J Med 2001;344:732-8
(3) Kamisawa T, et al. J Gasteroenterol 2003;38:982-4

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Beelden nu gerekend tot het spectrum van IgG4-gerelateerde ziekte

Table 2. Names of previously recognized conditions that comprise or may comprise parts of the IgG4-related disease spectrum

Mikulicz disease
Küttner tumor
Riedel thyroiditis
Eosinophilic angiocentric fibrosis
Multifocal fibrosclerosis
Lymphoplasmacytic sclerosing pancreatitis/ autoimmune pancreatitis
Inflammatory pseudotumor
Fibrosing mediastinitis
Sclerosing mesenteritis
Retroperitoneal fibrosis (Ormond disease)
Periaortitis/periarteritis
Inflammatory aortic aneurysm
Cutaneous pseudolymphoma
Idiopathic hypertrophic pachymeningitis
Idiopathic tubulointerstitial nephritis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Idiopathic cervical fibrosis

Stone JH, et al. Arthritis Rheum 2012;64:3061-7

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Idiopathic hypertrophic pachymeningitis
Idiopathic tubulointerstitial nephritis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Idiopathic cervical fibrosis

Niet al deze aandoeningen zijn IgG4 gerelateerde aandoeningen, maar je moet er aan denken

Stone JH, et al. Arthritis Rheum 2012;64:3061-7

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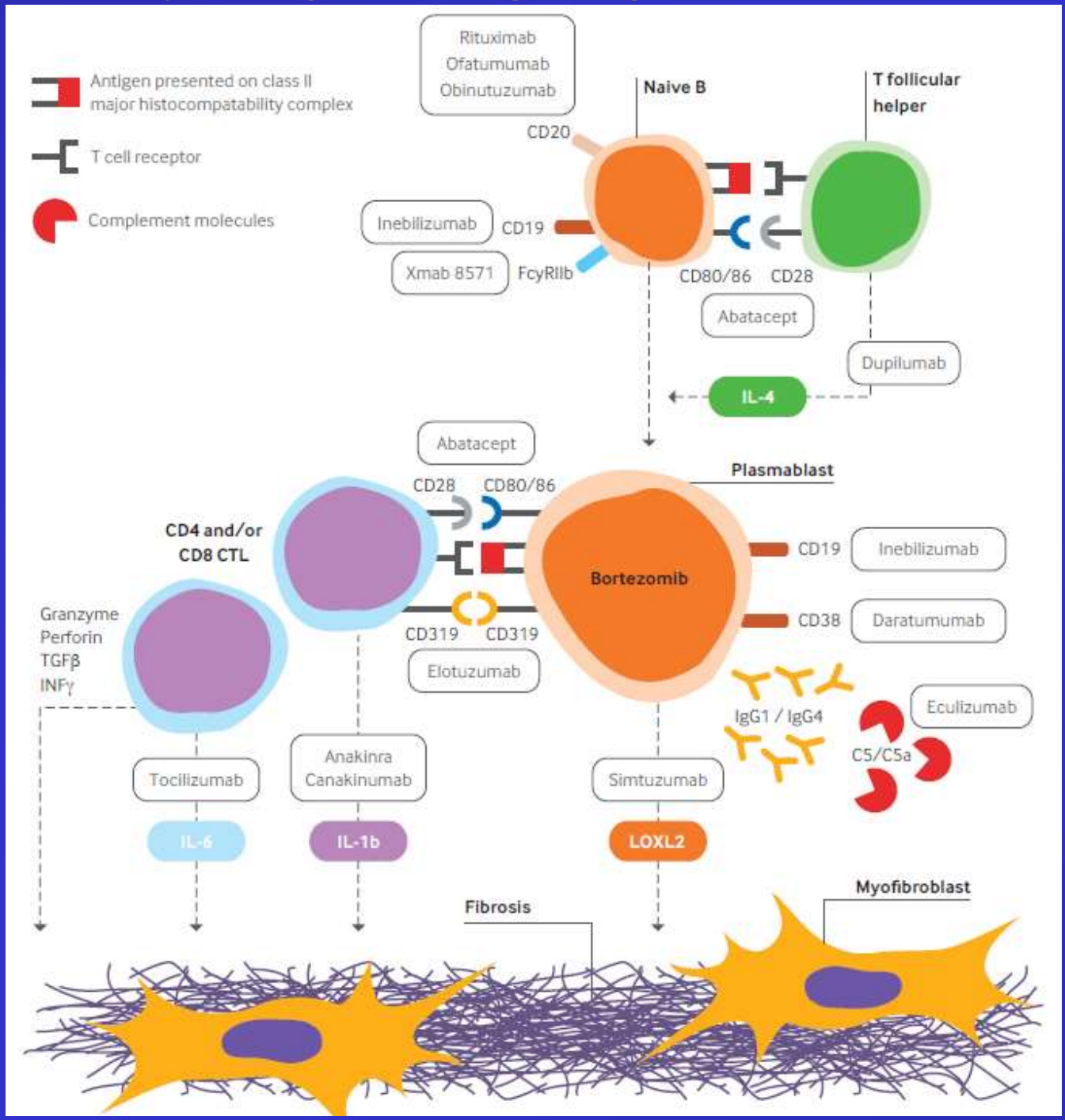
Pathofysiologie van IgG4-gerelateerde ziekte



Lanzilotta M, et al. BMJ 2020;369:m1067

IgG4-gerelateerde ziekte

Voorgeschiedenis:

- astma, eczeem, atopie

Algehele verschijnselen:

- koorts, malaise, gewichtsverlies
- lymfadenopathie

Laboratorium:

- matig verhoogde BSE, CRP
- verhoogd totaal eiwit, hypergammaglobulinaemie
- eosinofilie, verhoogd IgE

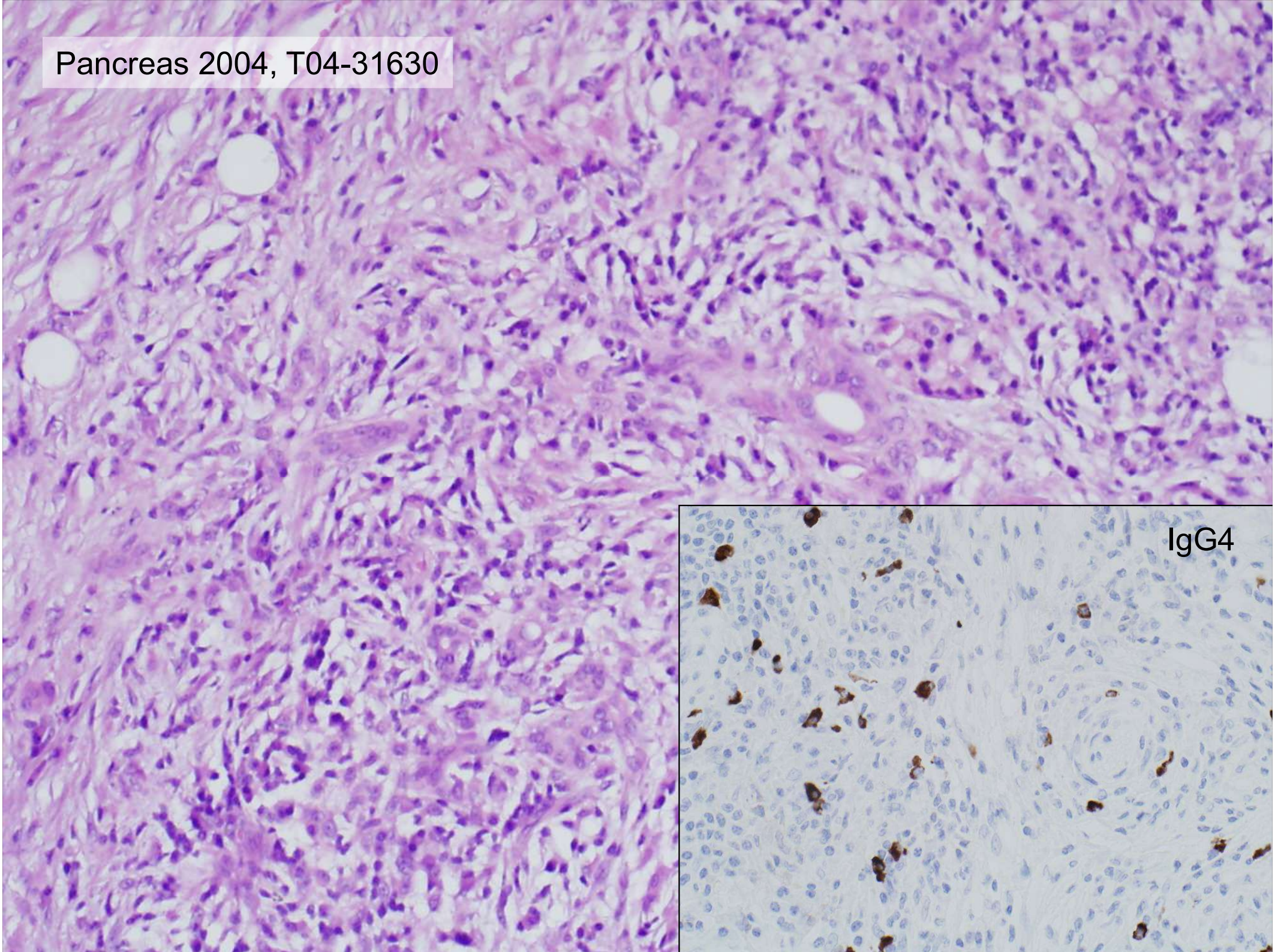
IgG4-gerelateerde ziekte

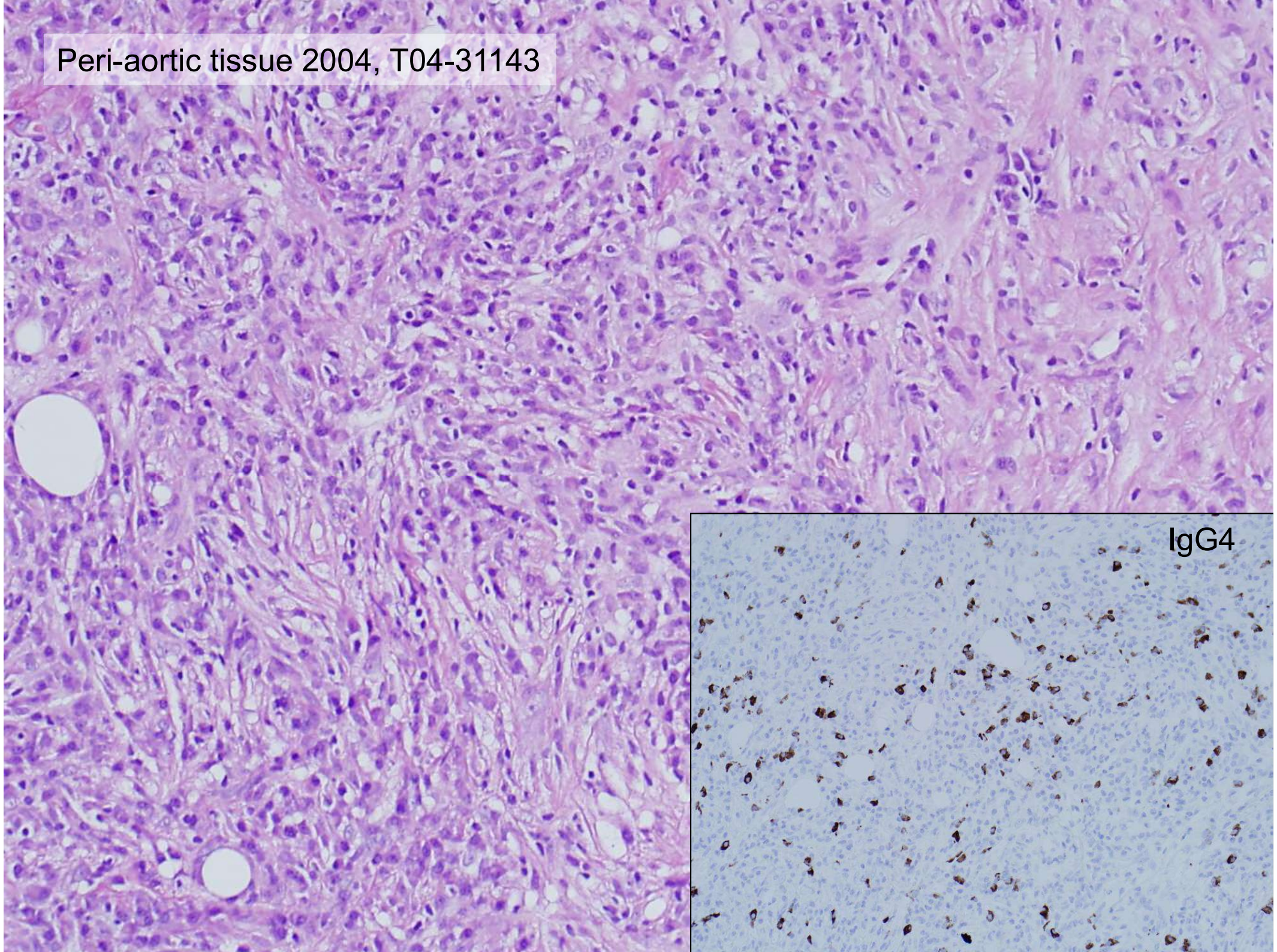
<u>Serologie:</u>

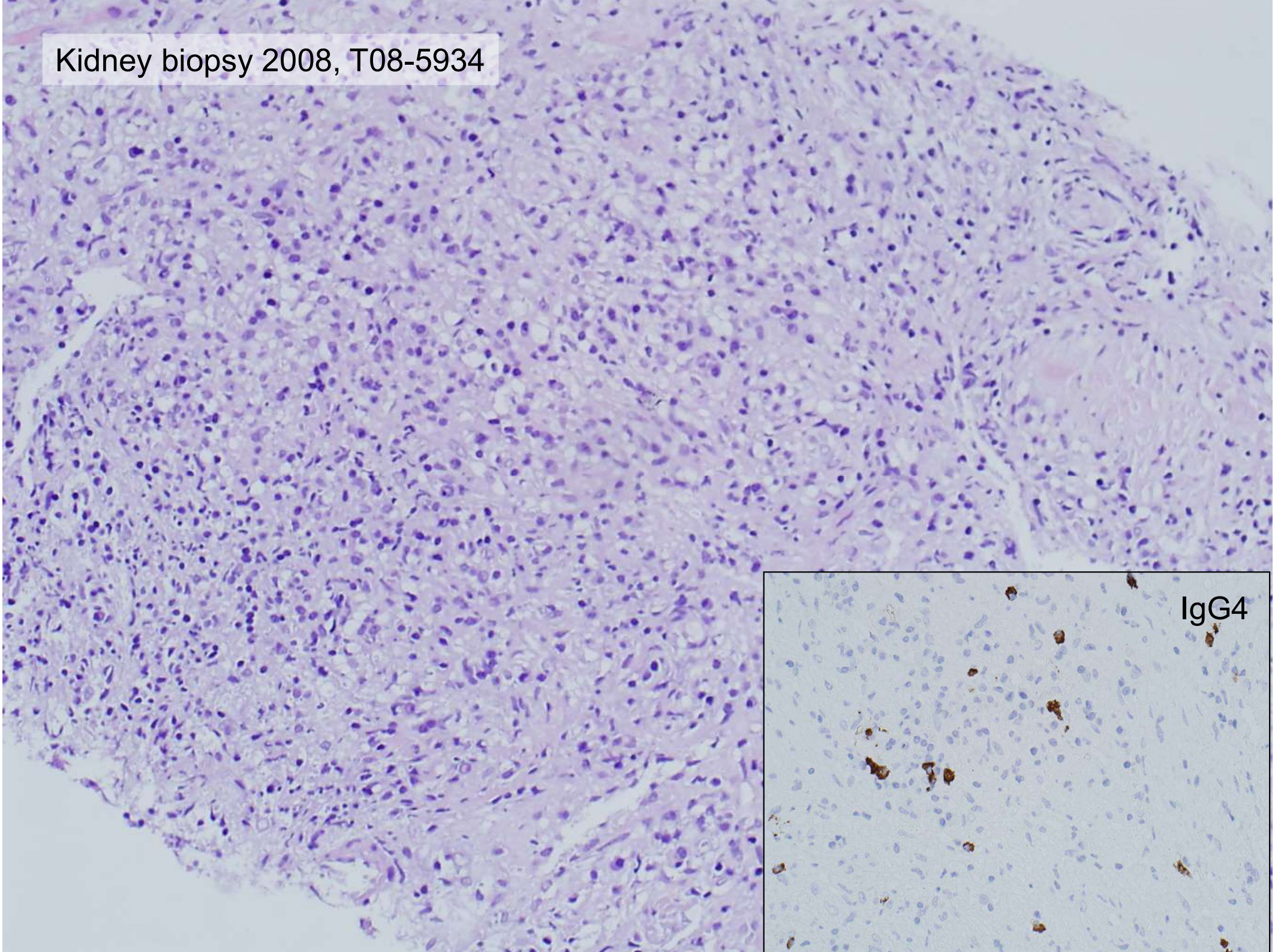
- sterk verhoogd IgG (> 15 g/l) en IgG4 (> 1,35 g/l, vaak extreem)
  * polyclonaal
  * bij 20-30% is serum IgG4 niet verhoogd
- ANA positief bij ca. 50%
  * anti-dsDNA, anti-Sm negatief
  * anti-SSA/SSB negatief
- complement C3 en/of C4 verlaagd bij ~50%
- eosinofilie (bloed, PA)

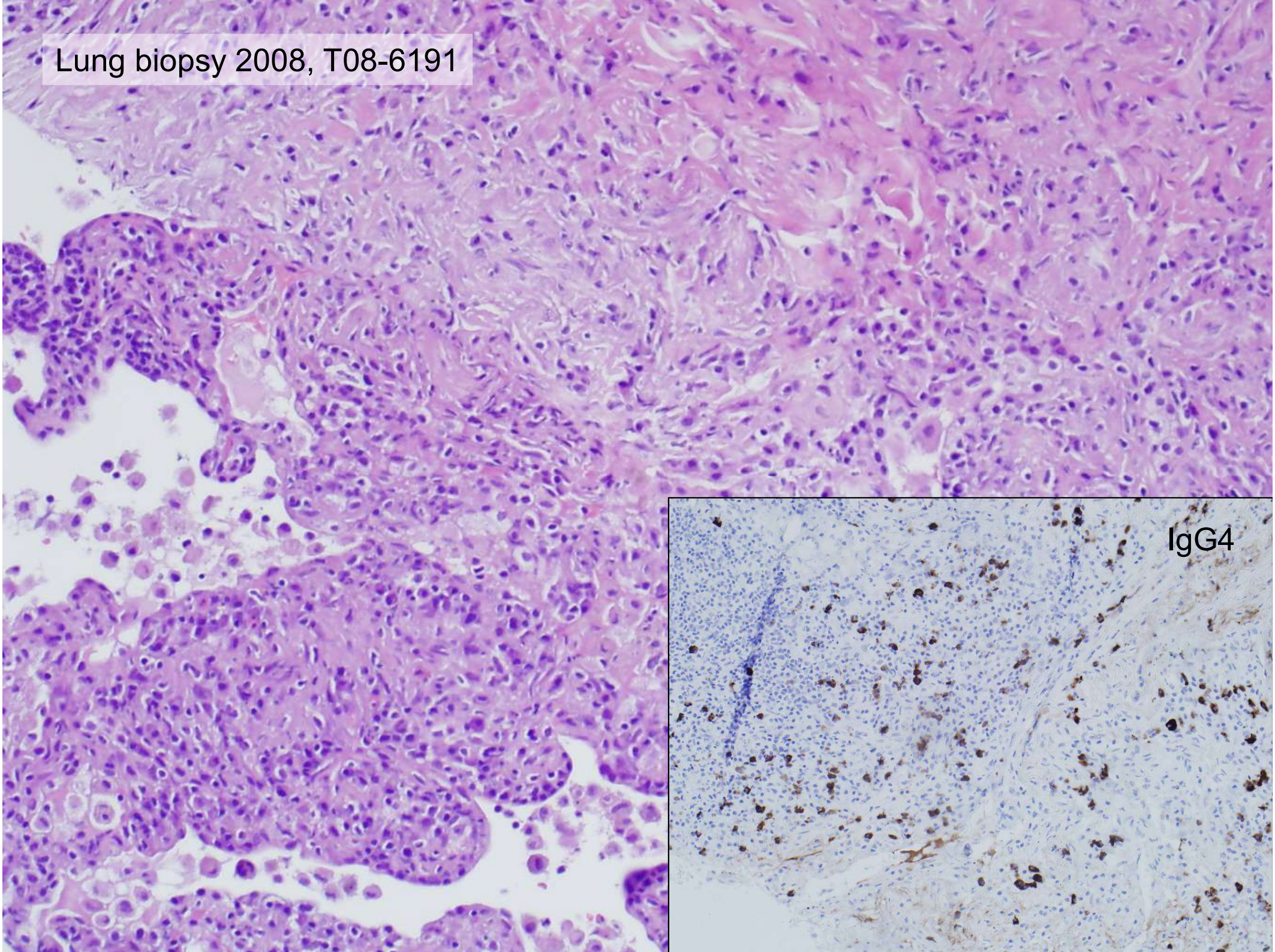
Differentiaal diagnose IgG4-RSD

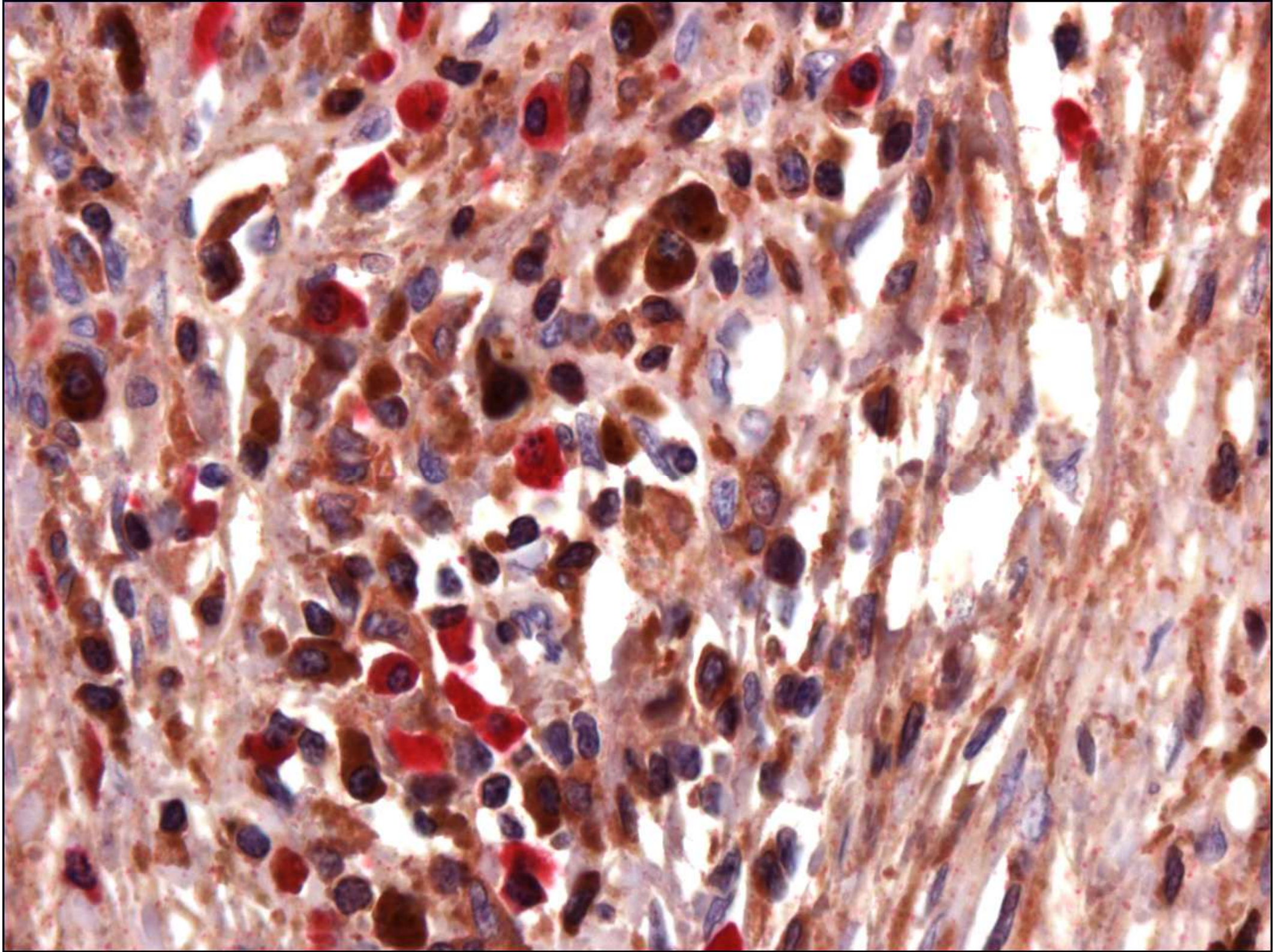
- maligniteiten (van de diverse organen)
- lymfomen
- infiltratieve lymfadenopathie
  * ziekte van Rosai-Dorfman
  * Castleman
  * sarcoidose
- systeemziekten
  * ziekte van Sjögren/SLE
  * AAV
- en vele andere (PSC, granulomateuze ziekten ..)


Pancreas 2004, T04-31630
IgG4


Peri-aortic tissue 2004, T04-31143
IgG4


Kidney biopsy 2008, T08-5934
IgG4


Lung biopsy 2008, T08-6191
IgG4



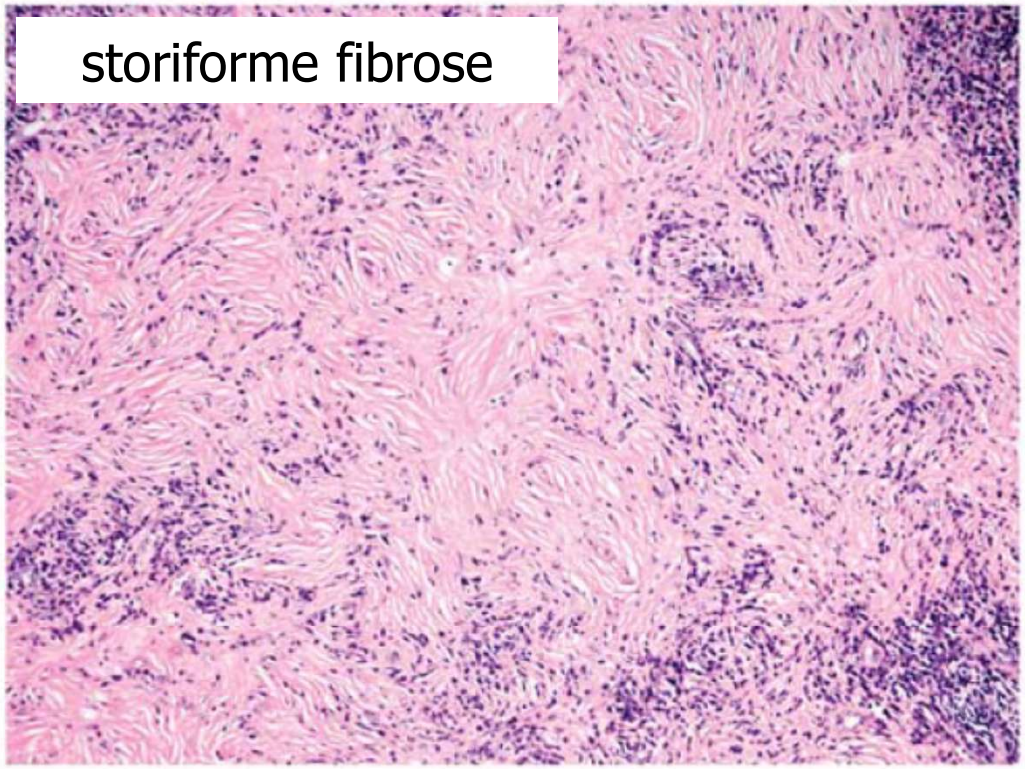
PA bij IgG4-gerelateerde systemische ziekte

- infiltratie van weefsel met
  - plasmacellen ($IgG4^+/IgG > 0.30$ of ≥ 10 $IgG4^+$/hpf)
  - eosinofielen
  - uitgesproken fibrose/sclerose
  - aanwezigheid granulomateuze kenmerken pleit tegen

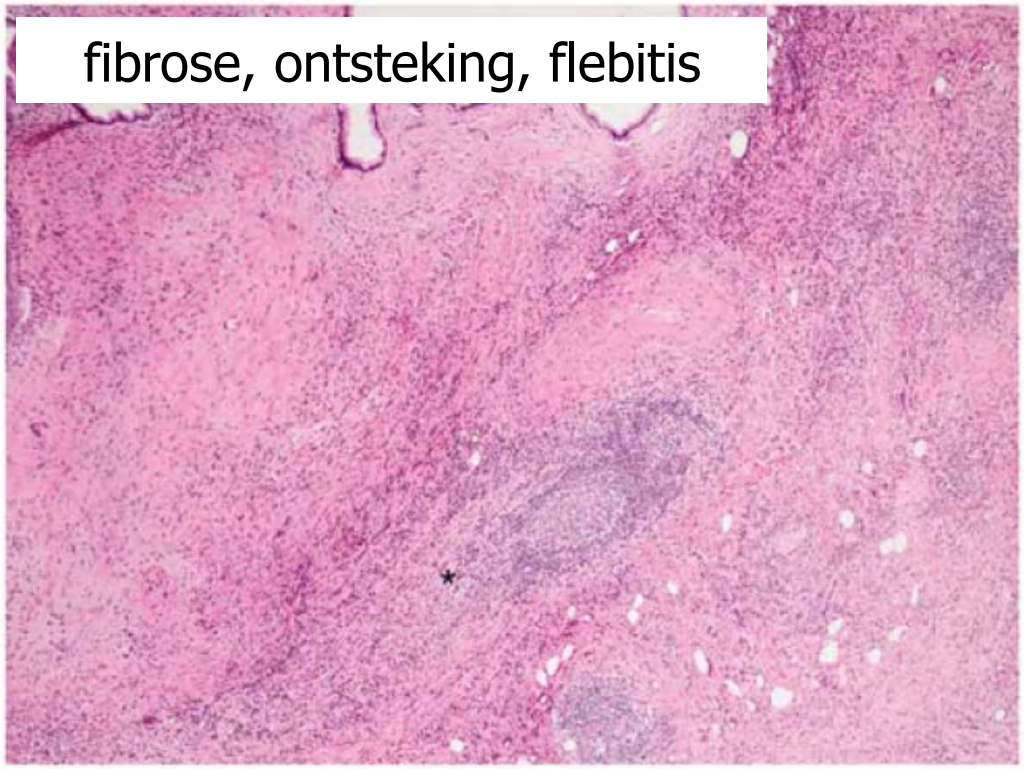
- denk aan de mogelijkheid

- kijk of een andere diagnose reëel is (sluit die uit)

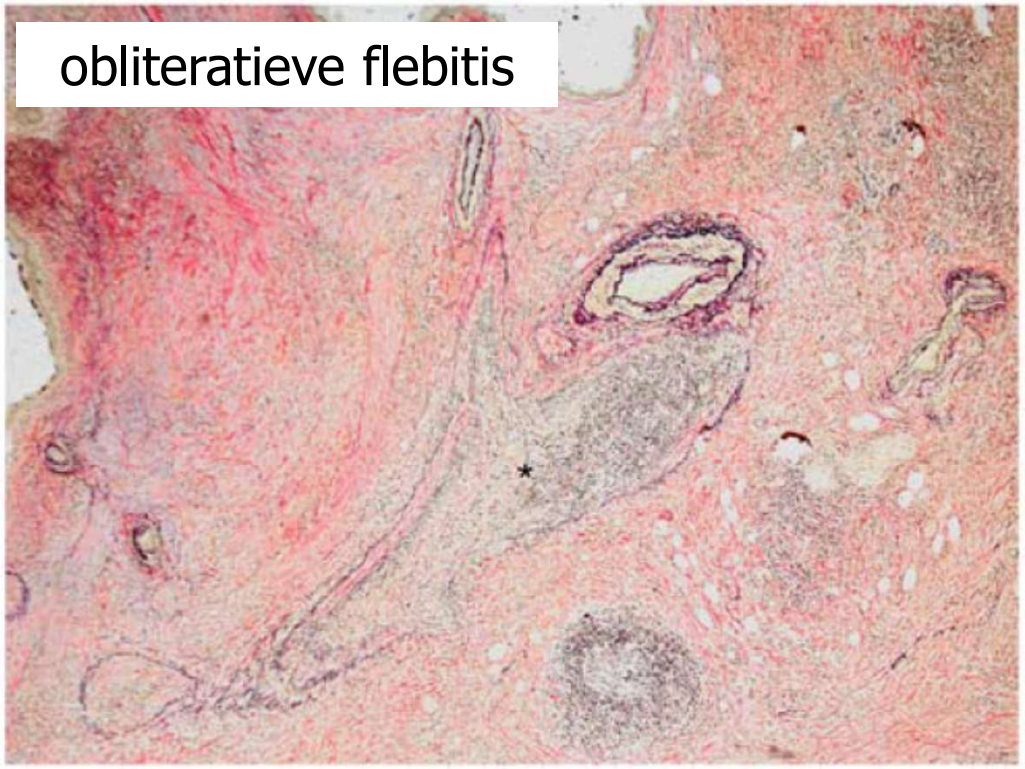
storiforme fibrose



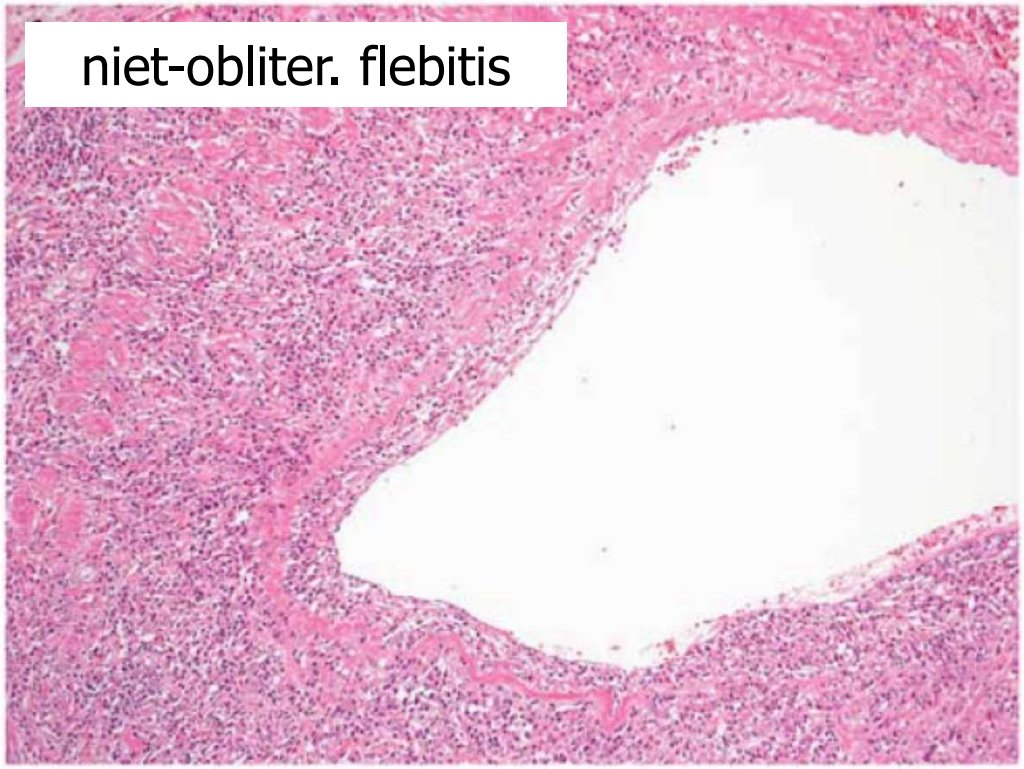
fibrose, ontsteking, flebitis

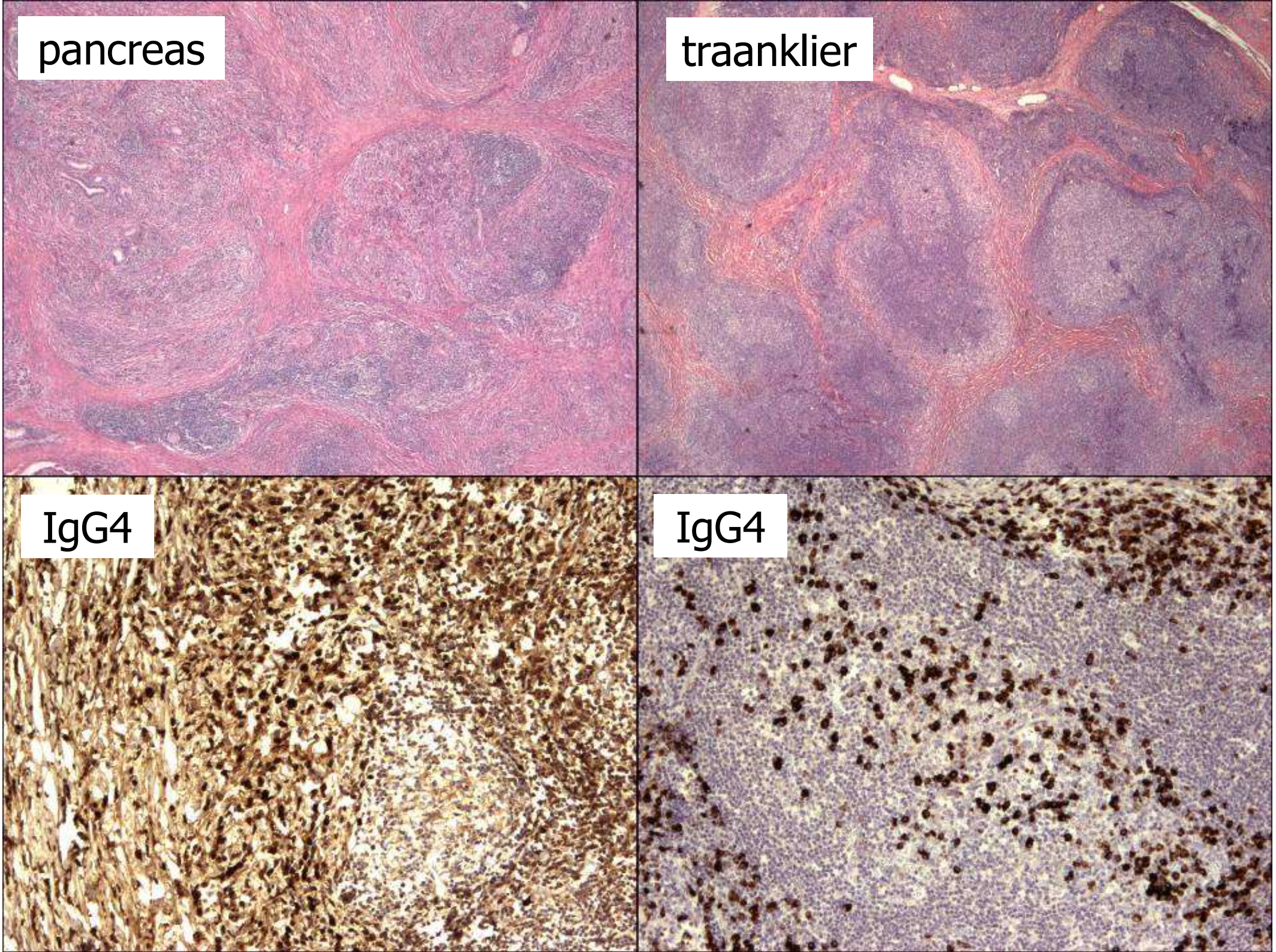


obliteratieve flebitis



niet-obliter. flebitis

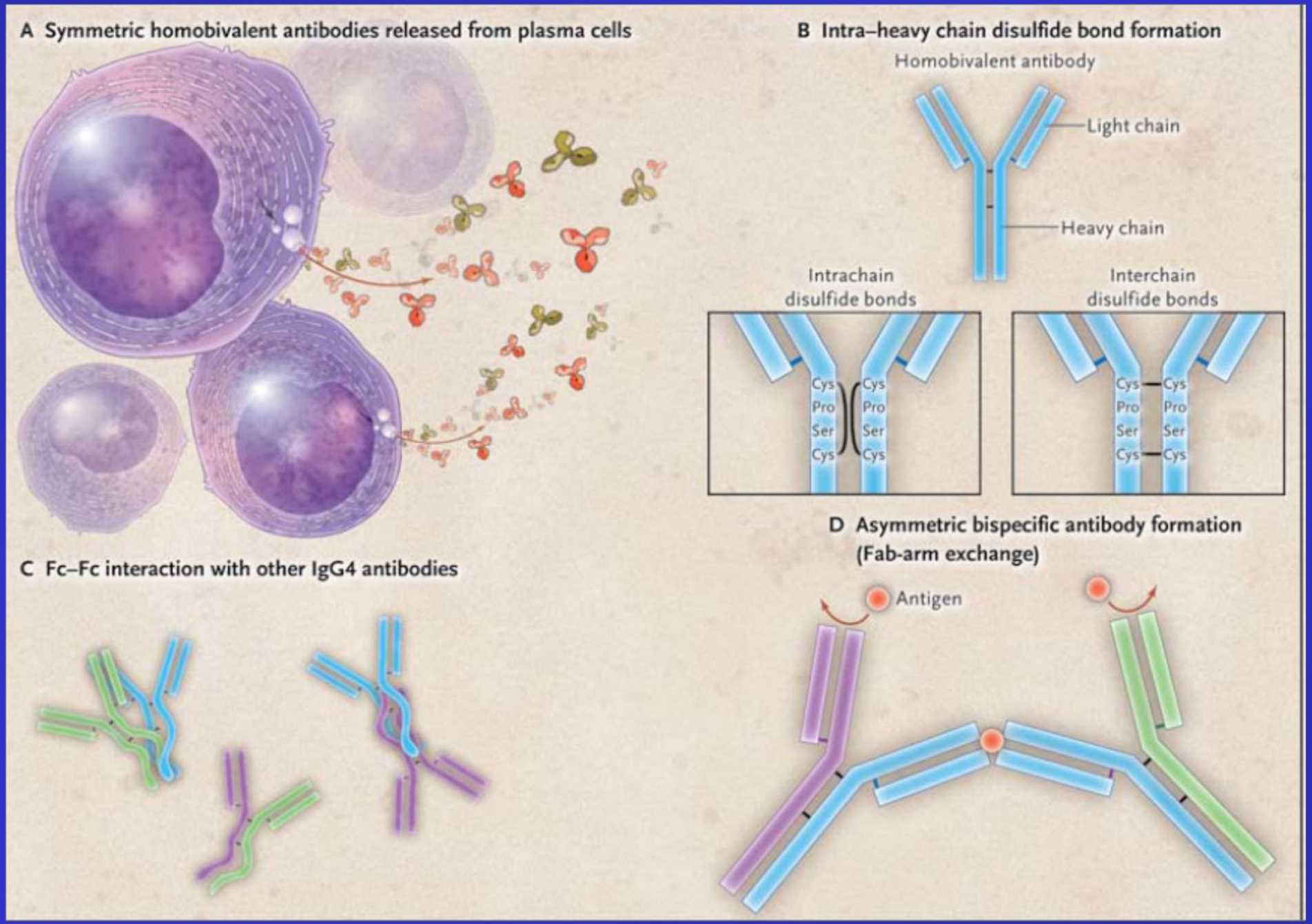



pancreas
traanklier
IgG4
IgG4

Pathofysiologie van IgG4-gerelateerde ziekte

- (volledig) onbekend
- niet mono- of oligoclonaal
- is IgG4 pathofysiologisch belangrijk of epifenomeen?
- “rare” vorm van allergie (‘overtrokken/extreme T_h2 respons’)
- relatie met Helicobacter pylori?
- lijkt te draaien om actieve $IgG4^+$ plasmacellen/plasmablasten
  - zijn dit de pathologische cellen?
  - uiting/aansturen van andere cellen (fibroblasten)

IgG4: unieke eigenschappen



Stone JH, et al. N Engl J Med 2012;366:539-51

Pathofysiologie van IgG4-gerelateerde ziekte

IgG4:

- normaal lage serum concentraties
- geen complement binding, beperkte Fc binding
- kan bi-specifieke complexen vormen
- gevormd na IL4 en IL13 stimulatie (//IgE)
- beschouwd als niet inflammatoir (blokkerend)
- IL13: ook betrokken bij fibrose (activatie van myofibroblasten)

Lymfadenopathie en IgG4-positieve cellen

Komt ook bij andere aandoeningen voor:

- reumatoide arthritis
- Castleman
- ziekte van Kimura
- EBV infectie
- AAV (MPA, GPA, eGPA)

Behalve IgG4 positieve cellen in lymfeklier

- fibrose/flebitis
- orgaanbetrokkenheid

Hoeveel IgG4 pos. cellen nodig voor diagnose?

	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

Deshpande V, et al. Modern Pathol 2012;25:1181-92

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Table 1 | Traditional and novel potential biomarkers of IgG4 related disease (IgG4-RD)

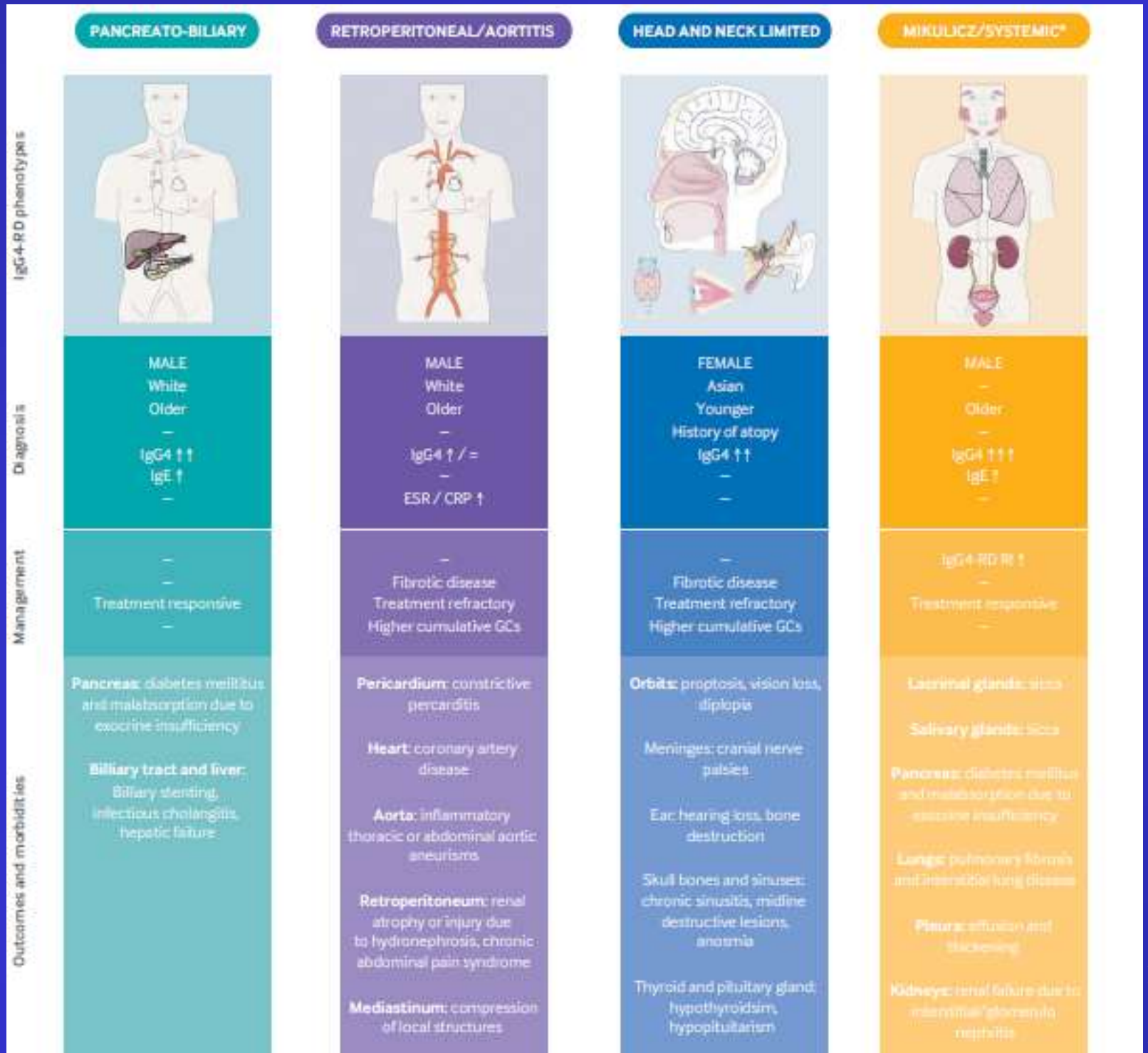
Type and subclass of biomarker	Examples	Comments
Traditional		
Diagnosis	Serum IgG4	Elevated in 55-97% of patients. Correlates with disease burden
	Serum IgG4:IgG ratio	When >10% it increases diagnostic specificity in case of normal serum IgG4
	Serum IgE and eosinophils	Elevated in 30% of patients regardless of atopic background
	CSF IgG4 indices	Elevated in IgG4 related hypertrophic pachymeningitis
	Plasmablasts and plasma cells	Expanded in peripheral blood regardless of serum IgG4 concentration
	Serum C3, C4	Consumption may suggest subclinical or overt renal involvement and should prompt urinalysis
	^{18}FDG-PET	Useful for staging purposes and for identification of alternative sites for biopsy sampling. Caution is needed when interpreting lymph node uptake because IgG4-RD lymphadenopathy is indistinguishable from reactive and neoplastic lymph nodes
Disease activity	Serum IgG4, IgE, and eosinophils	Decrease with disease response to treatment. May not normalize at disease remission in patients presenting with marked elevation at diagnosis. Mild oscillation should not prompt additional investigations. Marked (>twofold) increase after remission should raise possibility of disease flare
	Serum IgG4:IgG ratio	Decreases with disease response to treatment
	CSF IgG4 indices	Decrease with disease response to treatment
	Plasmablasts and plasma cells	Decrease with disease response to treatment and increase at flare
	Serum ESR/CRP	More often correlate with disease activity in case of retroperitoneal and aortic involvement
	Serum C3, C4	May normalize in case of remission and decrease during flares, especially in case of renal involvement
	^{18}FDG-PET	Reduced ^{18}FDG uptake in response to treatment. Caution is needed when interpreting lymph node uptake because IgG4-RD lymphadenopathy is indistinguishable from reactive lymph nodes
Predictors of relapse	Serum IgG4, IgE, and eosinophils	The higher the baseline values, the greater the risk of relapse and the shorter the time to relapse
Fibrosis	-	-
Novel*		
Diagnosis	Anti-galectin-3; laminin 511; annexin A11; prohibitin antibodies	Present in <30% of patients with IgG4-RD
	Serum IgG2	Elevated in cohort of patients with orbital IgG4-RD. Assessed only for orbital involvement
	Serum IgG4:IgG RNA ratio	Better performance than serum IgG4 for diagnosis of hepatobiliary IgG4-RD. Assessed only for biliary involvement
	CD4 and/or CD8 SLAMF7+ CTLs	Expanded in peripheral blood during active disease
Disease activity	Serum soluble interleukin 2 receptor	Normalizes at remission, even in patients with persistent elevation of serum IgG4
	Serum IgG4:IgG RNA ratio	Decreases with disease response to treatment. Assessed only for biliary involvement
	CD4 and/or CD8 SLAMF7+ CTLs	Decrease with disease response to treatment and increase with flare
	Serum C5, C5a	Elevated during active disease. Decrease with disease response to treatment
	Activated Tfh2 cells	Decrease with disease response to treatment
Predictors of relapse	Memory B cells	Decreased in peripheral blood at disease onset. Increase after glucocorticoid induced remission in patients who will relapse within 2 years
Fibrosis	Serum ELF score; CCL-18	Indirect biomarker of disease activity. Reflect collagen deposition at tissue sites

CRP=C-reactive protein; CSF=cerebrospinal fluid; CTL=cytotoxic T lymphocyte; ELF=enhanced liver fibrosis; ESR=erythrocyte sedimentation rate; FDG=fluoro-deoxyglucose; PET=positron emission tomography; Tfh2= type 2 follicular T helper.

*Novel potential biomarkers have been tested in single center cohorts and have not yet been externally validated.

Lanzilotta, M,, et al. BMJ 2020;369:m1067

IgG4-RD Phenotypes of disease



Lanzilotta, M,, et al. BMJ 2020;369:m1067

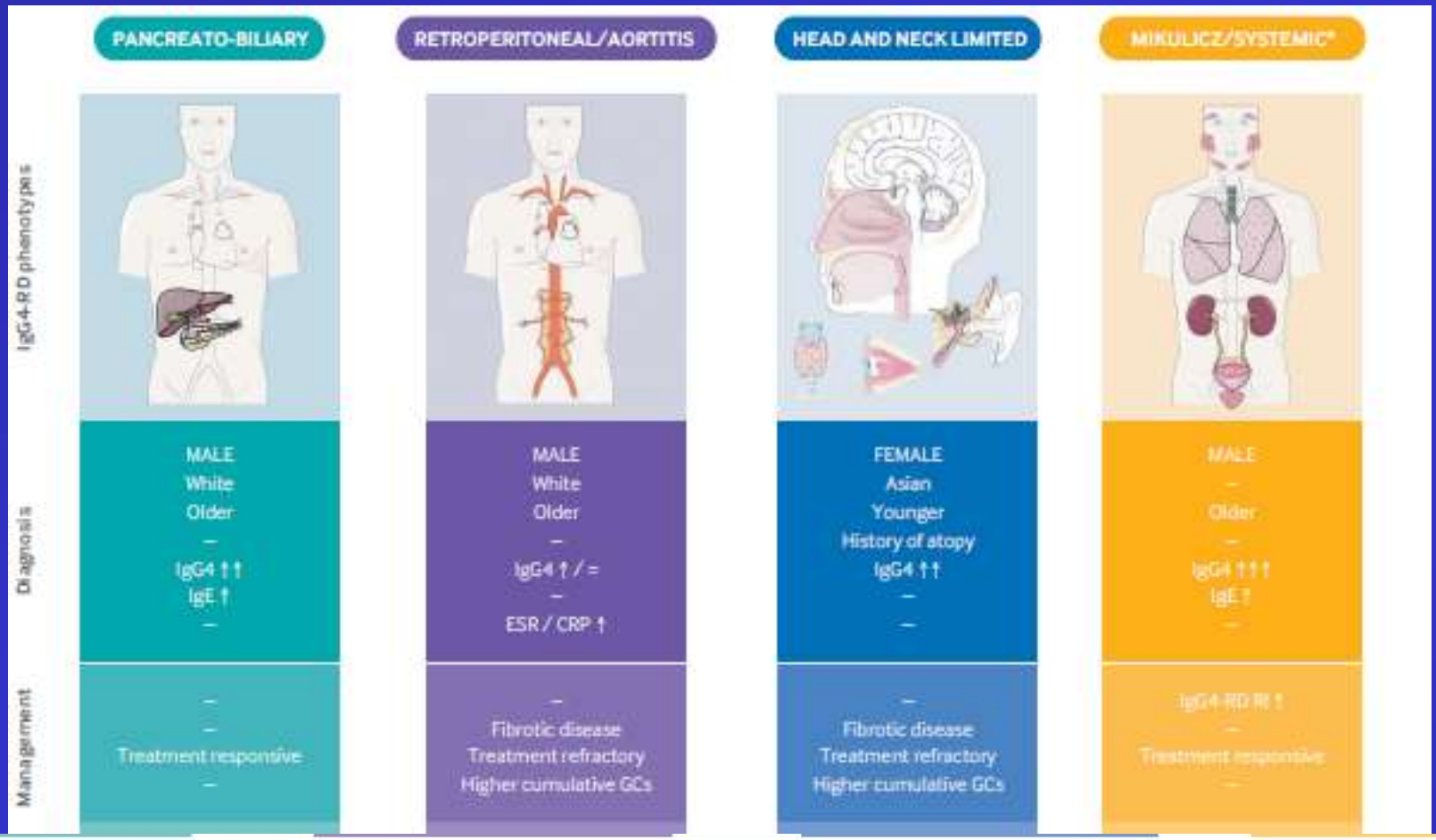
Patiënten met IgG4-gerelateerde ziekte UMCG

- 86 patiënten
  - 65 mannen / 21 vrouwen
  - leeftijd 48 - 83 jaar
- serum IgG4 verhoogd bij ca. 3/4 (max. 41 g/L)
- renale betrokkenheid 10 (+ 2 membraneuze glomerulopathie)
- retroperitoneale betrokkenheid 7 (4 zonder TIN)
- vaak andere diagnose eerder gesteld
  - maligniteit
  - Churg-Strauss syndroom (eGPA)
  - lymfoom

Behandeling van IgG4-gerelateerde ziekte

- bijna geen trials of prospectieve studies
- sommige manifestaties: spontaan herstel beschreven
- corticosteroiden
  - 0,5-1,0 mg/kg/d voor 2-6 weken
  - snelle response (enkele weken) in >90%
  - afbouwen in 3-6 maanden
  - relapse komt vaak voor (AIP)
    - 32% na 6 maanden
    - 56% na 1 jaar
    - 92% na 3 jaren
  - onderhoud met lagere dosis (2,5-5 mg/d)?

IgG4-RD Phenotypes of disease



Remission induction (disease onset/relapse)	**1** Oral PREDNISONE (0.6-1 mg/kg) for 3 weeks and then taper over 3-6 months **2** RITUXIMAB (two 1 g iv infusions 15 days apart)
Remission maintenance	**1** Low dose glucocorticoids **2** DMARDs: AZA – MTX – CTX – MMF – LFN – CSA **3** RITUXIMAB (two 1 g iv infusions 15 days apart/single 1 g infusion) every 6 months

Lanzilotta, M,, et al. BMJ 2020;369:m1067

Falen corticosteroiden/relapse in IgG4-gerelateerde ziekte

- azathioprine 2,0-2,5 mg/kg/d
- mycofenolaat mofetil 2 dd 500-1000 mg
- methotrexaat (wekelijks)
- 6-mercaptopurine, cyclofosfamide
- rituximab
  - enkele kleine series (m.n. aortitis)
  - inmiddels ook grotere series
- bortezomib
  - cases
- anti-CD38 (daratumumab)
  - case (+ lenalidomide)

Conclusies

- IgG4-gerelateerde ziekte is een infiltratieve, inflammatoire aandoening met uitgesproken fibrose/sclerose
    - vaak andere diagnose eerst
    - renale betrokkenheid niet zeer frequent
    - geen goede marker(s); IgG4 bij ca. 70-80% verhoogd

- Kan eigenlijk ieder orgaan/weefsel treffen en is vaak een multisysteemziekte

- Lymfadenopathie is een frequent onderdeel van dit ziektebeeld

- Corticosteroiden vormen de primaire behandeling

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Het spectrum van tubulo-interstitiële nefritis

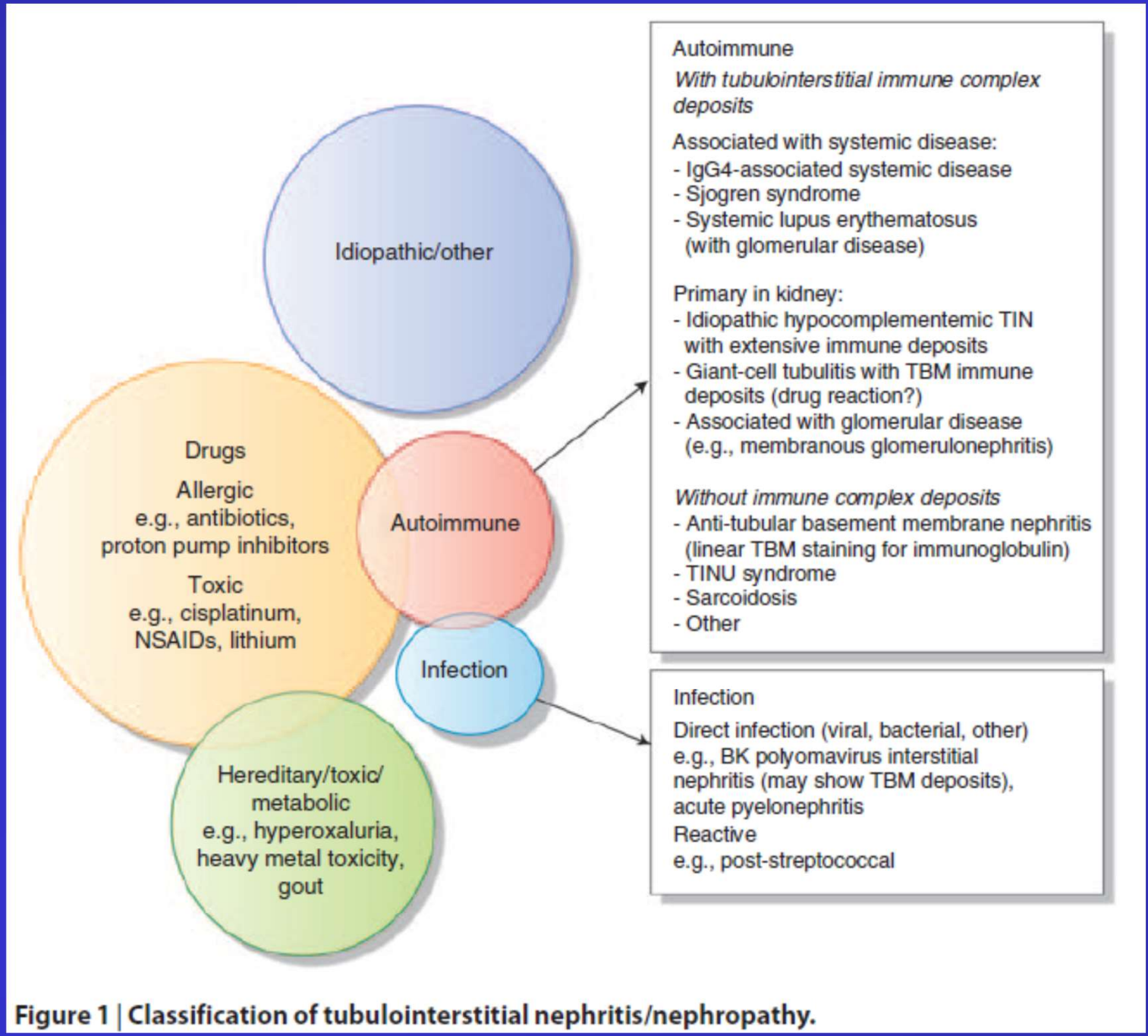

Figure 1 | Classification of tubulointerstitial nephritis/nephropathy.

Cornell LD. Kidney Int 2010;78:951-3

IgG4-gerelateerde TIN: simpele diagnose?

npg

1480

MODERN PATHOLOGY (2011) 24, 1480–1487

An abundance of IgG4 + plasma cells is not specific for IgG4-related tubulointerstitial nephritis

Donald C Houghton and Megan L Troxell

Department of Pathology, Oregon Health & Sciences University, Portland, OR, USA

Houghton DC, Troxell ML. Modern Pathol 2011;24:1480-7

IgG4-gerelateerde TIN: simpele diagnose?

Table 2 Numbers of cases in each IgG4+PC class, by principal diagnosis

Number	*Principal diagnosis*	IgG4+PC per ×200 field		
		<2	*2–10*	*>10 to >100*
2	Acute tubular injury	2		
1	Amyloidosis		1	
3	Arterionephrosclerosis	3		
	Glomerular diseases			
3	Acute GN, NOS	3		
1	Collapsing glomerulopathy		1	
8	Diabetic nephropathy	3	3	2
1	Fibrillary GN		1	
4	FSGS	3	1	
1	HSP nephritis	1		
5	IgA nephropathy	4	1	
6	Lupus nephritis	5		1
6	Membranoproliferative GN	4	2	
8	Membranous GN	4	3	1
3	Mesangiopathic GN, NOS	3		
1	Monoclonal GN	1		
	Necrotizing GN			
4	Granular deposits by IF	1	1	2
4	Linear deposits by IF	2	1	1
8	Pauci-immune by IF	4	2	2
1	Sclerosing glomerulopathy, NOS	1		
2	Light-chain-cast nephropathy	2		
1	Light chain deposit disease	1		
2	Pyelonephritis	1	1	
1	Thrombotic microangiopathy	1		
	Tubulointerstitial nephritis			
7	Hypersensitivity TIN	5	2	
1	TIN-uveitis syndrome	1		
3	Sjogren's TIN	1	2	
12	Idiopathic TIN	7	3	2
1	Reflux nephopathy		1	
100	Totals	63	26	11

100 biopten met interstitiëel infiltraat

- kleuring voor IgG4 en CD138

- 37% matig-veel IgG4$^+$ plasmacellen

- geen patiënten met IgG4-RSD

- wel verschillen met IgG4-RSD/TIN

Houghton DC, Troxell ML. Modern Pathol 2011;24:1480-7

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Verschillen IgG4-gerelateerde TIN vs. niet IgG4-gerelateerde TIN

- meer $IgG4^+$ plasmacellen in IgG4-gerelateerd TIN
- infiltraat en fibrose veel uniformer in IgG4-gerelateerde TIN
- scherpe rand tussen pathologisch en niet pathologisch nierweefsel in IgG4-gerelateerde TIN
- meer eosinofielen in infiltraat in IgG4-gerelateerde TIN
- eilandjes met plasmacellen in IgG4-gerelateerde TIN
- klinische verschillen: serum IgG4, extra-renale manifestaties

Houghton DC, Troxell ML. Modern Pathol 2011;24:1480-7

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Clinicopathologic Features of IgG4-Related Kidney Disease

Alessia Buglioni[1], Sarah M. Jenkins[2], Samih H. Nasr[1], Pingchuan Zhang[1], Ian W. Gibson[3], Mariam P. Alexander[1], Loren P. Herrera Hernandez[1], Mary E. Fidler[1], Naoki Takahashi[4], Marie C. Hogan[5] and Lynn D. Cornell[1]

Renal biopsies/nephrectomies 2001-2023

- 125 IgG4-RD
  - biopsy n=120
    - acute/chronic KD 97 (78%)
    - proteinuria 21 (17%)
    - mass lesion 19 (15%)
  - nephrectomy for renal mass n=5

- 1.3% of renal biopsies showing acute/chronic TIN (6/462)

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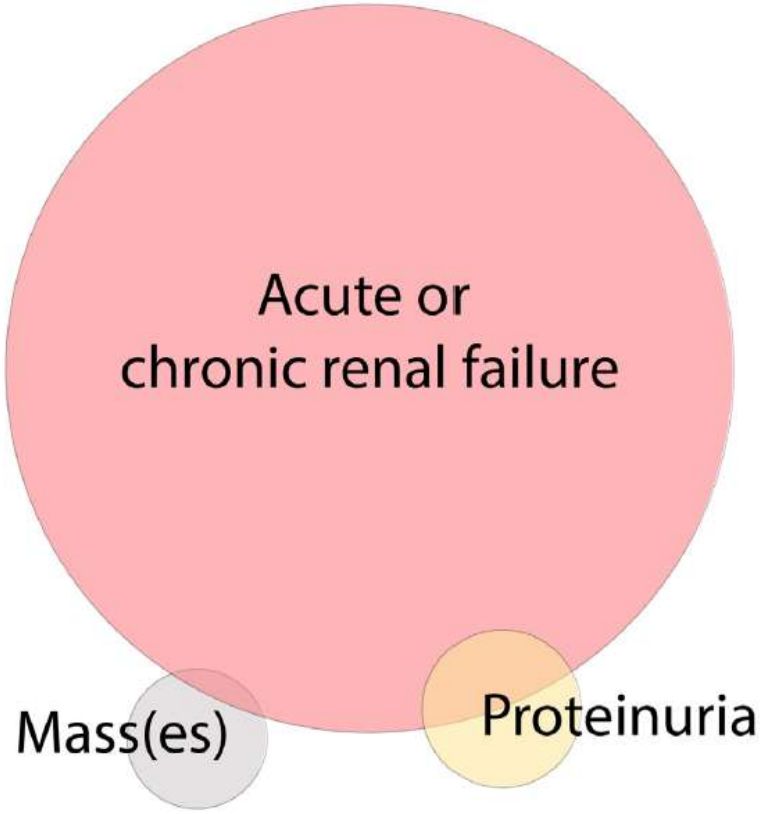

Figure 1. Primary indication for biopsy/nephrectomy in IgG4-RKD. Distribution of primary indication for diagnostic procedure in our cohort. Most patients underwent biopsy for acute and/or chronic renal failure, while a smaller percentage underwent biopsy/nephrectomy for mass lesion(s) or proteinuria, with some overlap in primary indication. The size of the circles and degree of overlap is proportional to the number of patients in each category.

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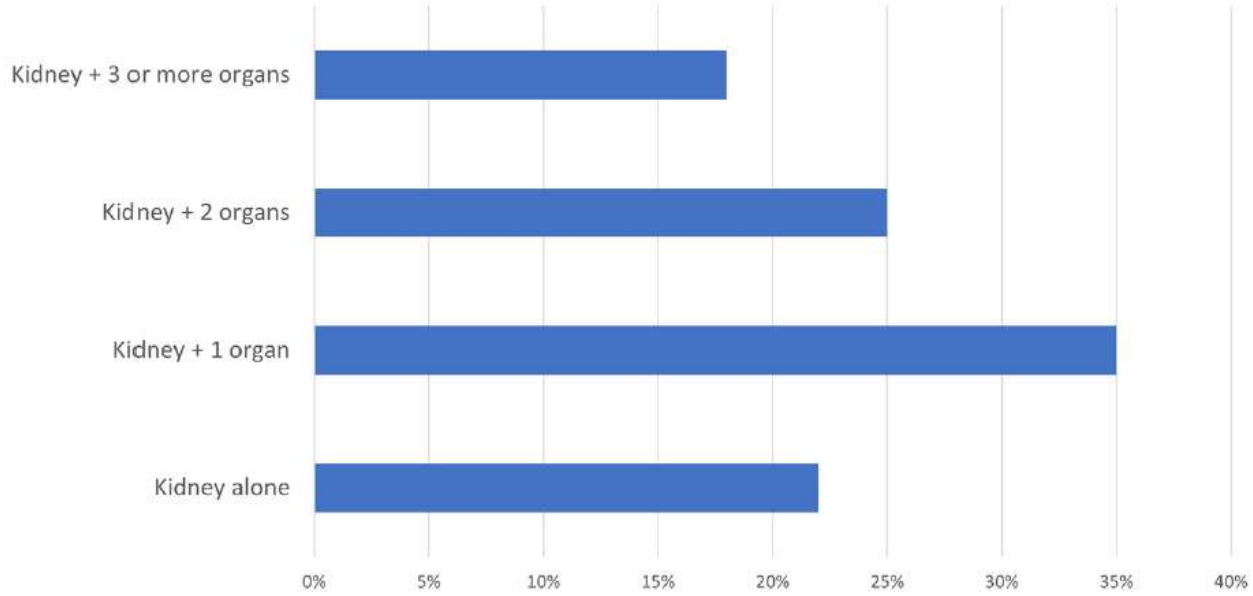

Figure 2. Multi-organ involvement in IgG4-RKD. Number of organs involved besides kidney in IgG4-RKD.