ERKNet
The European Rare Kidney Disease Reference Network

WGIKD
Working Group on Inherited Kidney Disorders

WELCOME TO

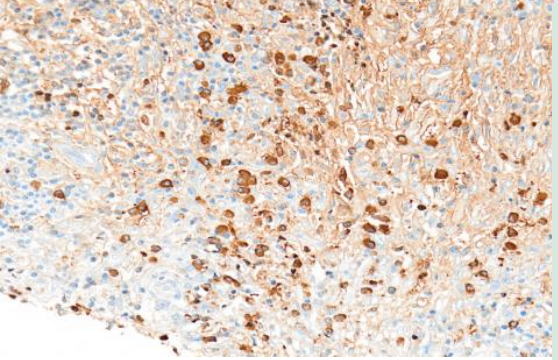
ERKNet
Advanced Webinars on Rare Kidney Disorders

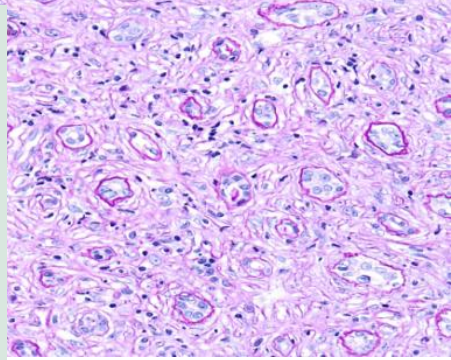
Date: 30 November 2021

Topic: IgG4 related diseases

Speaker: Giacomo Quattrocchio (Turin, Italy)

Moderator: Jack Wetzles (Nijmegen, Netherlands)





A blac ight

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

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

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

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

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

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

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

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

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

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

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

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

Pancreas
- Pancreatic cancer

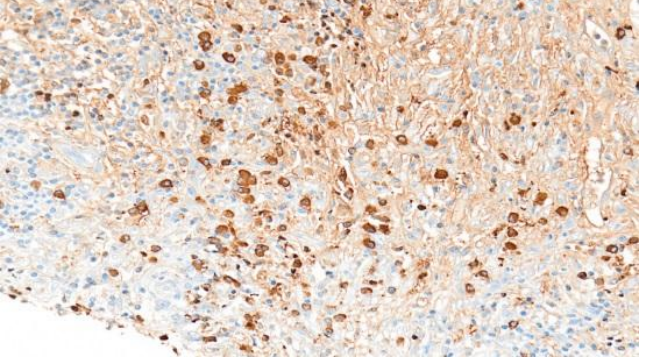
Biliary tree
- Pancreatic cancer
- Cholangiocarcinoma
- Primary sclerosing cholangitis

Liver
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Primary sclerosing cholangitis

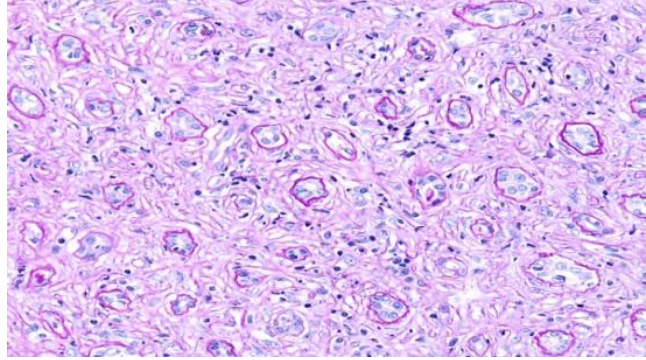
Prostate
- Benign prostatic hypertrophy

Skin
- Cutaneous lymphoma

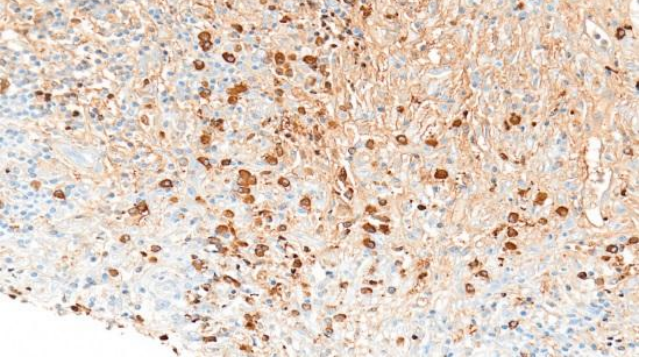
Lancet 2015, **385**: 1460-71

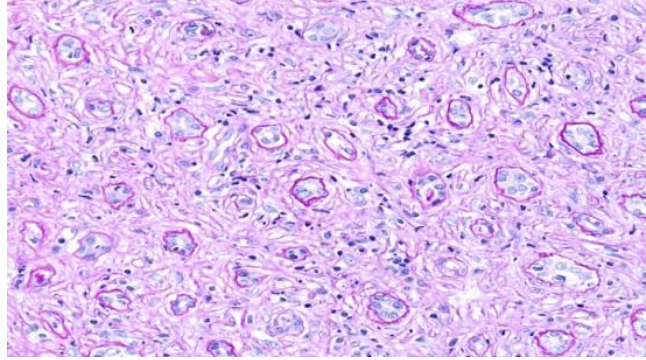


IgG4-RDs



- IgG4-Related Diseases
- IgG4-Related Kidney Disease
- Clinical Features
- Laboratory Features
- Imaging Features
- Pathological Features
- Pathophysiological Mechanisms
- Treatment





IgG4-RDs

- **IgG4-Related Diseases**
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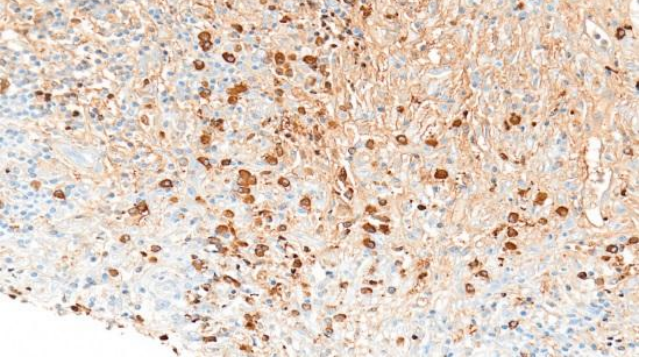
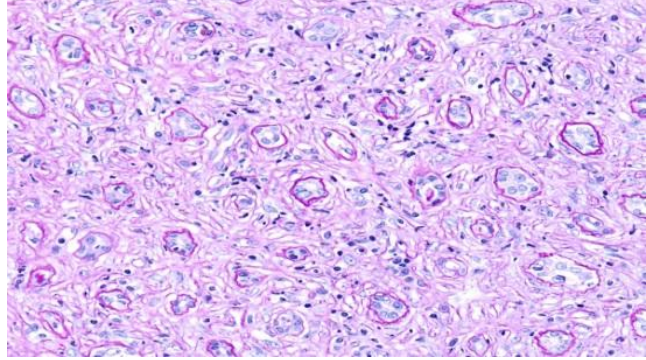
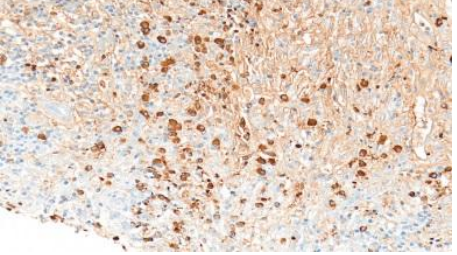


IgG4-Related Diseases



- Systemic immune-mediated condition
- Tumefactive, tumor-like lesions
- Dense lymphoplasmacytic tissue infiltrate
- Predominance of IgG4-positive plasma cells
- Storiform fibrosis
- Obliterative phlebitis
- Tissue osinophilia
- Elevated serum IgG4 concentrations



IgG4-Related Diseases:
the story begins in the pancreas …

Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K:

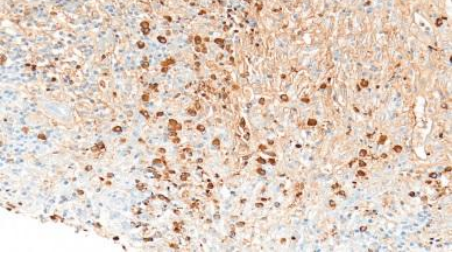
High serum IgG4 concentrations in patients with sclerosing pancreatitis.

N Engl J Med 344: 732–738, 2001

Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H:

A new clinicopathological entity of IgG4-related autoimmune disease.

J Gastroenterol 38: 982–984, 2003



IgG4-Related Diseases:

… but rapidly becomes systemic …

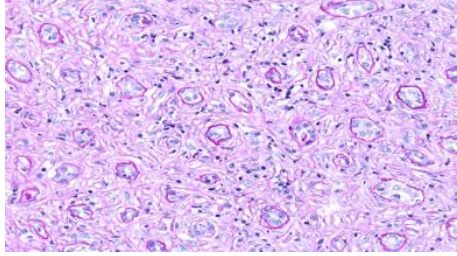
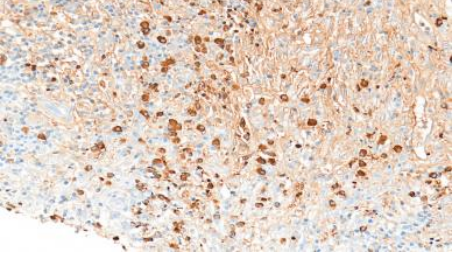


Table 1 | Major organ manifestations of IgG4-related disease

Pancreas	Type 1 autoimmune pancreatitis
Salivary glands	Sialadenitis
Eye/orbit/lacrymal glands	Orbital inflammation/pseudotumor and dacryoadenitis
Aorta/artery/retroperitoneum periaortitis	Periaortitis/periarteritis and retroperitoneal fibrosis
Kidney	Tubulointerstitial nephritis and pyelitis
Lymph nodes	Lymphadenopathy
Lung	Lung disease (inflammatory pseudotumor, alveolar interstitial disease, and pleuritis)
Biliary system	Sclerosing cholangitis and cholecystitis
Liver	Pseudotumor and hepatopathy
Central/peripheral nervous system	Pachymeningitis and infraorbital nerve swelling
Endocrine system	Hypophysitis and thyroiditis
Others	Prostatitis, mastitis, mediastinitis, and pericarditis skin (nodules and papules)

Kidney International (2014) **85**, 251–257



IgG4-Related Diseases:
… *and changes Disease Taxonomy!*

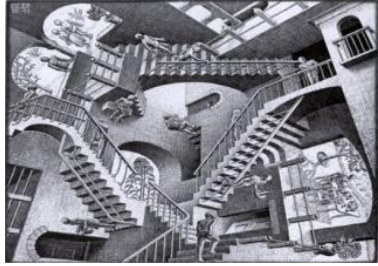
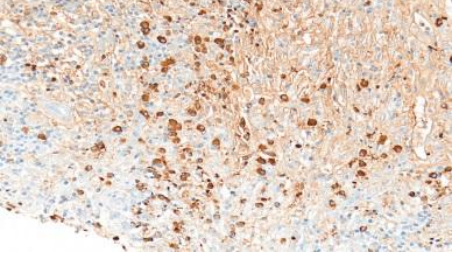


Table 1. Previously Recognized Conditions Now Acknowledged to Fall within the Spectrum of IgG4-Related Disease.

Mikulicz's syndrome (affecting the salivary and lacrimal glands)
Küttner's tumor (affecting the submandibular glands)
Riedel's thyroiditis
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)
Mediastinal fibrosis
Retroperitoneal fibrosis (Ormond's disease)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

NEJM 2012, **366**: 539-551

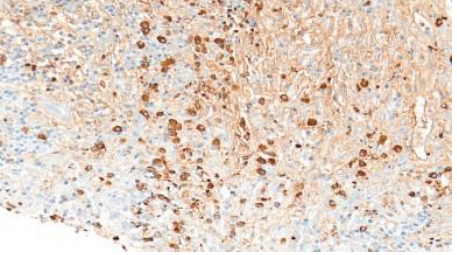


IgG4-Related Diseases

Question 1

How many patients with IgG4-RD have you seen in the last 2 years?

- 1-2
- 4-5
- 8-10
- >10



IgG4-Related Diseases:
Epidemiology

Prevalence: unknown

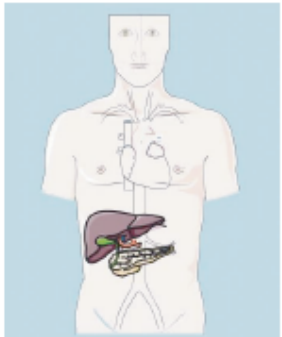
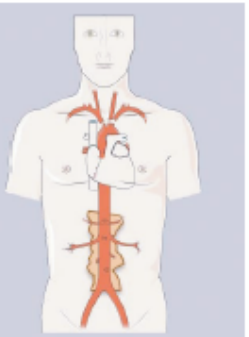
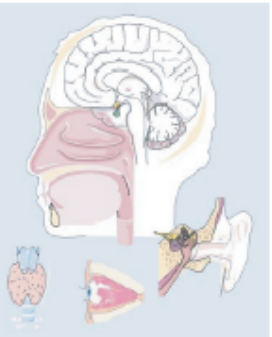
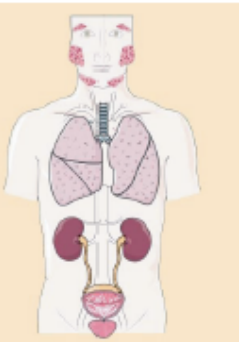
Underrecognition

Japan: 0.8 –> 3.1 cases per 100,000

Male:Female ratio variable

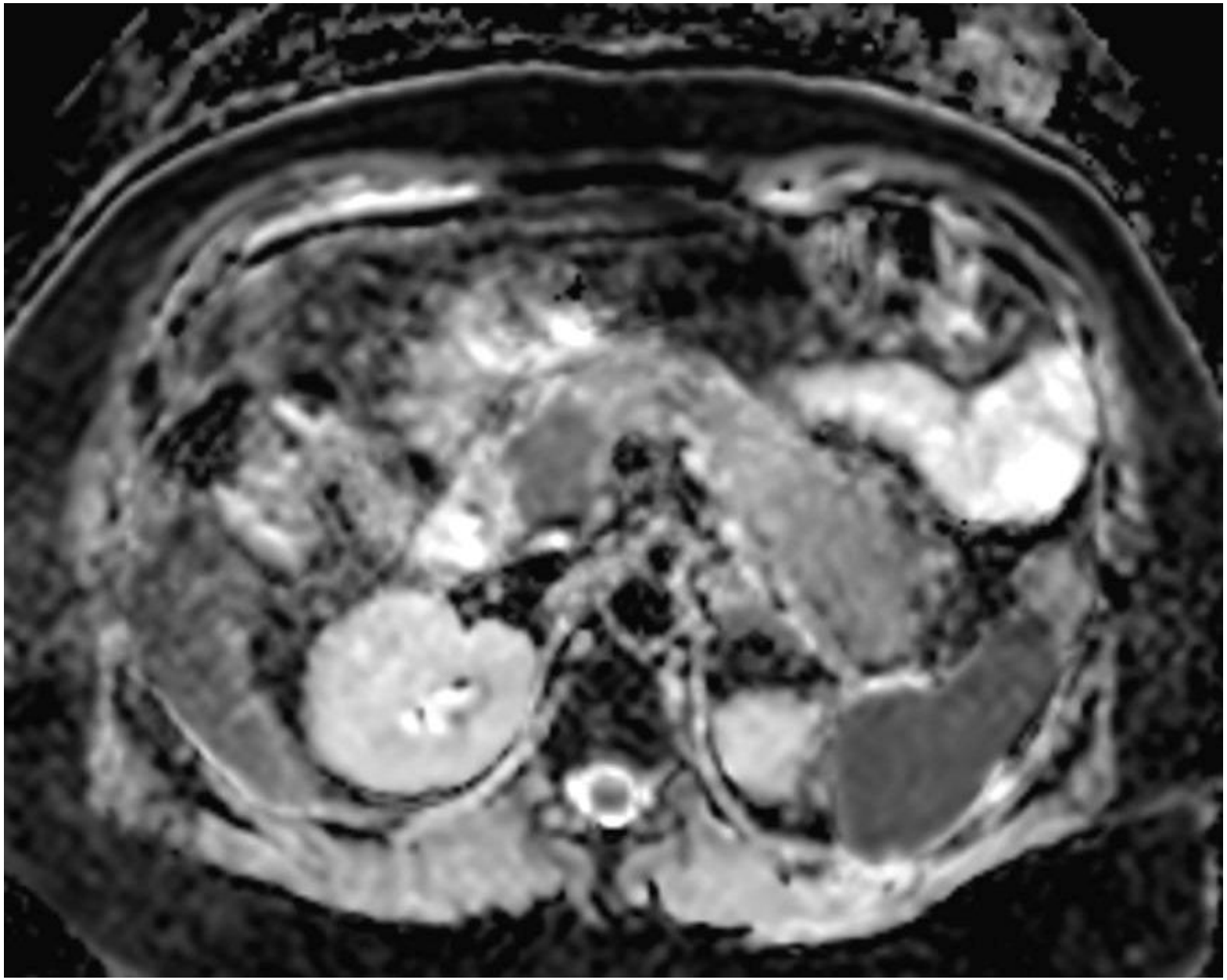
Age: 60-70 y - children

Clinical phenotypes

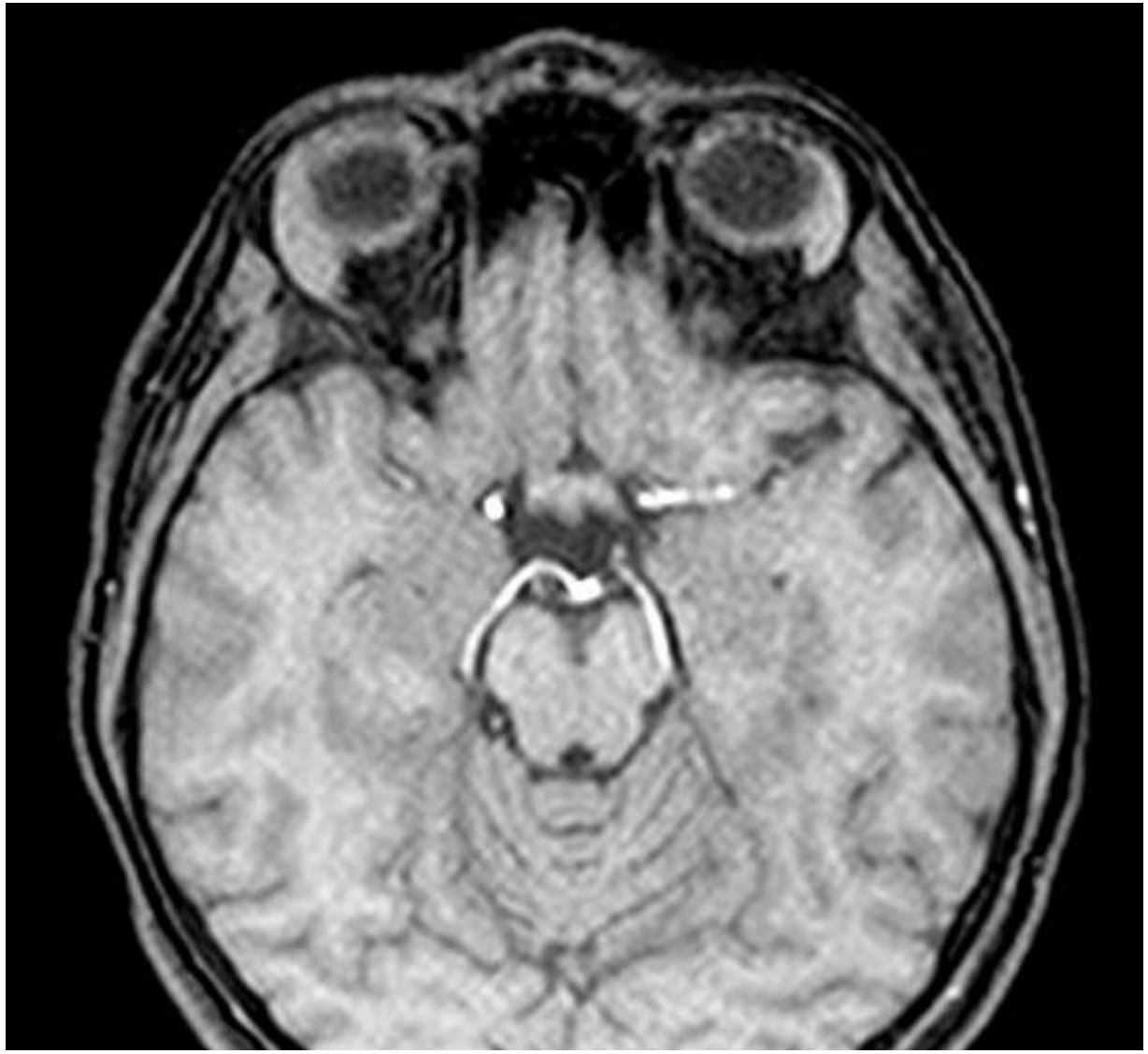
IgG4-RD phenotypes	PANCREATO-BILIARY	RETROPERITONEAL/AORTITIS	HEAD AND NECK LIMITED	MIKULICZ/SYSTEMIC*
				
Diagnosis	MALE White Older – IgG4 ↑↑ IgE ↑ –	MALE White Older – IgG4 ↑ / = – ESR / CRP ↑	FEMALE Asian Younger History of atopy IgG4 ↑↑ – –	MALE – Older – IgG4 ↑↑↑ IgE ↑ –
Management	– – Treatment responsive –	– Fibrotic disease Treatment refractory Higher cumulative GCs	– Fibrotic disease Treatment refractory Higher cumulative GCs	IgG4-RD RI ↑ – Treatment responsive –
Outcomes and morbidities	**Pancreas**: diabetes melititus and malabsorption due to exocrine insufficiency **Billiary tract and liver**: Billiary stenting, infectious cholangitis, hepatic failure	**Pericardium**: constrictive percarditis **Heart**: coronary artery disease **Aorta**: inflammatory thoracic or abdominal aortic aneurisms **Retroperitoneum**: renal atrophy or injury due to hydronephrosis, chronic abdominal pain syndrome **Mediastinum**: compression of local structures	**Orbits:** proptosis, vision loss, diplopia Meninges: cranial nerve palsies Ear: hearing loss, bone destruction Skull bones and sinuses: chronic sinusitis, midline destructive lesions, anosmia Thyroid and pituitary gland: hypothyroidsim, hypopituitarism	**Lacrimal glands:** sicca **Salivary glands:** sicca **Pancreas:** diabetes mellitus and malabsorption due to exocrine insufficiency **Lungs:** pulmonary fibrosis and interstitial lung disease **Pleura:** effusion and thickening **Kidneys:** renal failure due to interstitial/glomerulo nephritis

Ann Rheum Dis 2019

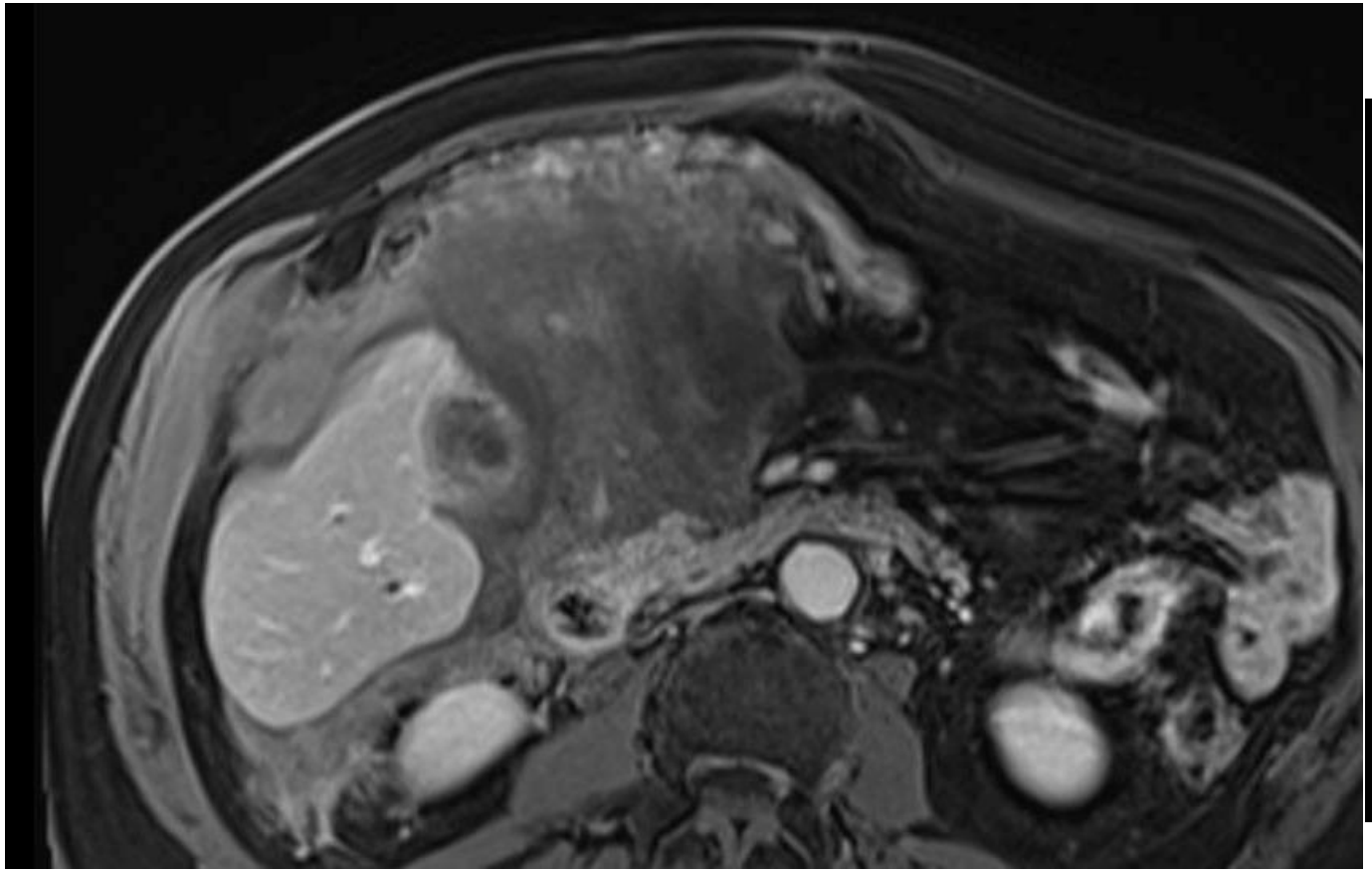
IgG4-related pancreatitis

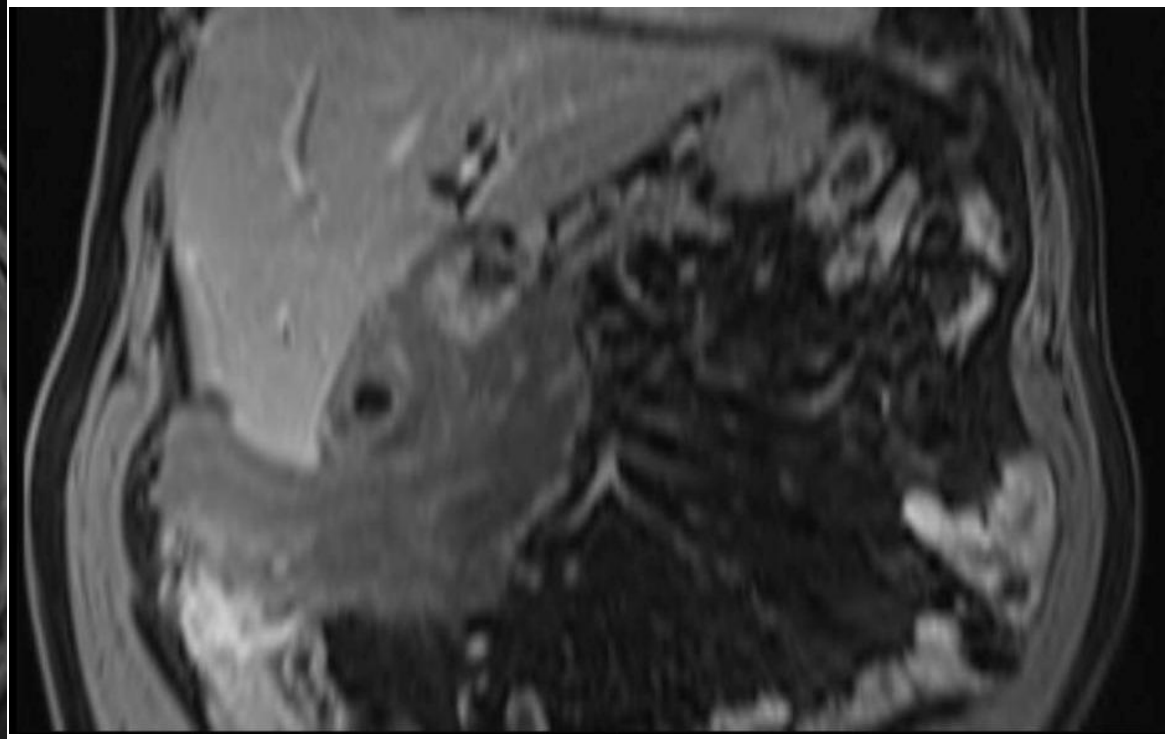


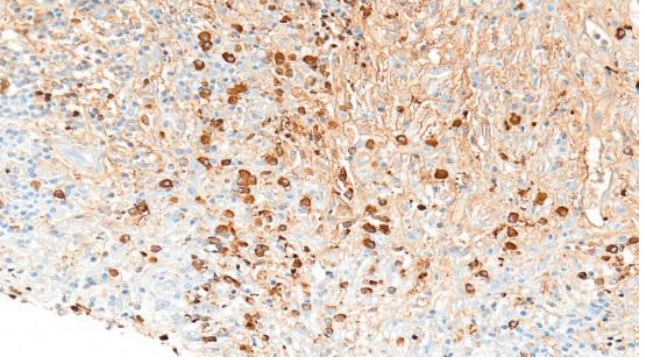
IgG4-related dacryoadenitis



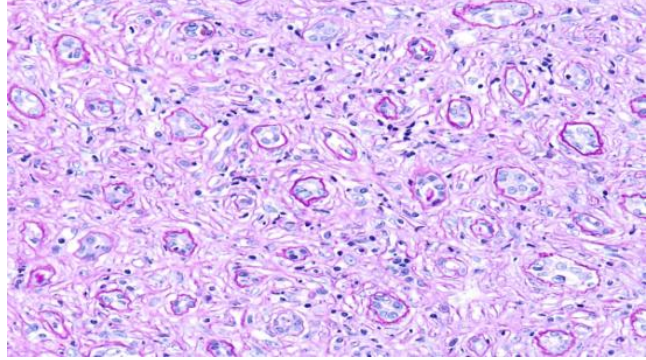
IgG4-related sclerosing mesenteritis



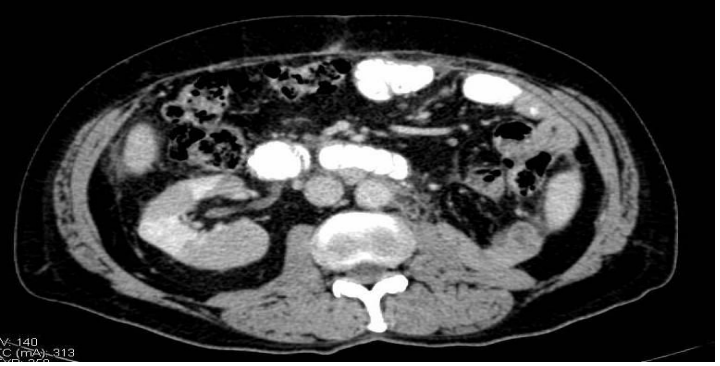




IgG4-RDs

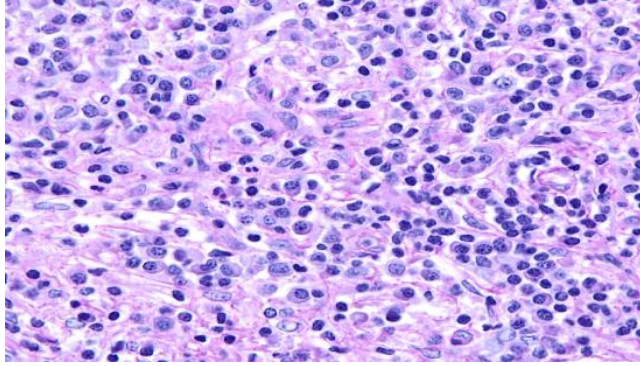


- IgG4-Related Diseases
- **IgG4-Related Kidney Disease**
- Clinical Features
- Laboratory Features
- Imaging Features
- Pathological Features
- Pathophysiological Mechanisms
- Treatment

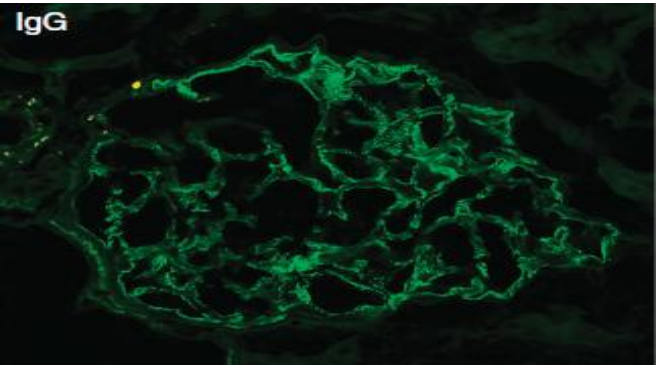


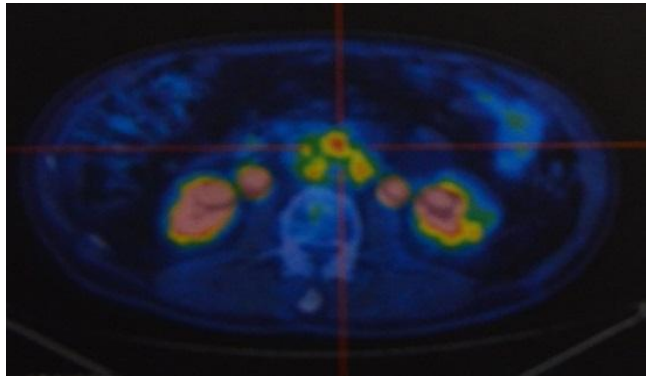
IgG4-RKD

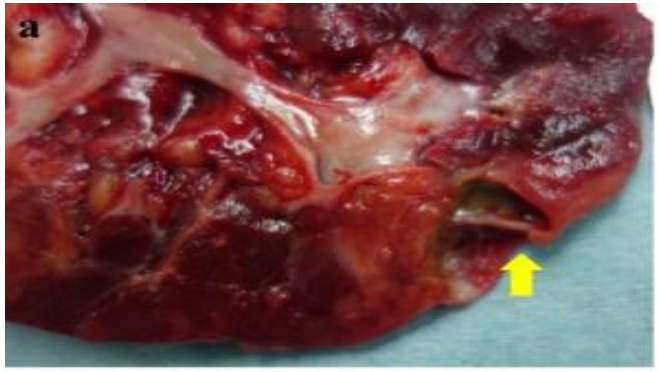
(15% of patients)

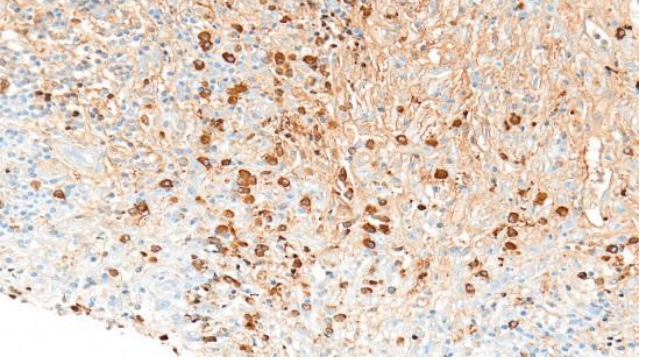


- Peculiar radiologic lesions (kidney, pelvis)
- Tubulointerstitial nephritis
- Membranous/other glomerulonephritides
- Retroperitoneal fibrosis
- (Renal cysts ?)
- («Lupus sine lupo!»)









IgG4-RKD

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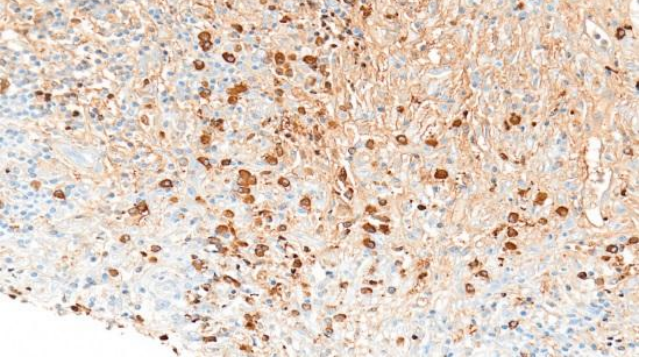
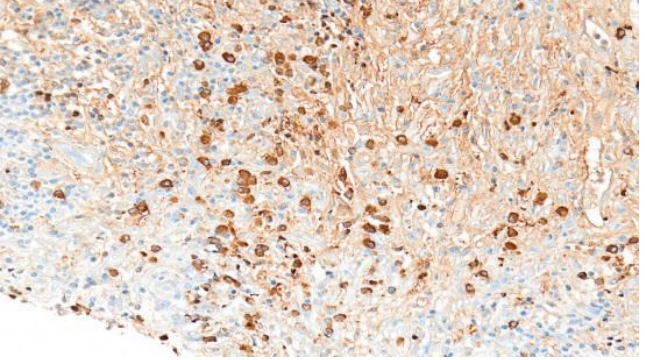
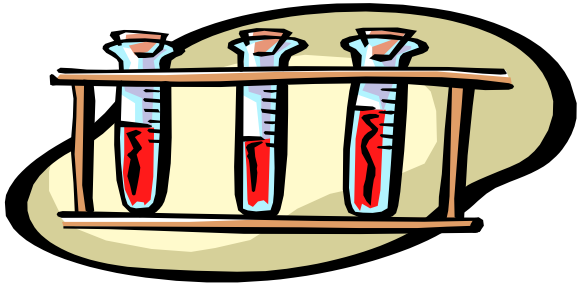


IgG4-RKD
Clinical Features

- Male gender: 75-85%
- Average age: 65 years
- Acute / Progressive chronic renal failure
- Edema
- Renal mass lesions
- Mild systemic symptoms
- Multi-organ involvement



IgG4-RD



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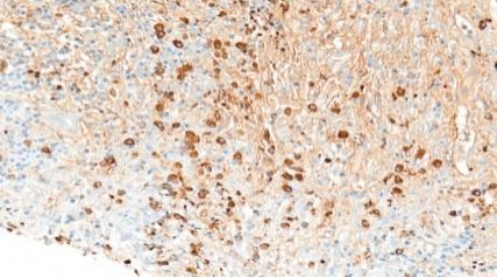
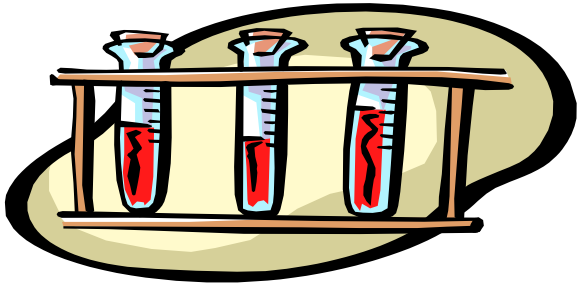


IgG4-RKD

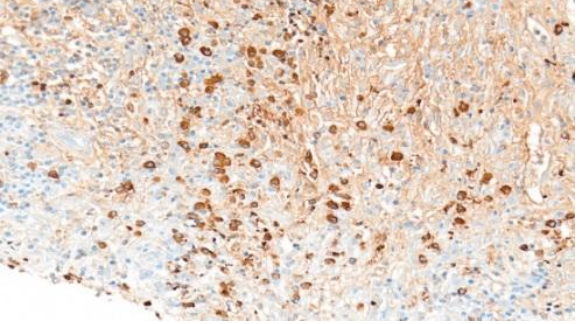
Laboratory Features



- Hypergammaglobulinemia: 80-90%
- Elevated serum IgG4 levels: 50-70%
- IgG4:IgG>10% - IgG4:IgG1>24%
- Hypocomplementemia C3 and/or C4: 50-70%
- Elevated IgE levels: 60-70%
- Eosinophilia: 35-50%
- Antinuclear antibodies: 30%
- Rheumatoid Factors: 20-30%

- Acute / Rapidly Progressive Renal Failure
- Proteinuria and/or hematuria: 50%

- ***Circulating plasmablasts***



IgG4-RKD

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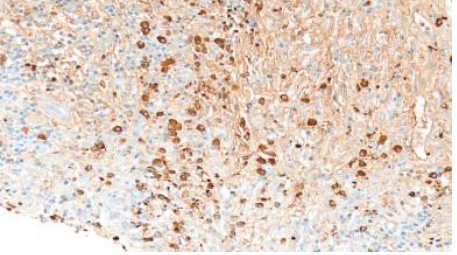
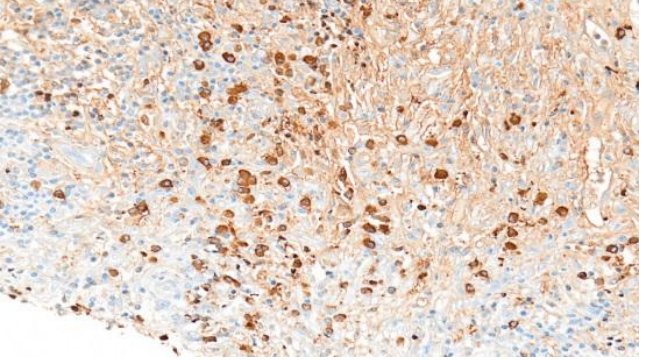


IgG4-Related Diseases

Question 2

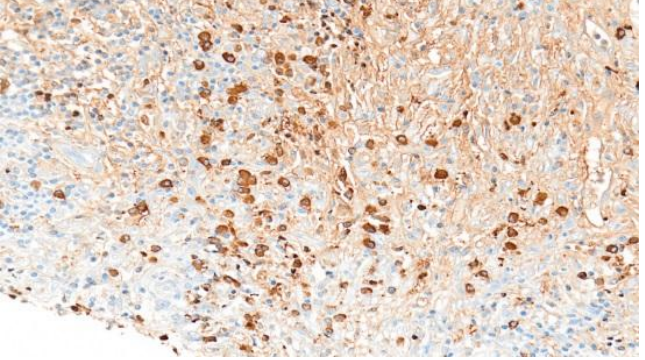
Which radiologic imaging do you use for the diagnosis and follow-up of patients?

- CT
- MRI
- PET



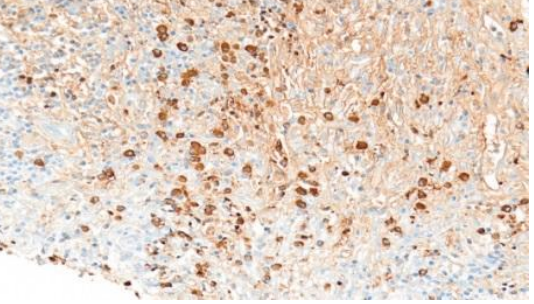
IgG4-RKD
Imaging Features

- Ultrasonography
- Computed Tomography
- Magnetic resonance
- Fluorodeoxyglucose PET
- (Gallium Scintigraphy)

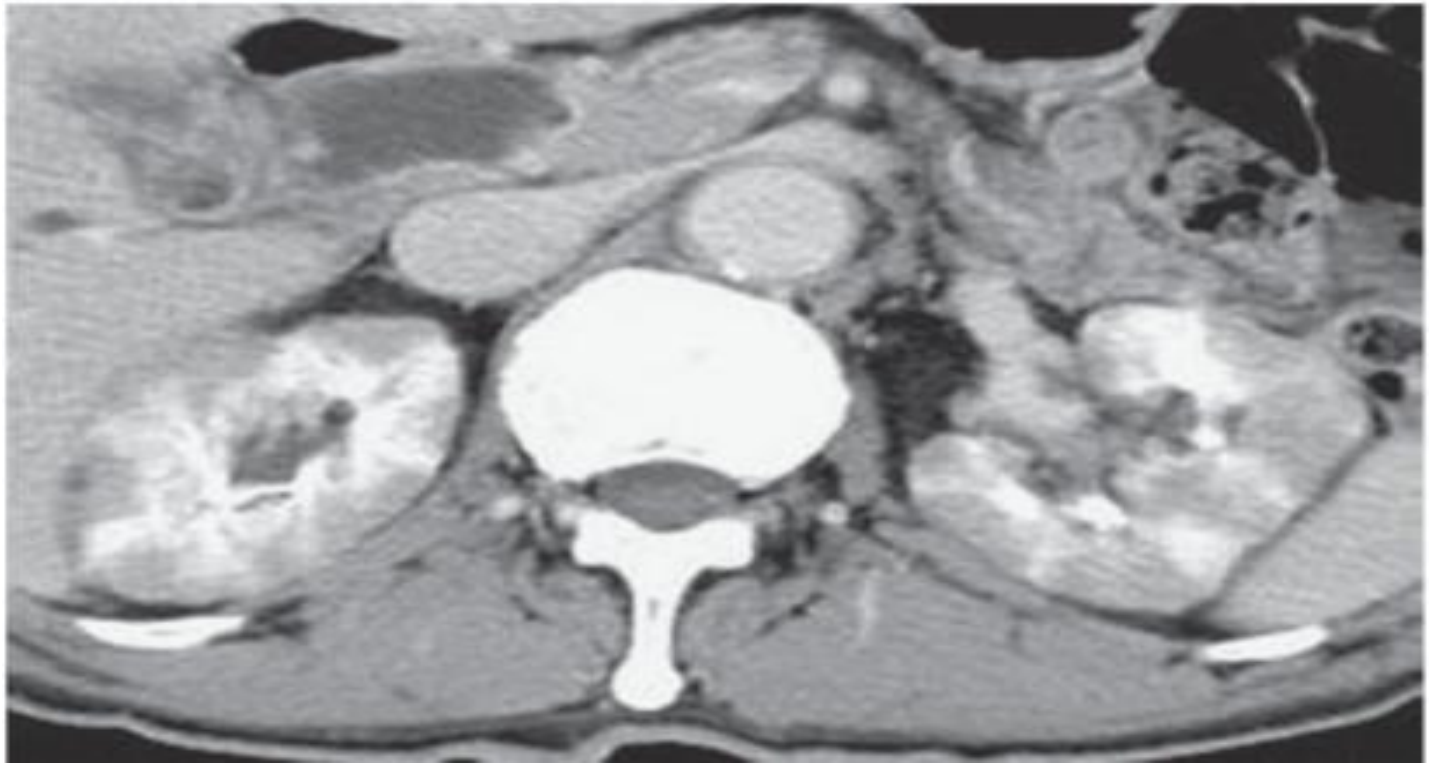


IgG4-RKD
Imaging Features

- ***Multiple low-density lesions***
- ***Kidney enlargement***
- ***Mass lesions***
- ***Thickening of the pelvic wall***
- *Diffuse and focal infiltration*
- ***Encasement by inflammatory and fibrotic tissue***
- *Cystic lesions*

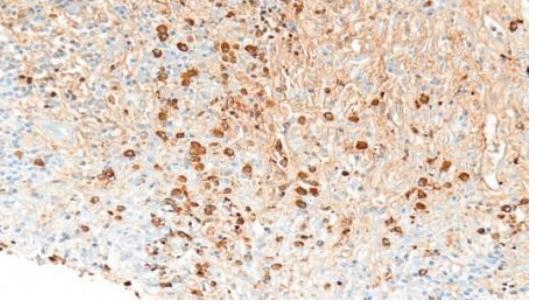


IgG4-RKD
Imaging Features



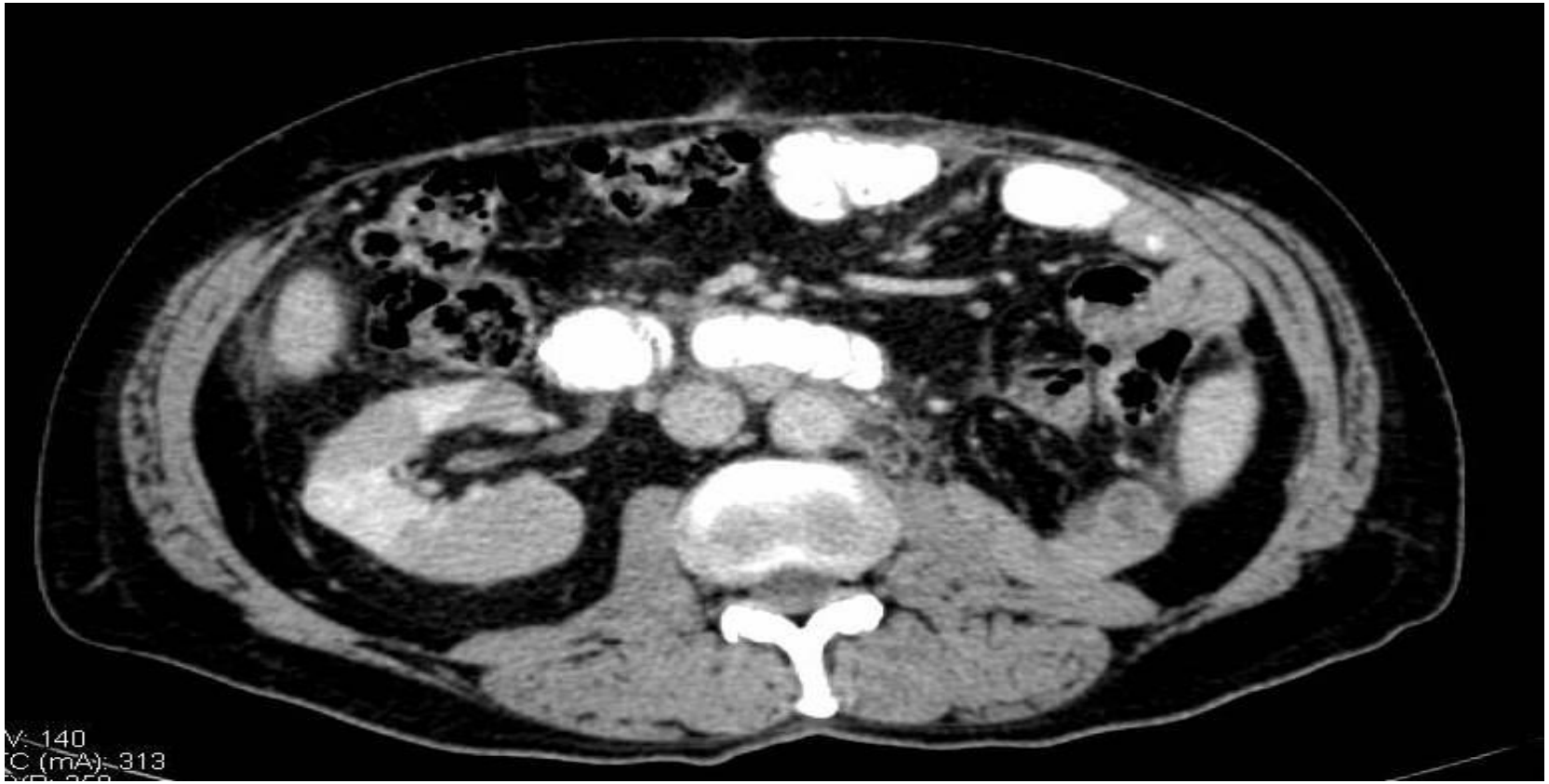
CT: Multiple low-density lesions

Kidney International (2014) **85**, 251-257

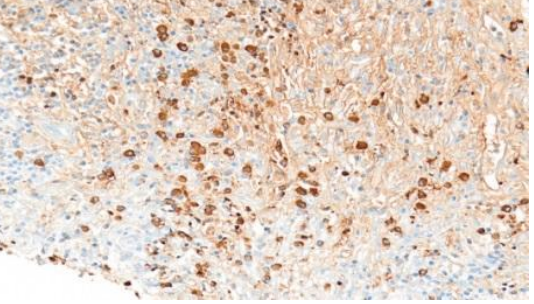


IgG4-RKD

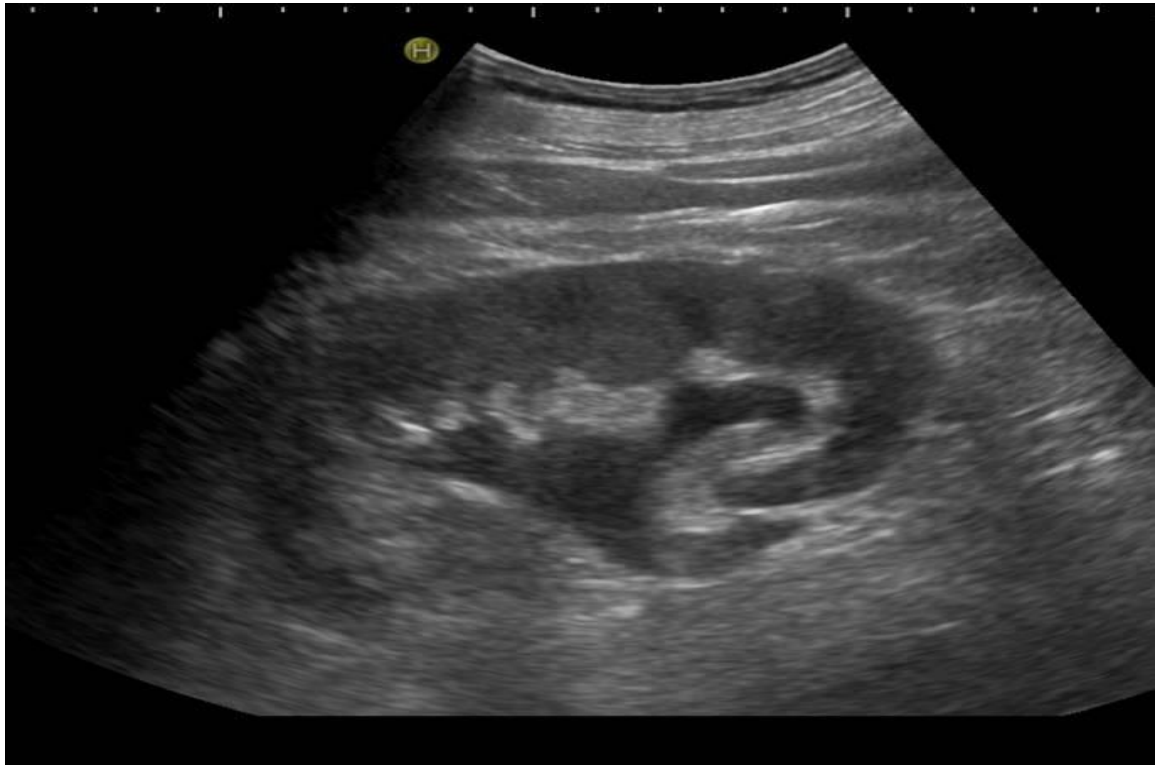
Imaging Features

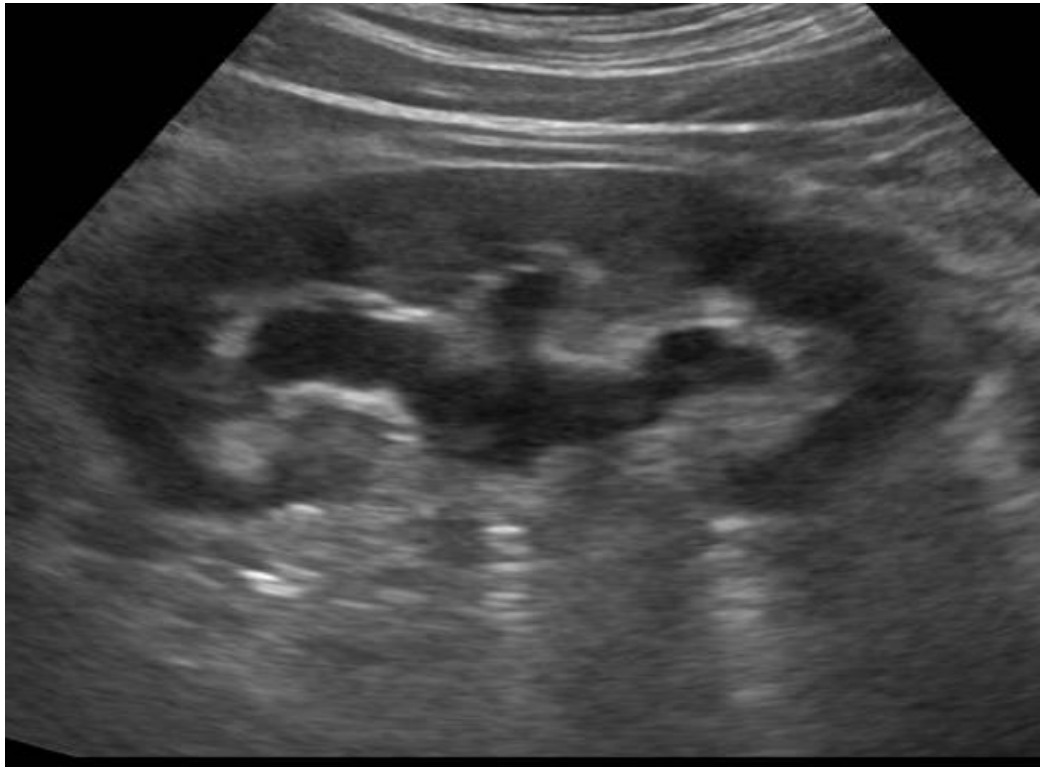


CT: Low-density lesions in a uninephrectomized patient

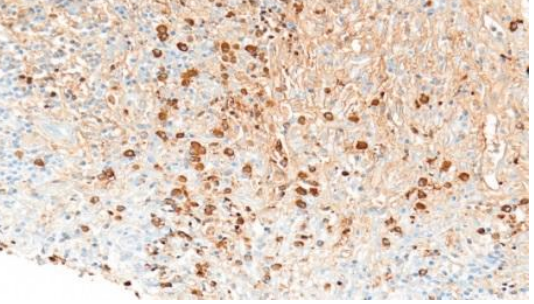


IgG4-RKD
Imaging Features



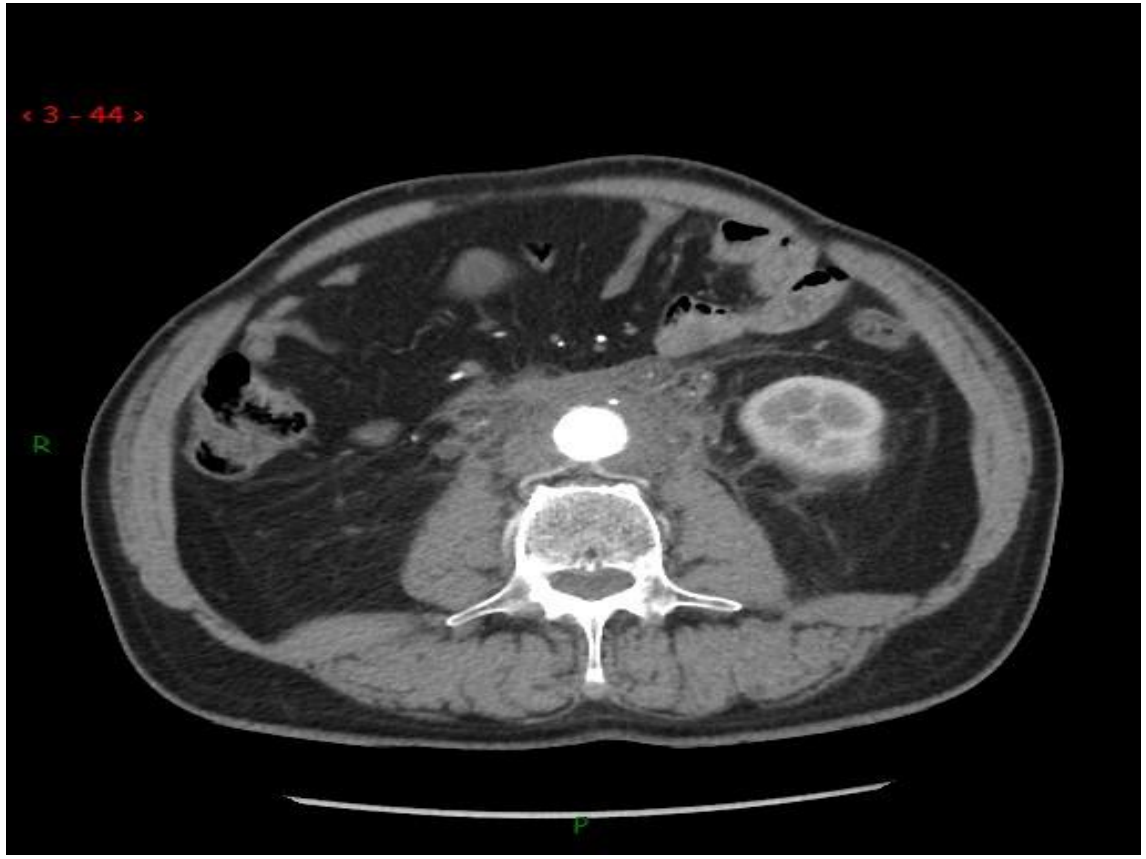


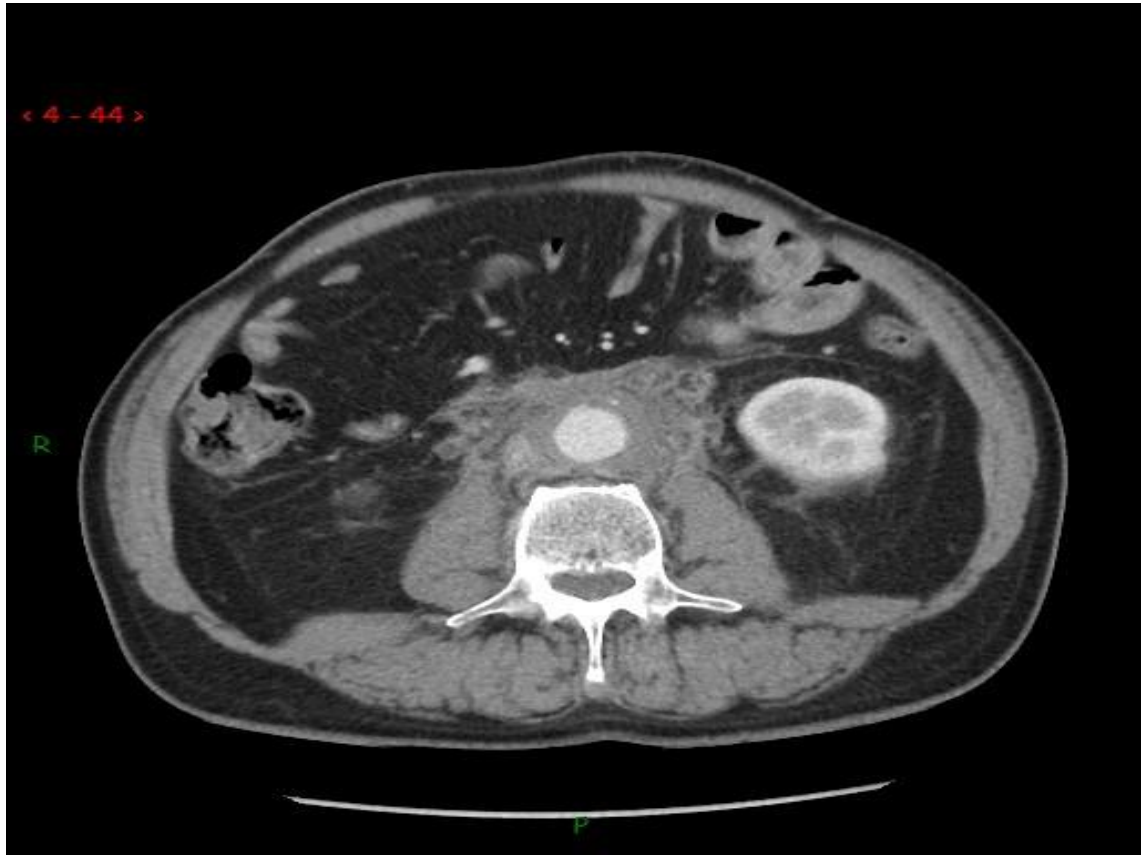
US: bilateral hydronephrosis in periaortitis/RPF



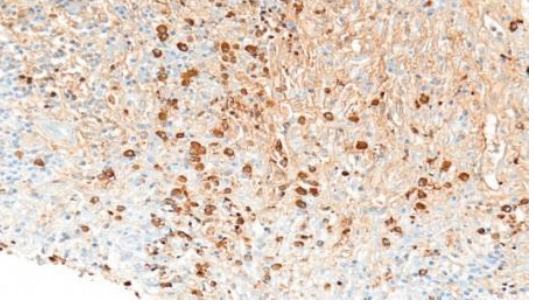
IgG4-RKD

Imaging Features



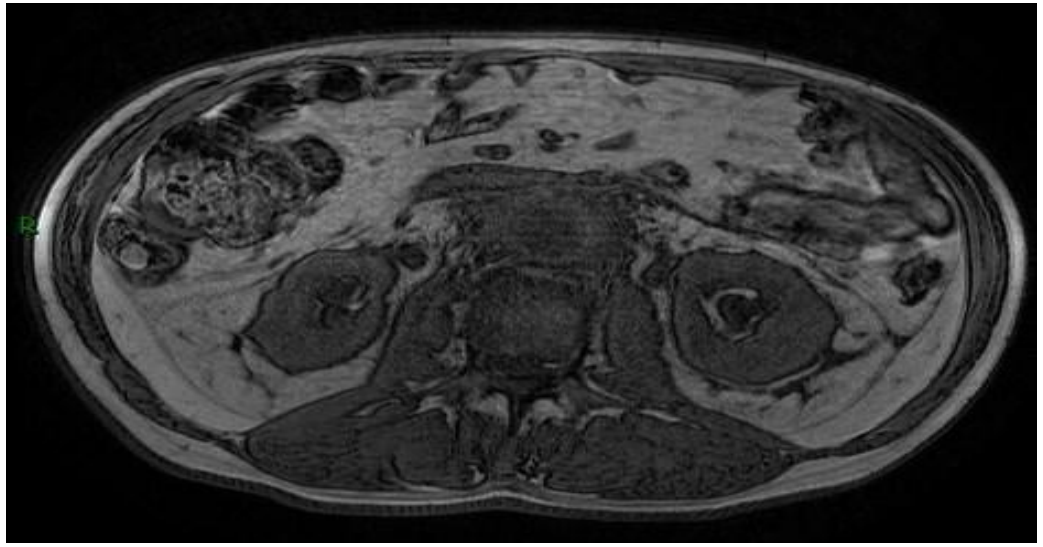


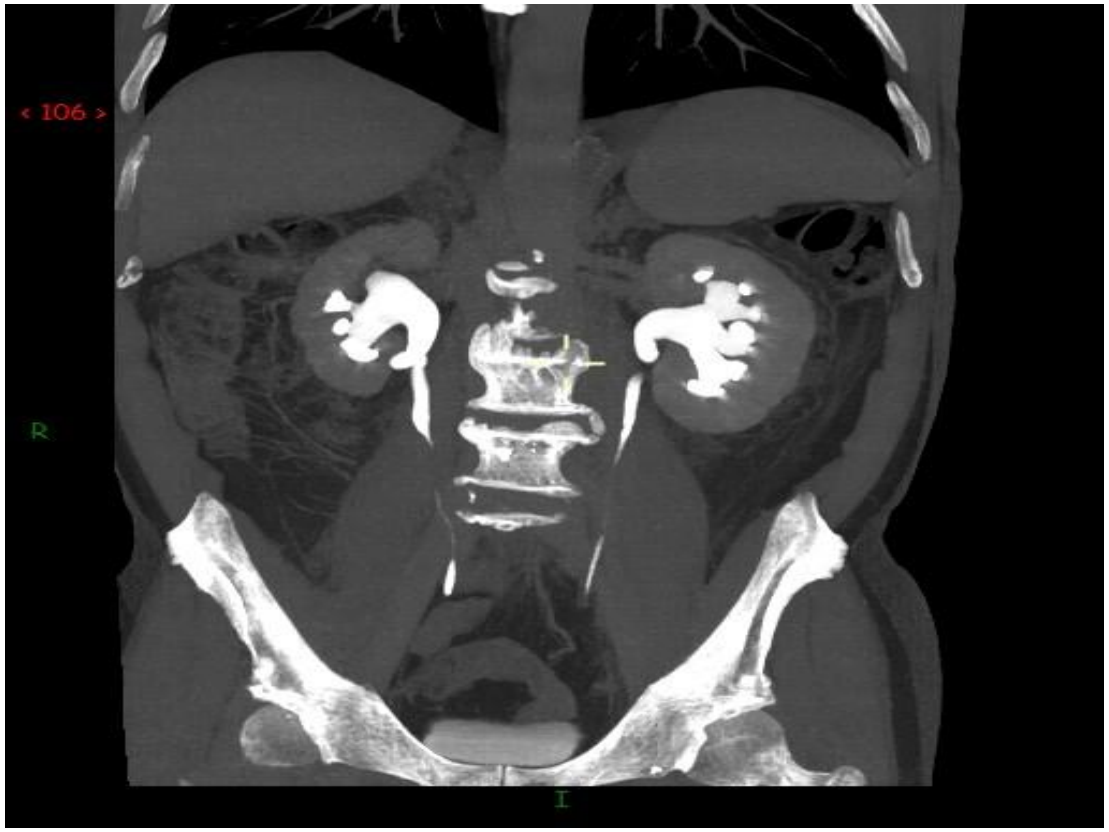
CT: inflammatory periaortic, retroperitoneal tissue

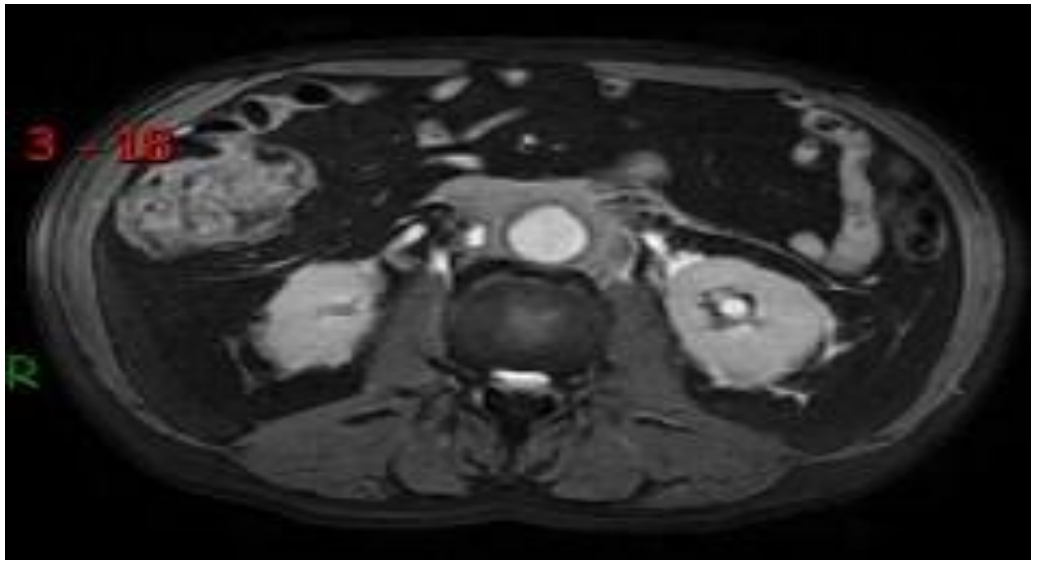


IgG4-RKD

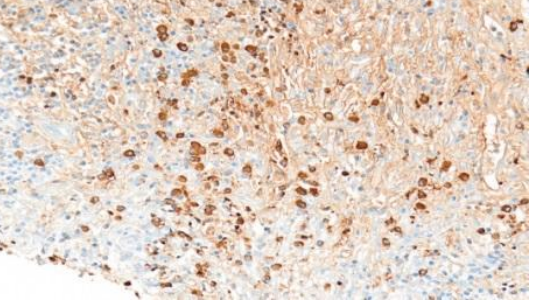
Imaging Features





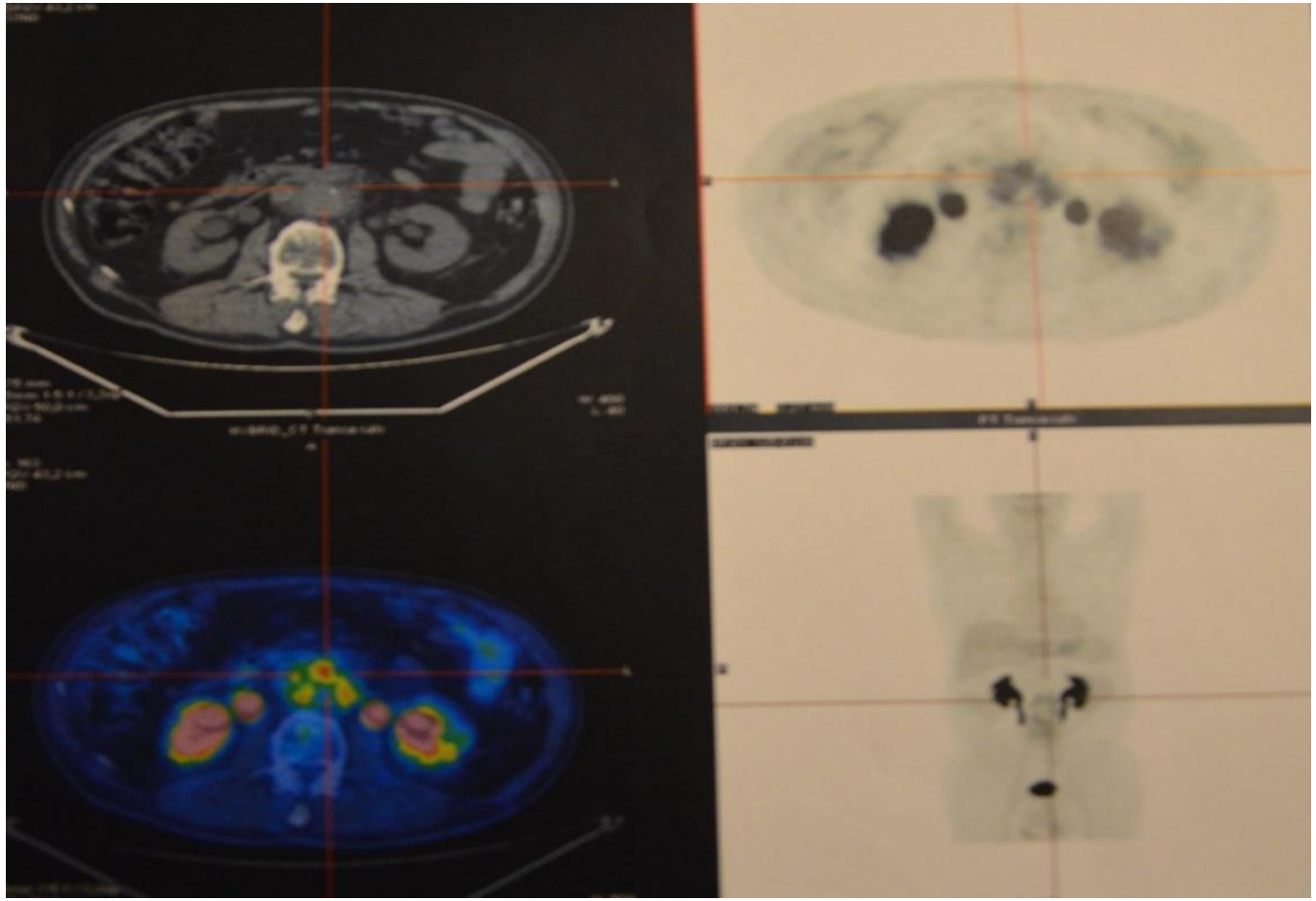


MRI: parenchymatous periaortic tissue. Bilateral hydronephrosis.



IgG4-RKD

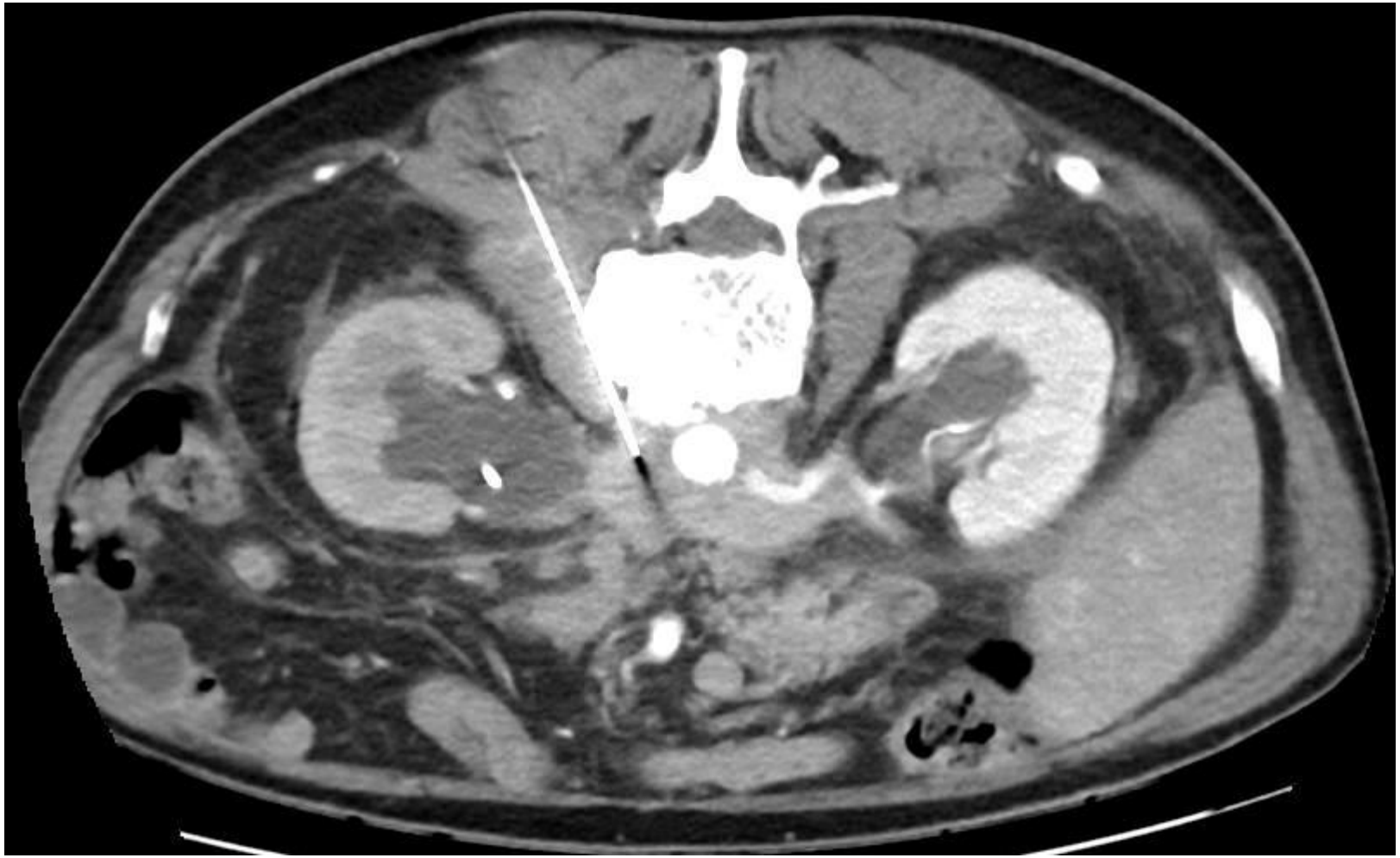
Imaging Features

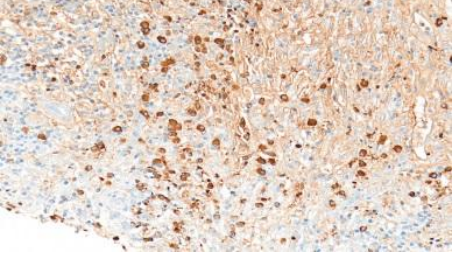


FDG-PET scan: retroperitoneal lesions with high metabolic activity

IgG4-RKD

RPF & Periaortitis





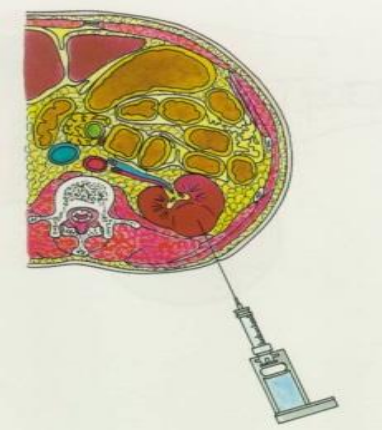
IgG4-Related Diseases

Question 3

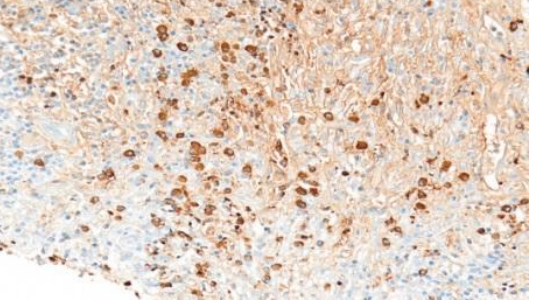
Which organ do you usually choose for diagnostic biopsy?

- Lymphonodes
- Pancreas
- Kidney
- Periaortic tissue

IgG4-RKD



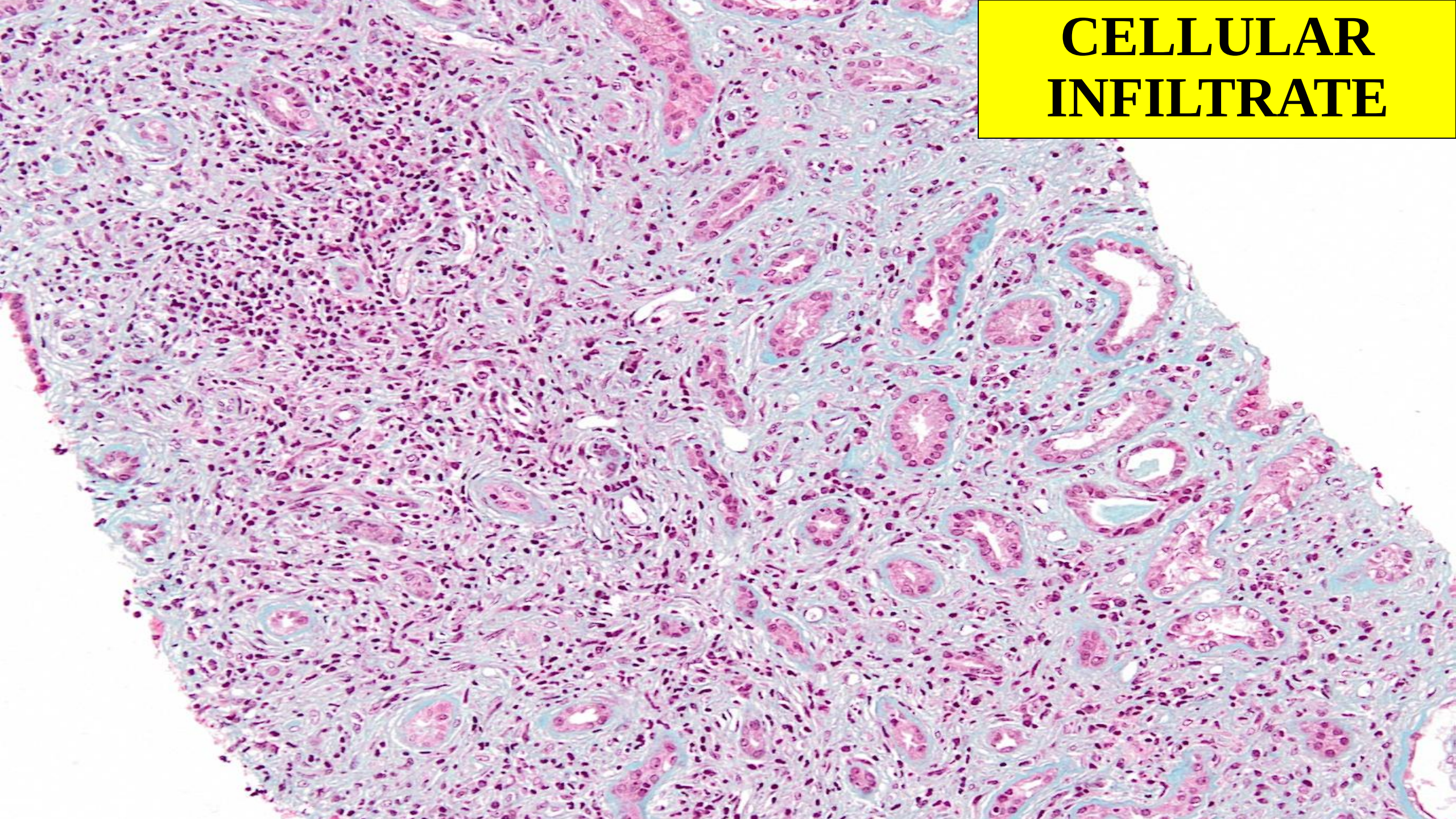
- IgG4-Related Diseases
- IgG4-Related Kidney Disease
- Clinical Features
- Laboratory Features
- Imaging Features
- **Pathological Features**
- Pathophysiological Mechanisms
- Treatment

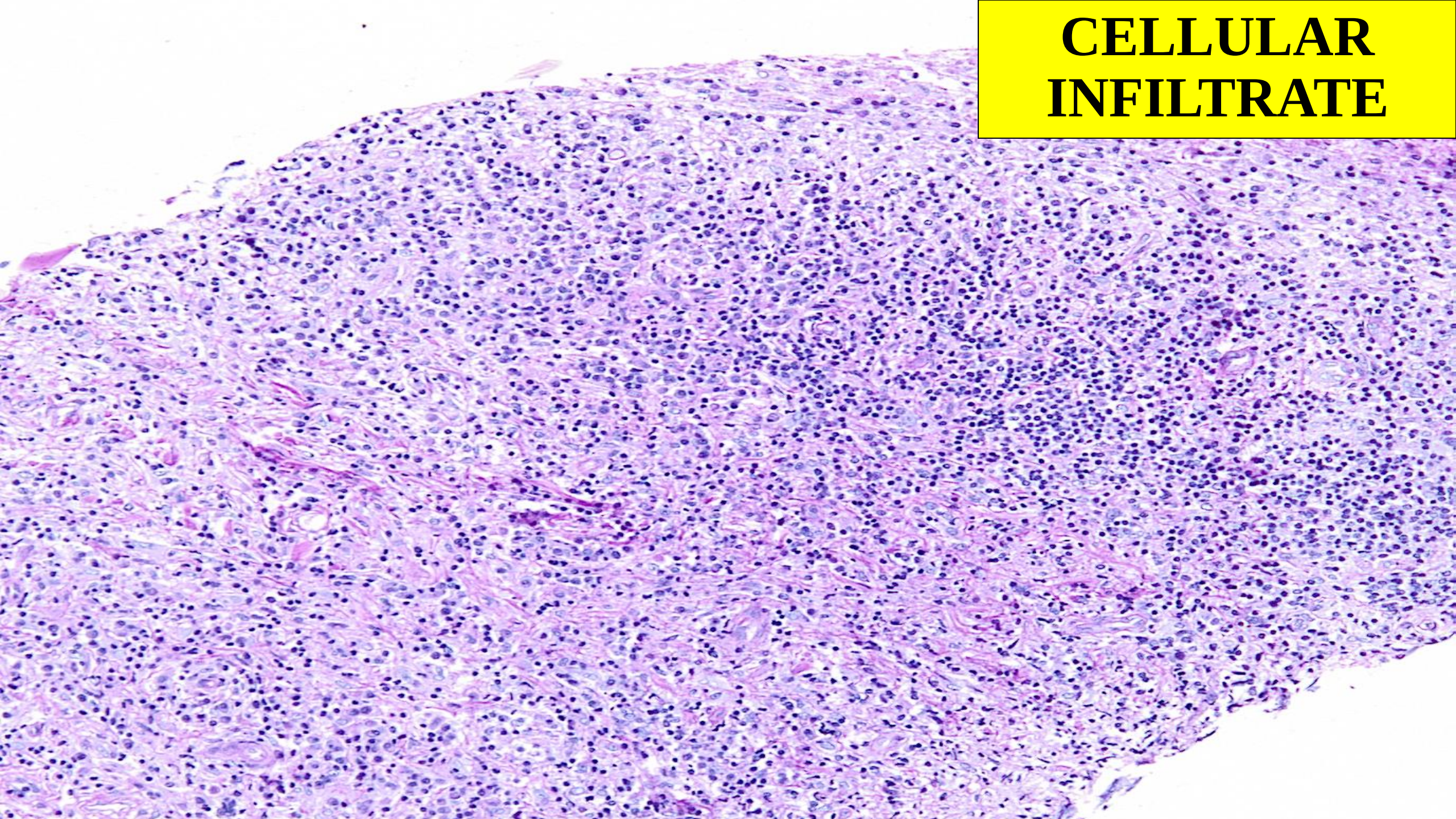


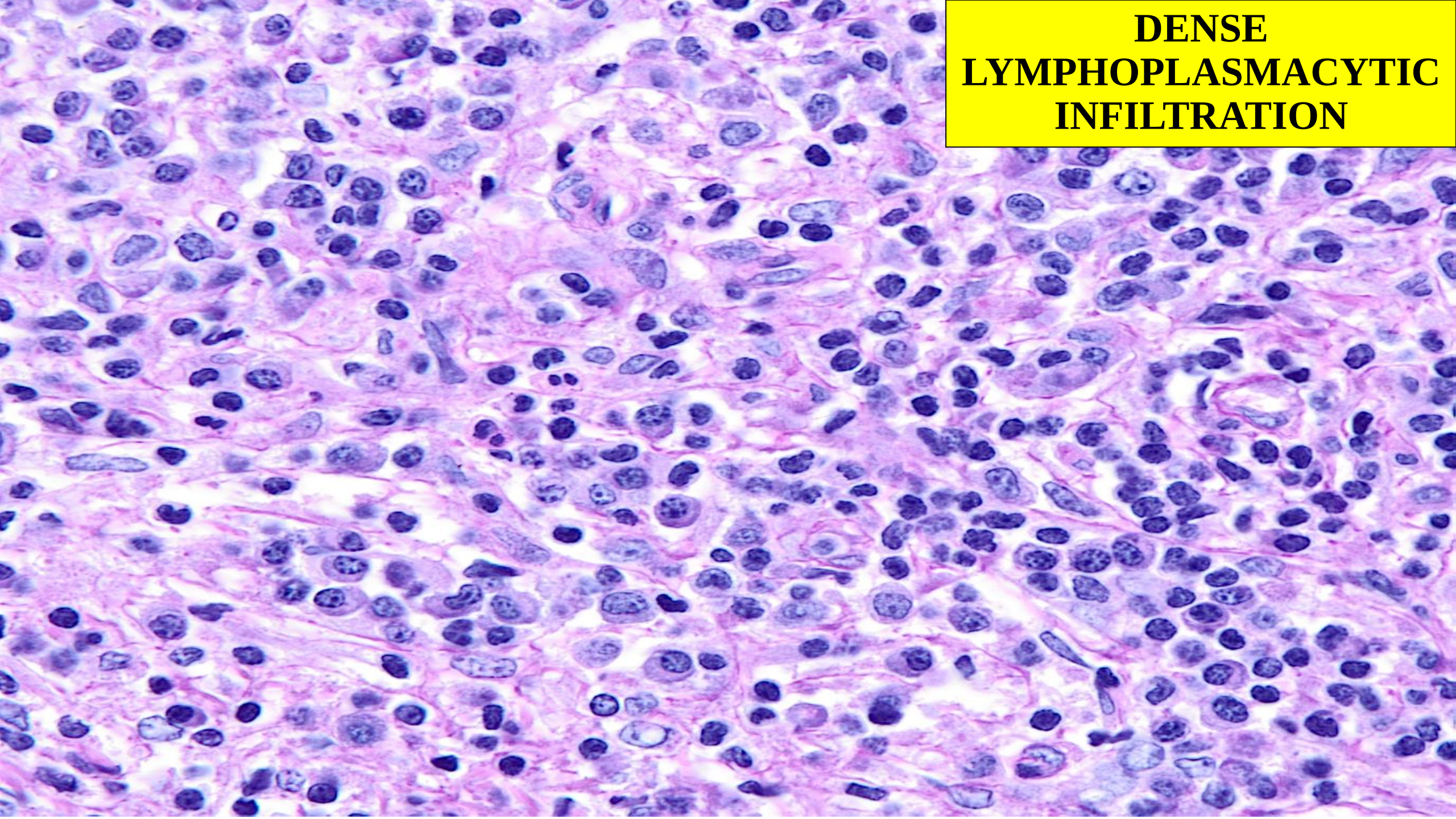
IgG4-RKD
Pathological Features

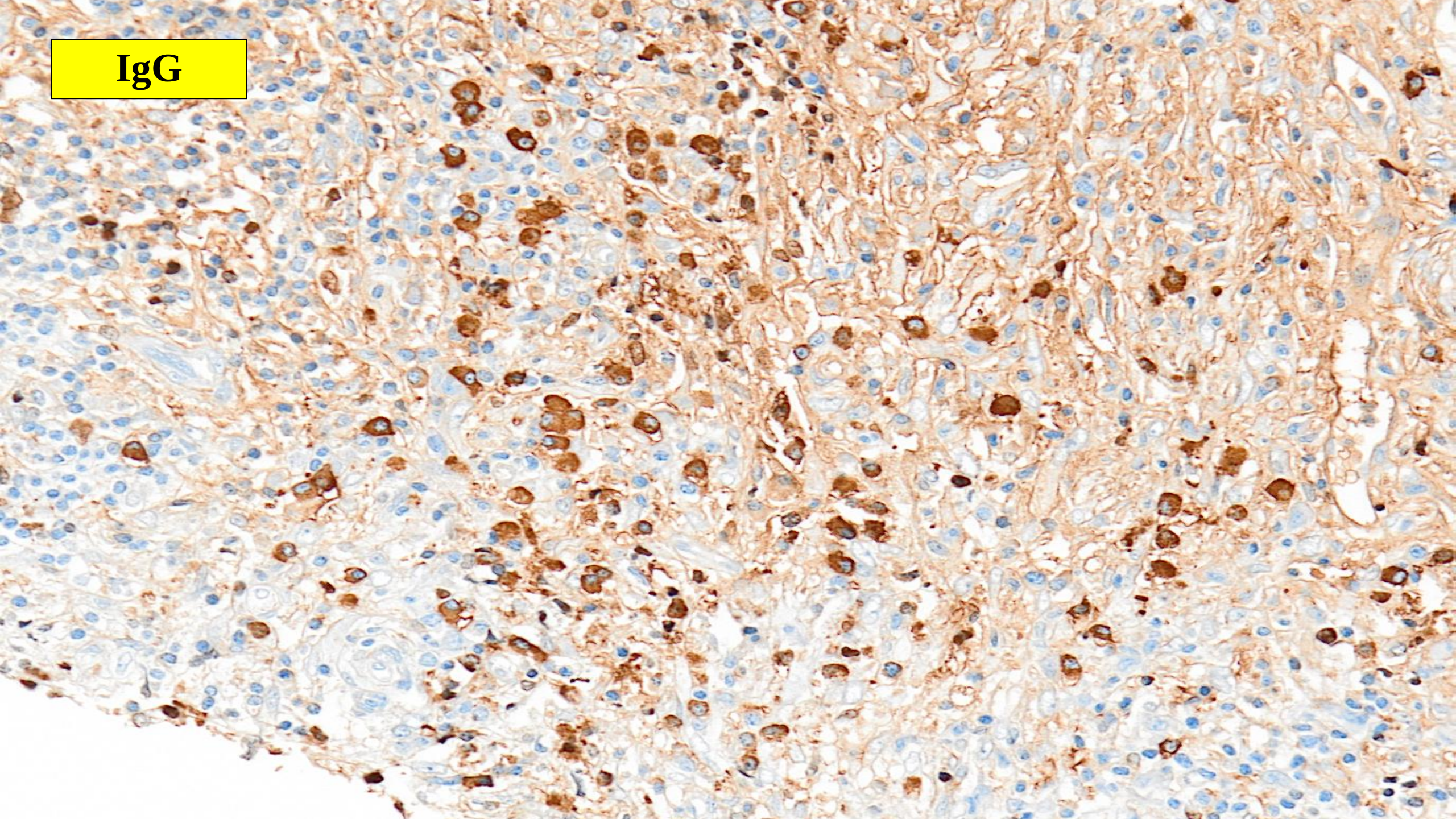
1.Tubulointerstitial nephritis

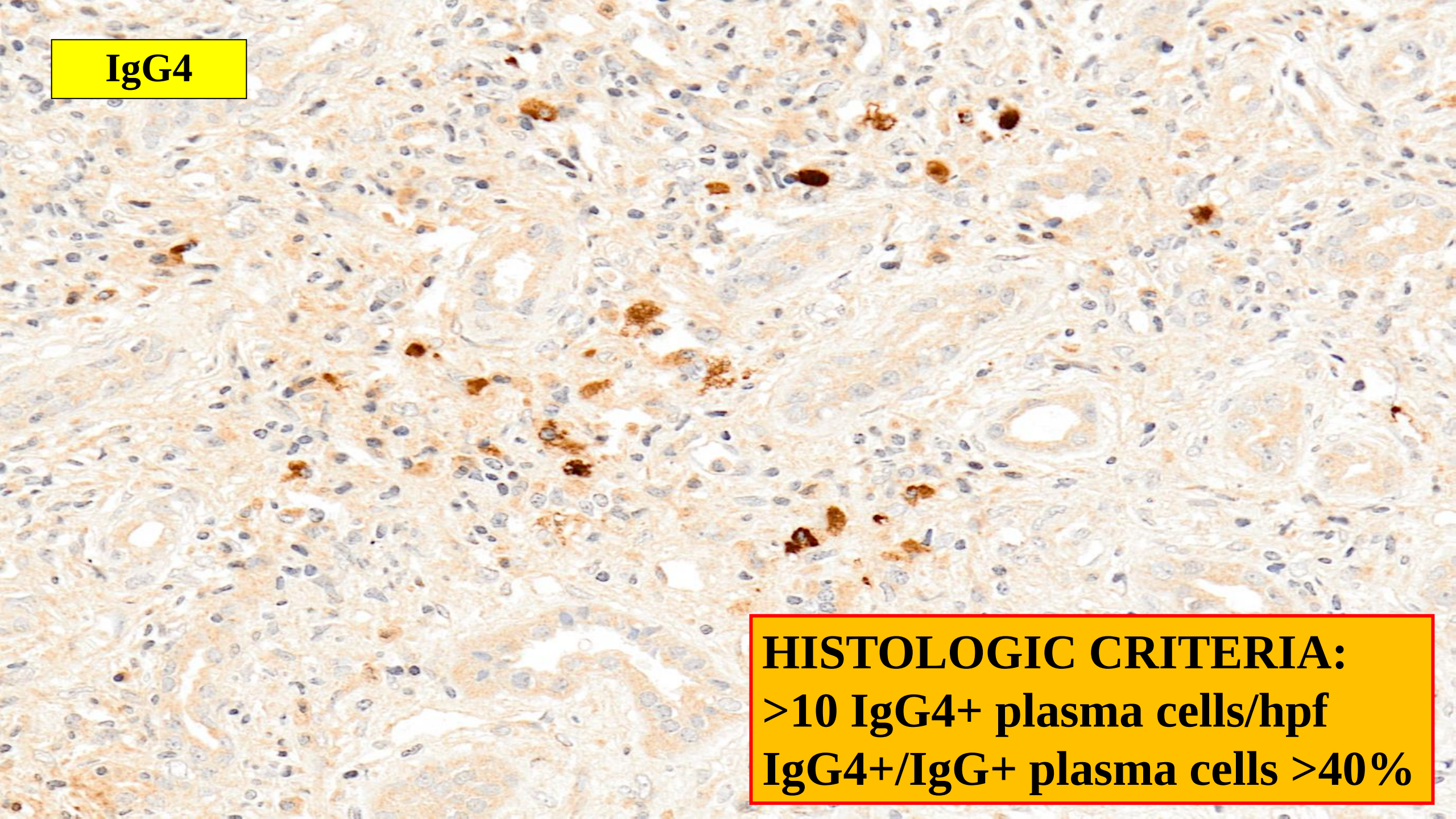
- *Dense tubulointerstitial lymphoplasmacytic infiltrate*
- *Predominance of IgG4+ plasma cells / plasmablasts*
- *Storiform fibrosis*
- *(obliterative phlebitis, eosinophils infiltrate)*


CELLULAR
INFILTRATE

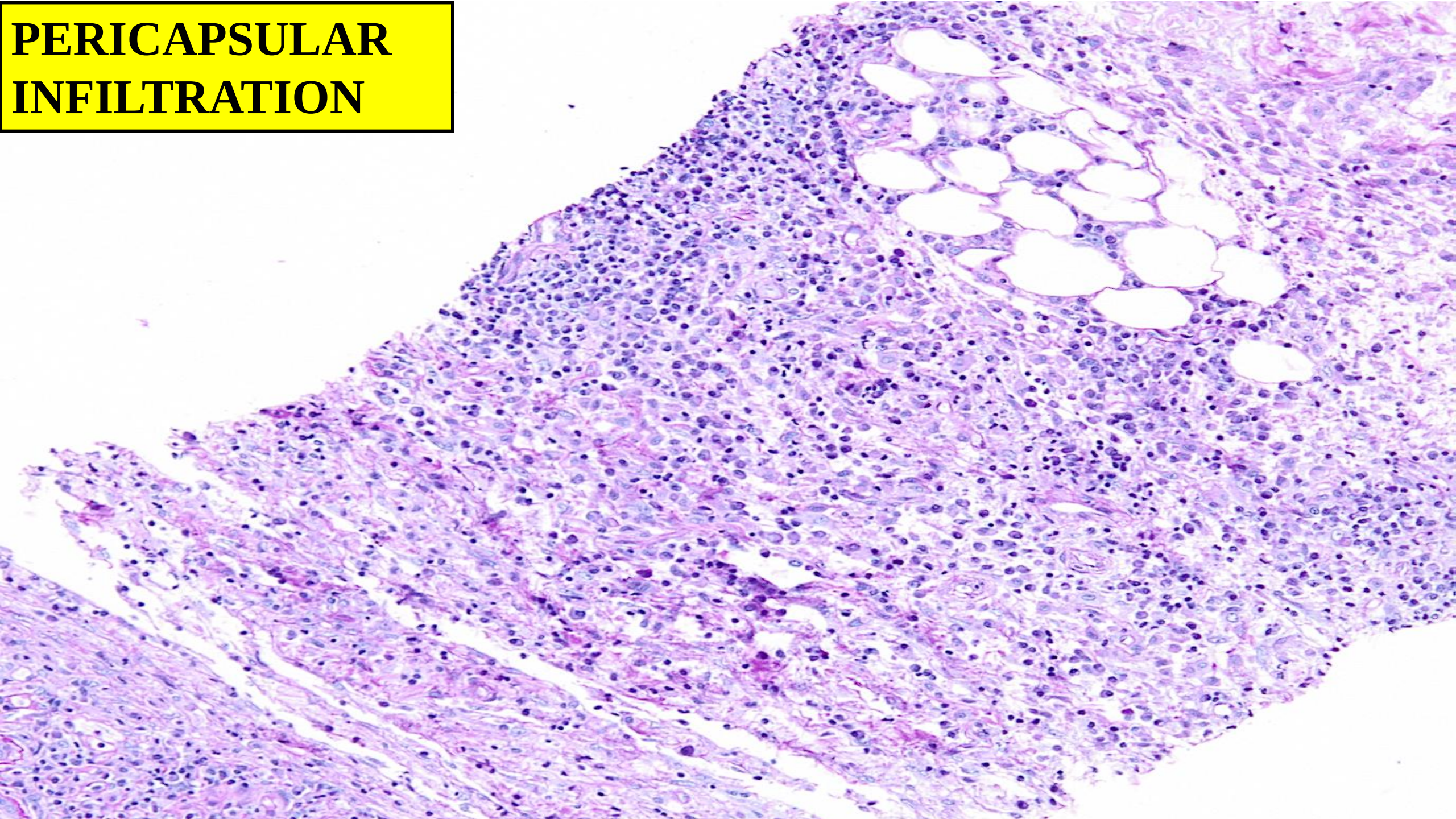

CELLULAR
INFILTRATE

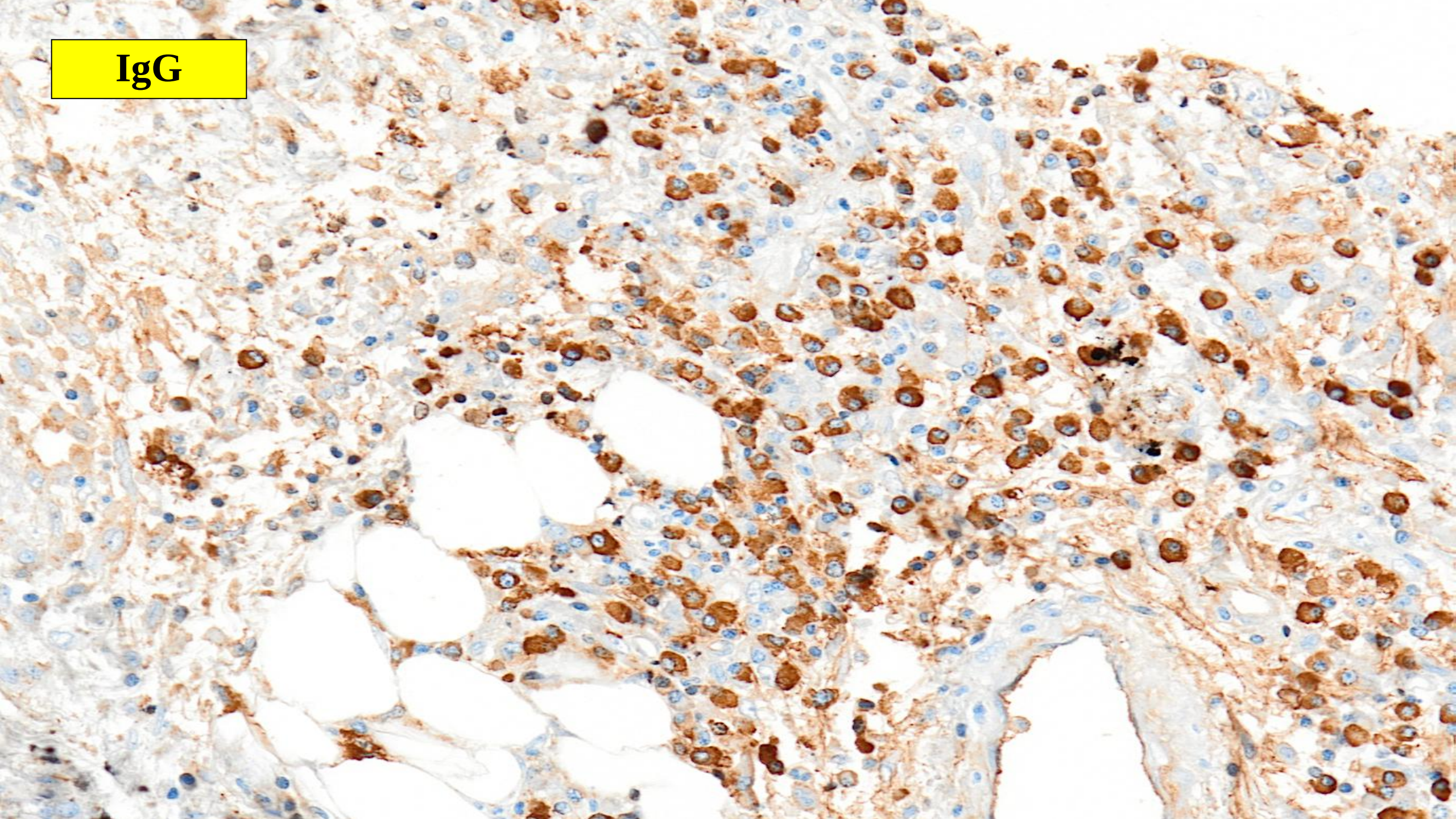

DENSE
LYMPHOPLASMACYTIC
INFILTRATION

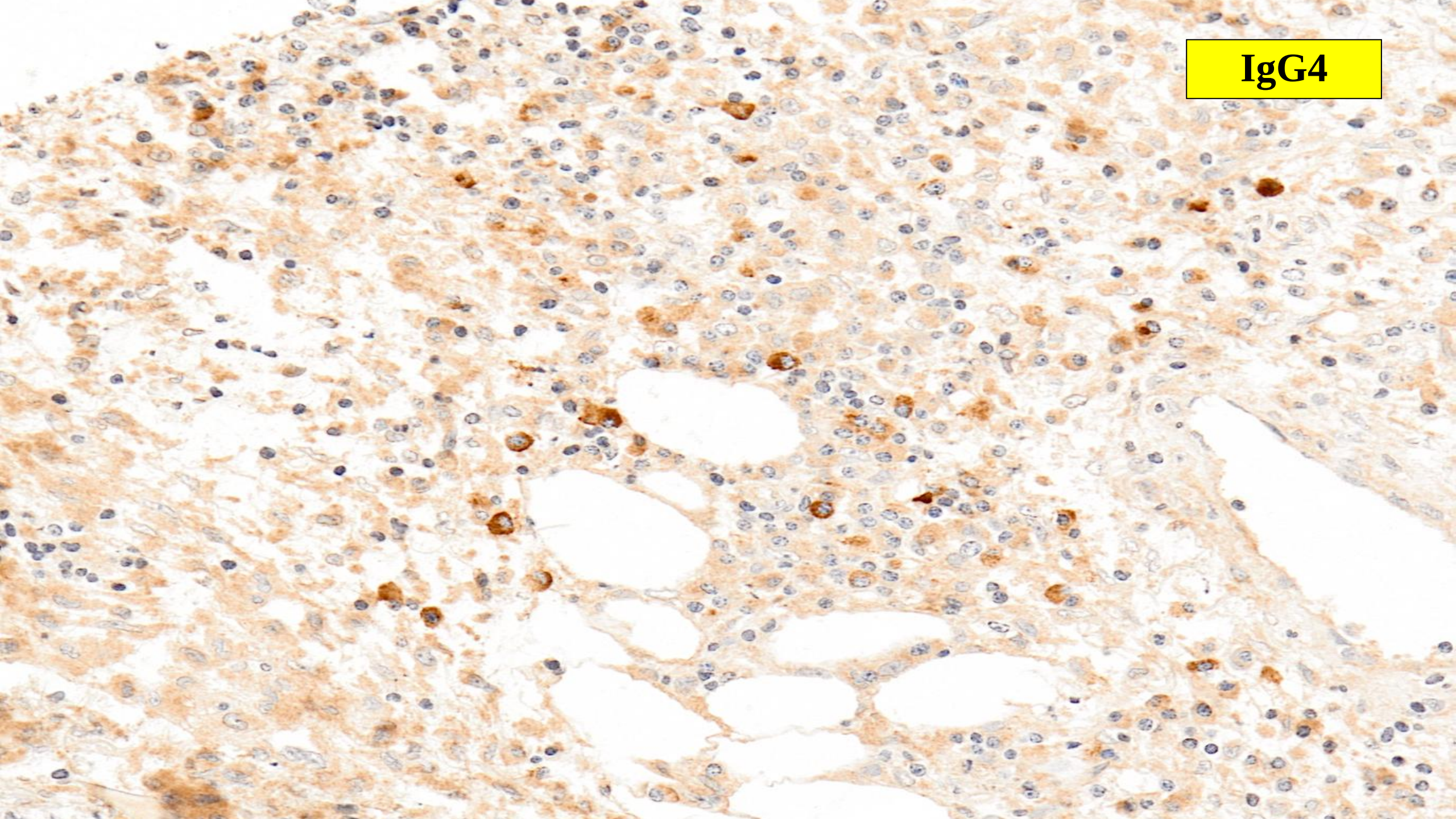

IgG


IgG4
HISTOLOGIC CRITERIA:
>10 IgG4+ plasma cells/hpf
IgG4+/IgG+ plasma cells >40%

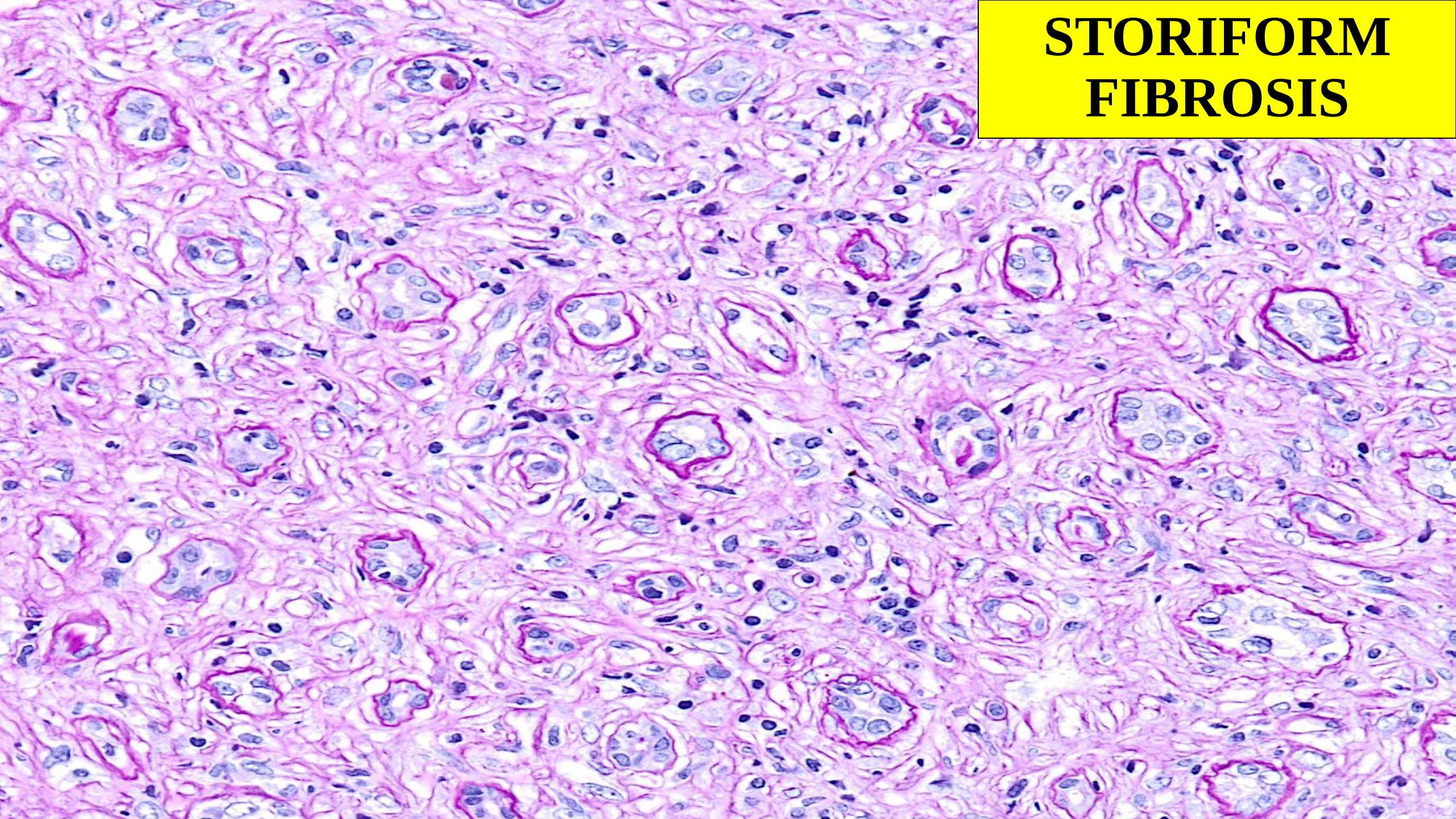
PERICAPSULAR INFILTRATION

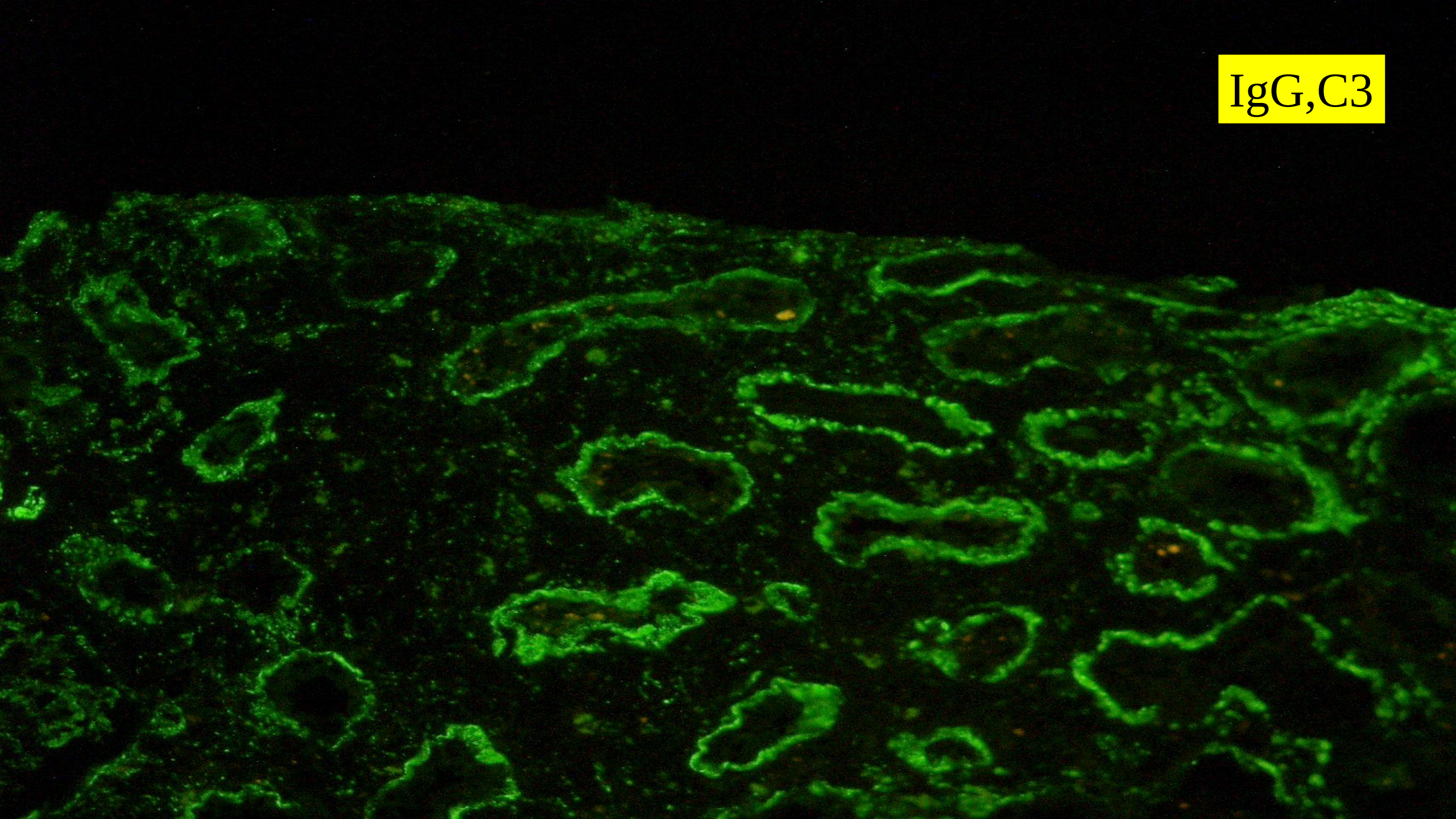


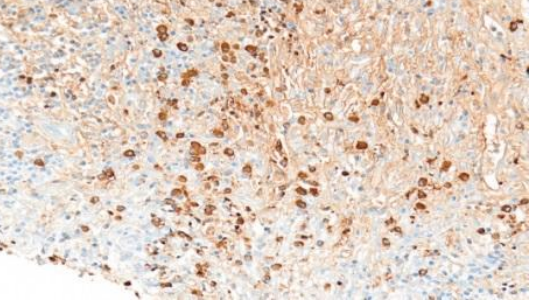

IgG


IgG4

STORIFORM FIBROSIS


STORIFORM
FIBROSIS

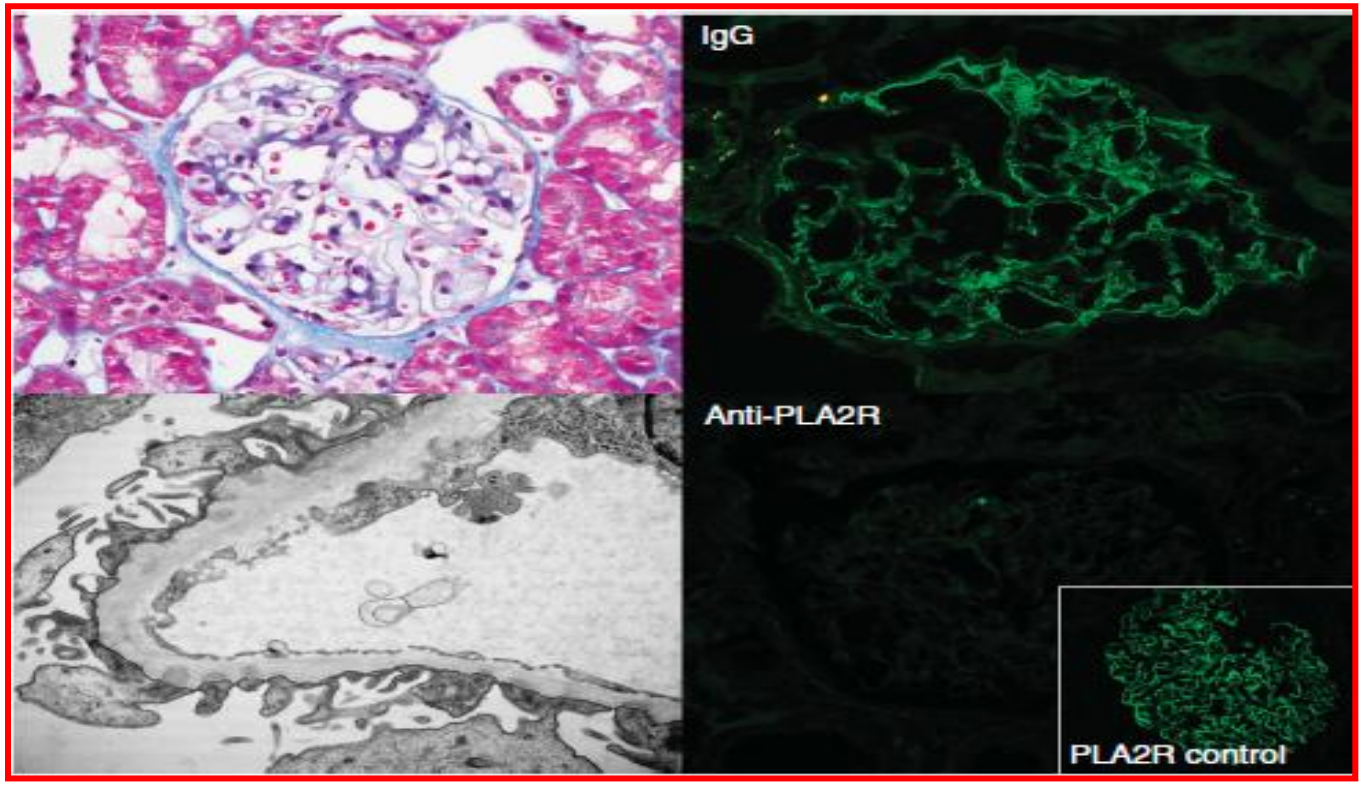

IgG,C3



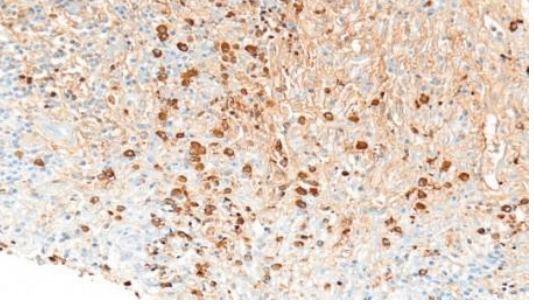
IgG4-RKD

Pathological Features

2. Membranous glomerulonephritis



Kidney International (2013) **83**, 455-462

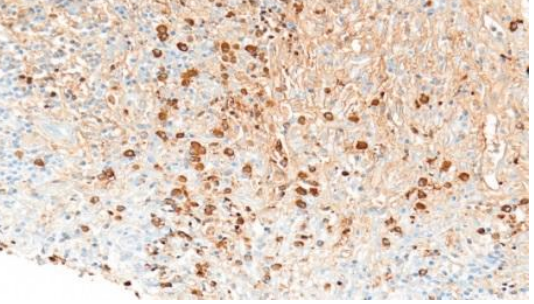


IgG4-RKD

Pathological Features

3. Other glomerulonephritides:

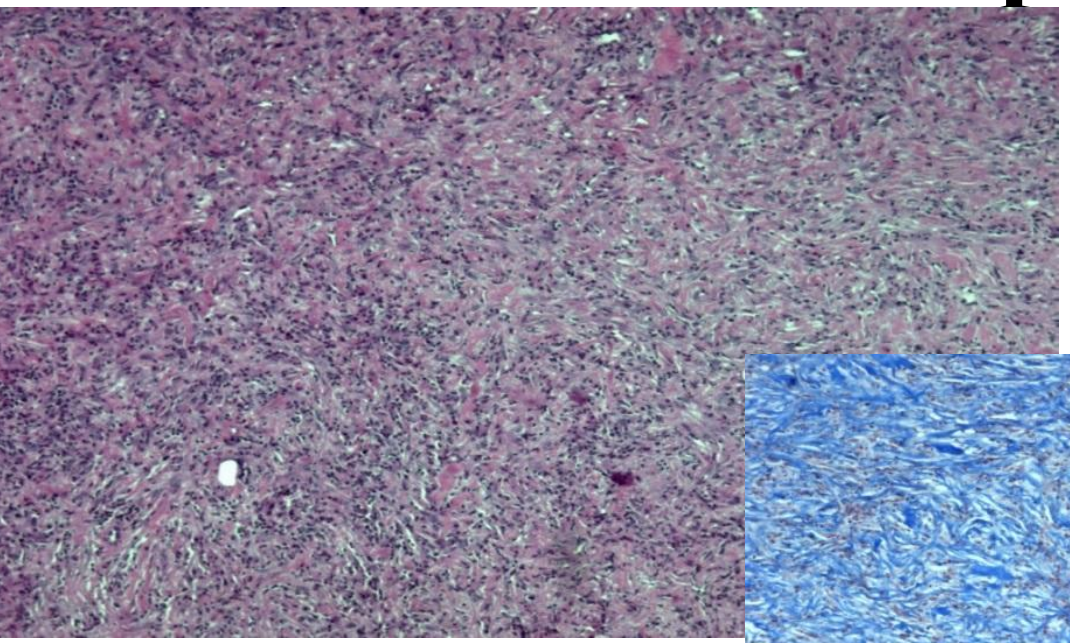
- ✓ IgA – HS purpura
- ✓ Endocapillary proliferative
- ✓ Membrano-proliferative
- ✓ Mesangial proliferative

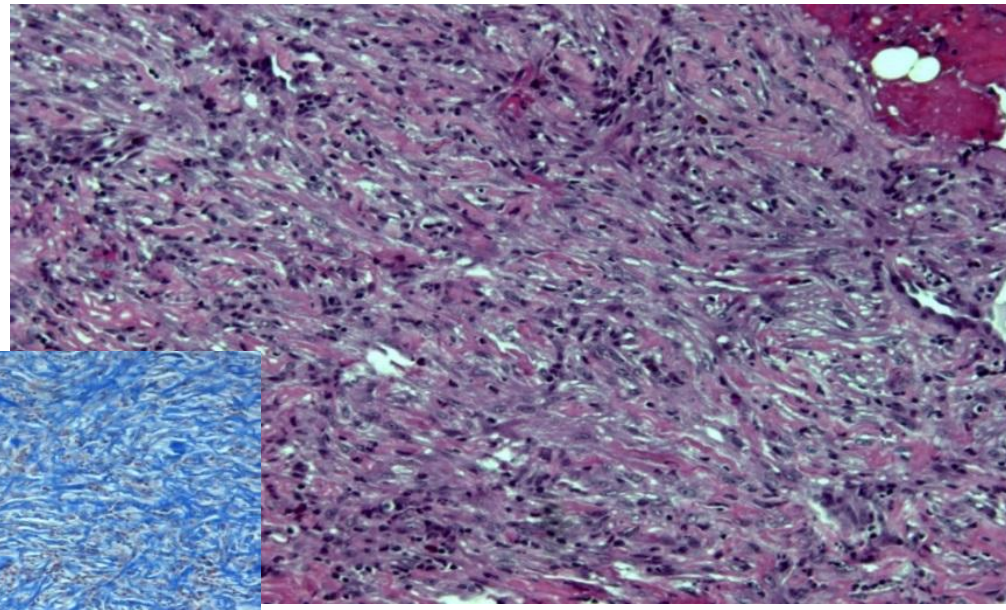


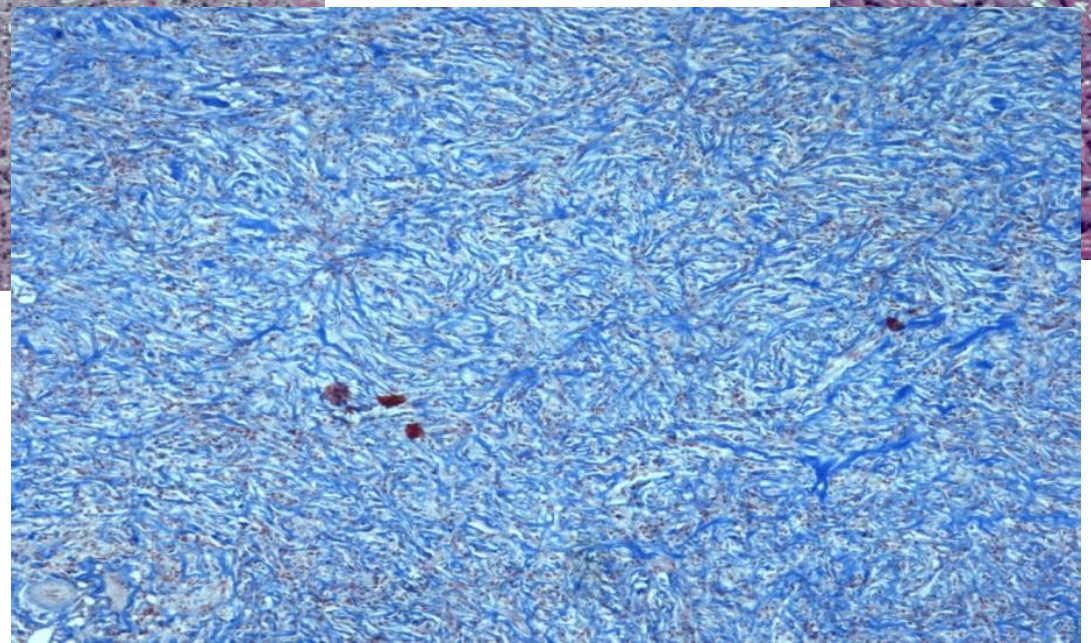
IgG4-RKD

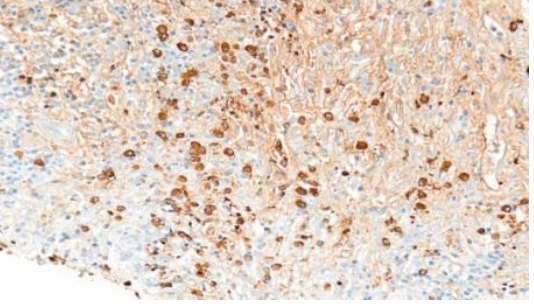
Pathological Features

4. Retroperitoneal fibrosis







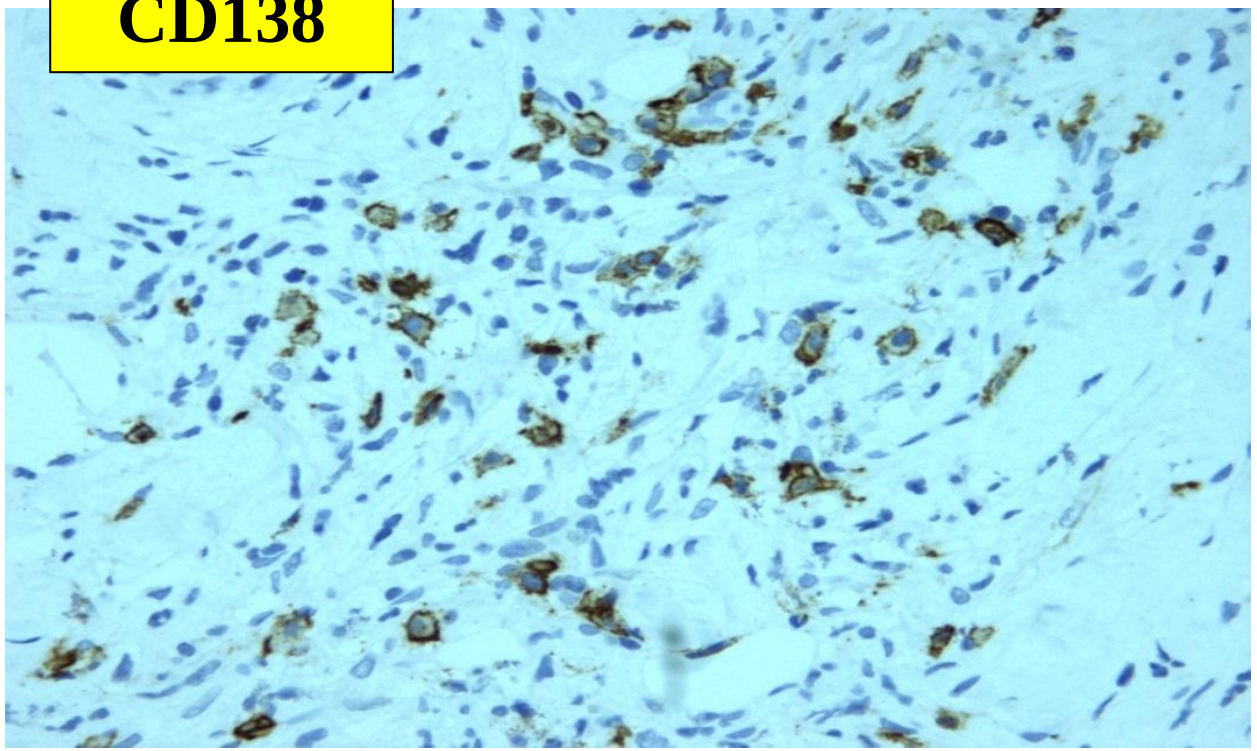


IgG4-RKD

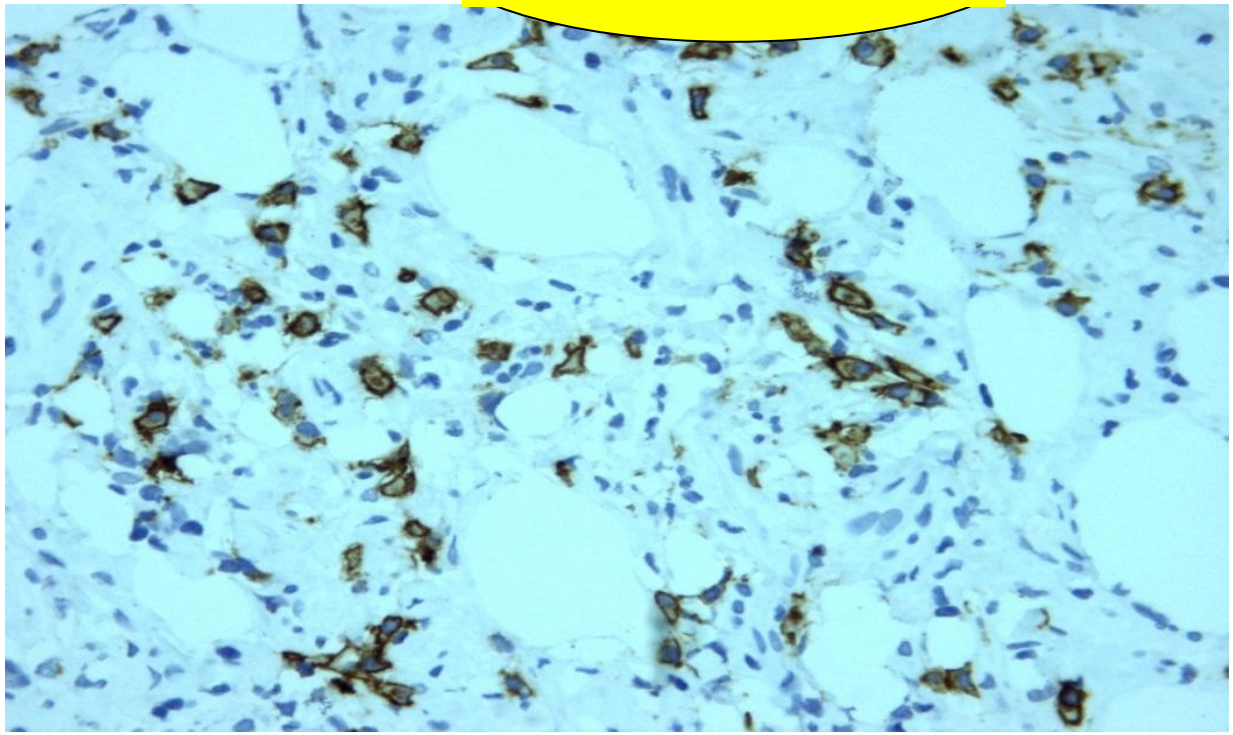
Pathological Features

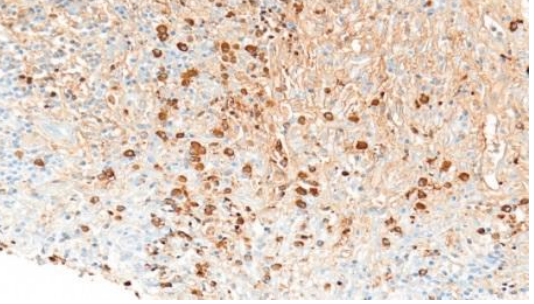
Retroperitoneal fibrosis

CD138



PC > 50 x HPF

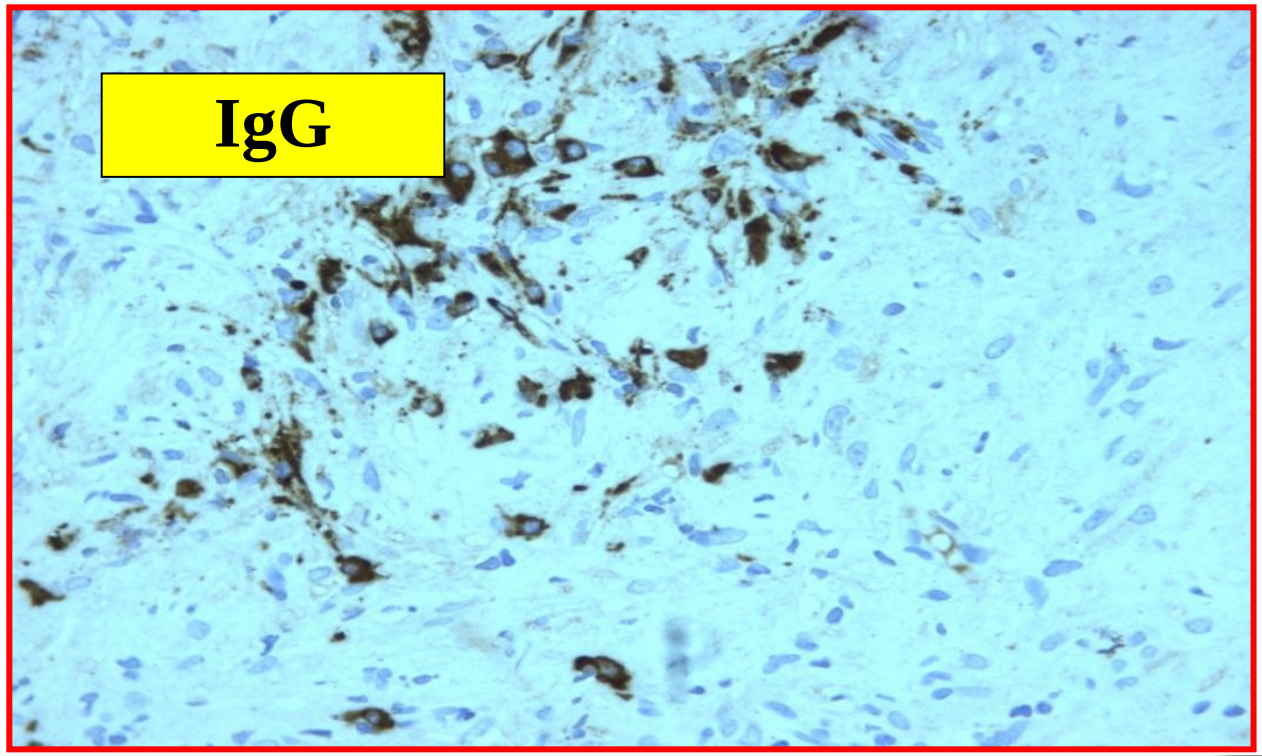


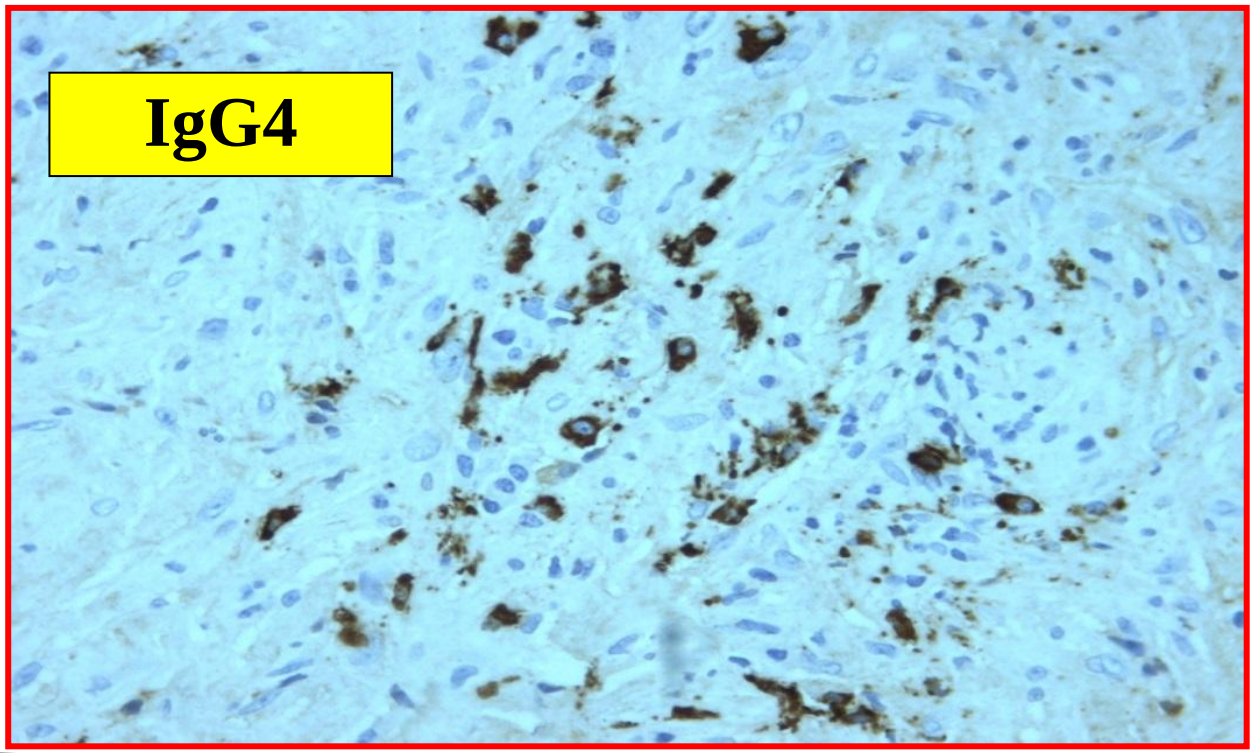


IgG4-RKD

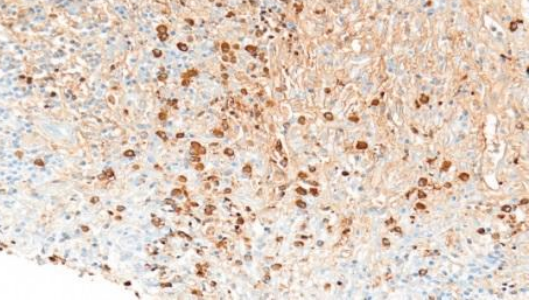
Pathological Features

Retroperitoneal fibrosis





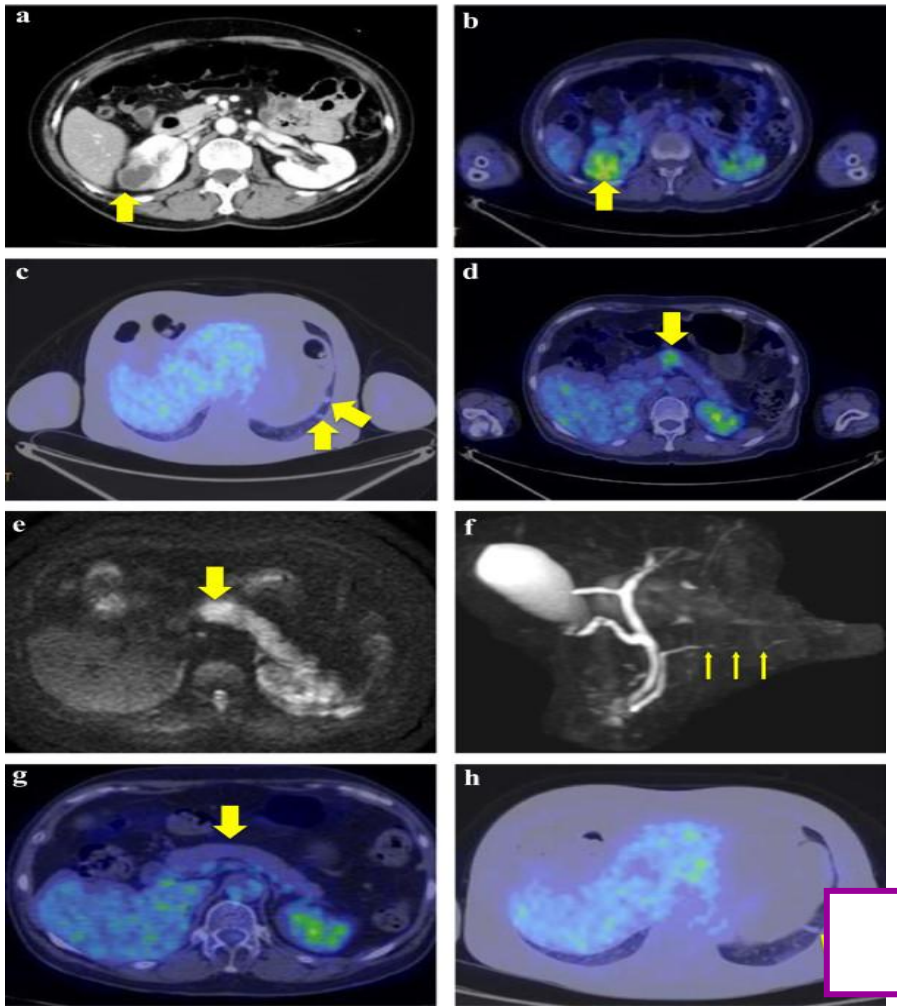
PC: 70% IgG, mostly IgG4

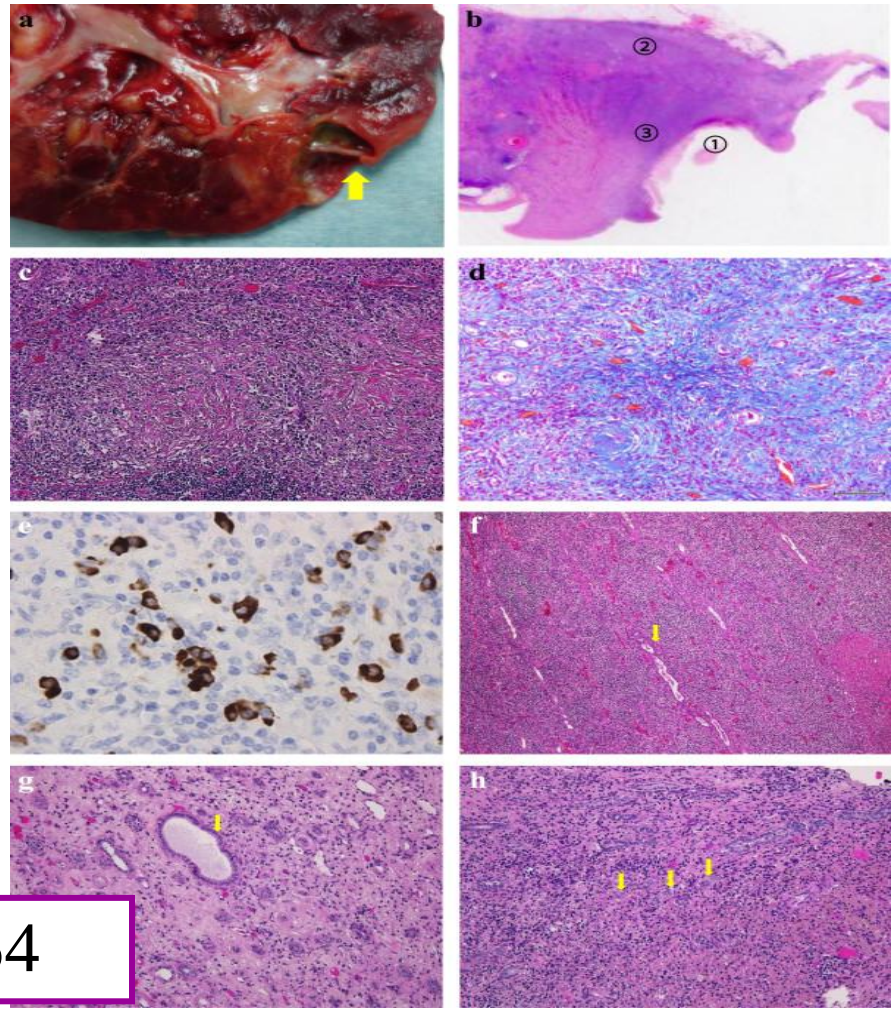


IgG4-RKD

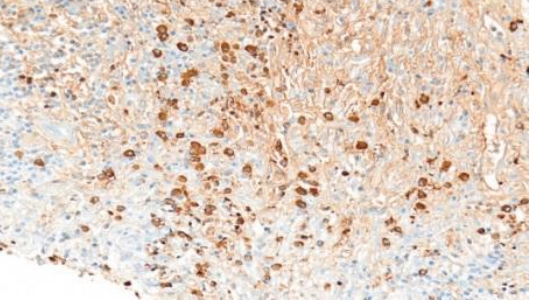
Pathological Features

Renal cysts ?





BMC Urology 2014, **14**: 54



IgG4-RKD

Pathological Features

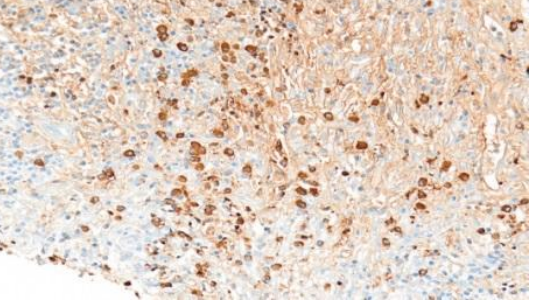
«Lupus sine lupo!»

IgG4-negative IgG4-related disease

- *BMJ Case Rep 2013*
- *Mod Rheumatol 2014*

These cases suggest that a condition that closely mimics IgG4-RD may develop even in the absence of IgG4 and plasma cells.

Curr Opin Nephrol Hypertens 2015



IgG4-RKD

Diagnosis: is histology sufficient …?

Diagnostic criteria for IgG4-RKD

Table 3. Proposed diagnostic criteria for IgG4-related TIN

Histology	Plasma cell–rich tubulointerstitial nephritis with >10 IgG4 + plasma cells/hpf field in the most concentrated field[a]
	Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy[b]
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement
	Diffuse marked enlargement of kidneys
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Includes autoimmune panceatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis

Diagnosis of IgG4-TIN requires the histologic feature of plasma cell–rich TIN with increased IgG4 + plasma cells and at least one other feature from the categories of "imaging", "serology", or "other organ involvement".
[a]Mandatory criterion.
[b]Supportive criterion, present in >80% of cases.

PATTERN A, B, C

JASN (2011) **22**: 1343-1352

Table 4. Diagnostic criteria for IgG4-related kidney disease (IgG4-RKD) [37].

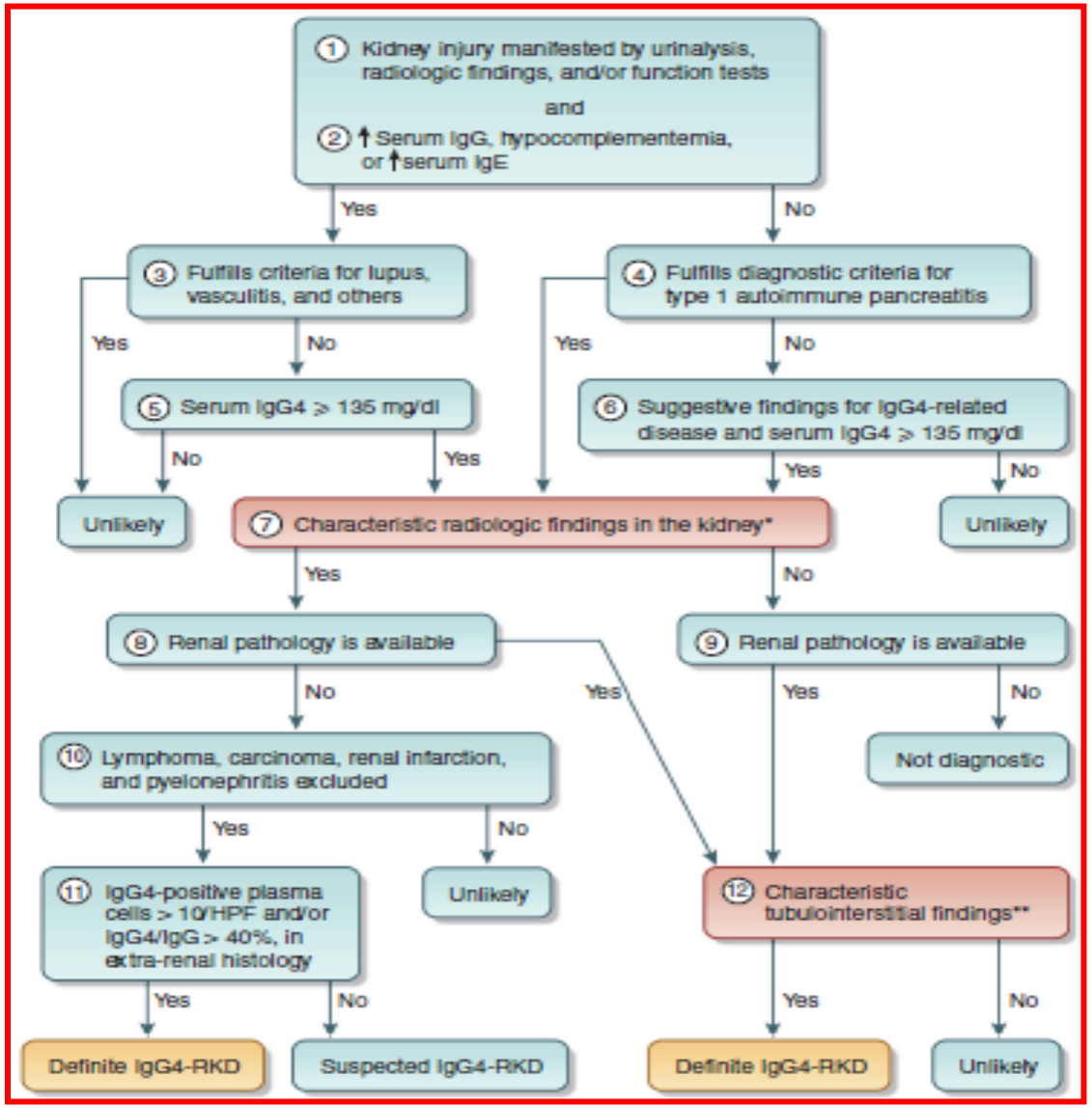
1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level
2. Abnormal renal radiologic findings:
   a. Multiple low-density lesions on enhanced computed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

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

Appendix:
1. Clinically and histologically, the following diseases should be excluded: Wegener's granulomatosis, Churg–Strauss syndrome, extramedullary plasmacytoma
2. Radiologically, the following diseases should be exduded: malignant lymphoma, urinary tract carcinomas, renal infarction and pyelonephritis (rarely, Wegener's granulomatosis, sarcoidosis and metastatic cardnoma)
3. Cases with suspected disease according to the diagnostic algorithm are classified into probable or possible IgG4-RKD according to these criteria

Mod Rheumatol (2017) **27**: 381-391

Diagnostic algorithm for IgG4-RKD



Kidney International (2014) **85**: 251-257

Arthritis & Rheumatology
Vol. 72, No. 1, January 2020, pp 7–19
DOI 10.1002/art.41120

American College of Rheumatology
Empowering Rheumatology Professionals

SPECIAL ARTICLE

The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease

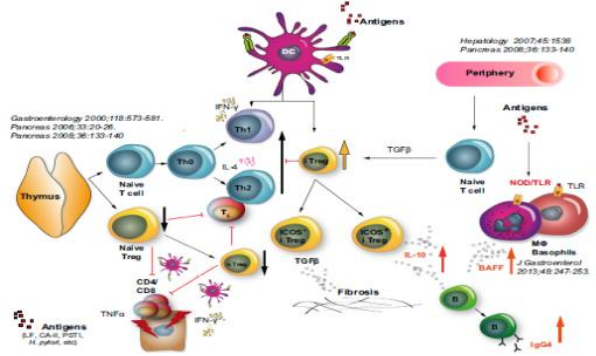
- Step 1: entry criteria
- Step 2: exclusion criteria
- Step 3: inclusion criteria
- Step 4: total inclusion points ≥20

Table 4 The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD

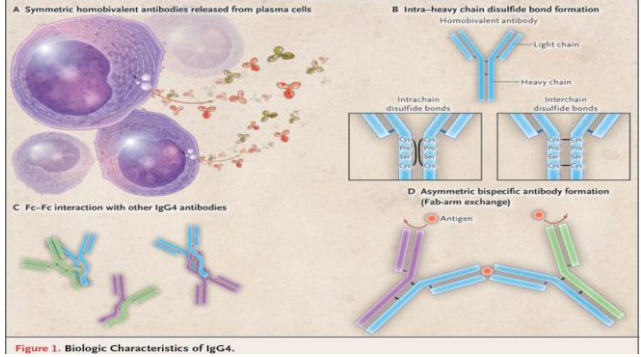
Step	Categorical assessment or numerical weight
Step 1. Entry criteria	
Characteristic* clinical or radiological involvement of a typical organ (eg, pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges or thyroid gland (Riedel's thyroiditis)) OR pathological evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain aetiology in one of these same organs	**Yes**† or No
Step 2. Exclusion criteria: domains and items‡	Yes or **No**§
Clinical	
Fever	
No objective response to glucocorticoids	
Serological	
Leucopenia and thrombocytopenia with no explanation	
Peripheral eosinophilia	
Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase)	
Positive SSA/Ro or SSB/La antibody	
Positive double-stranded DNA, RNP or Sm antibody	
Other disease-specific autoantibody	
Cryoglobulinemia	
Radiological	
Known radiological findings suspicious for malignancy or infection that have not been sufficiently investigated	
Rapid radiological progression	
Long bone abnormalities consistent with Erdheim-Chester disease	
Splenomegaly	
Pathological	
Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
Markers consistent with inflammatory myofibroblastic tumour	
Prominent neutrophilic inflammation	
Necrotizing vasculitis	
Prominent necrosis	
Primarily granulomatous inflammation	
Pathologic features of macrophage/histiocytic disorder	
Known diagnosis of the following:	
Multicentric Castleman's disease	
Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present)	
Hashimoto thyroiditis (if only the thyroid is affected)	

Step 3. Inclusion criteria: domains and items¶	
Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining**	0–16, as follows:
	Assigned weight is 0 if the IgG4+:IgG+ ratio is 0%–40% or indeterminate and the number of IgG4+ cells/hpf is 0–9.‡‡ Assigned weight is 7 if: (1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+cells/hpf is 0–9 or indeterminate or (2) the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is ≥10 or indeterminate. Assigned weight is 14 if: (1) the IgG4+:IgG+ ratio is 41%–70% and the number of IgG4+ cells/hpf is ≥10 or (2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50. Assigned weight is 16 if the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is ≥51.
Serum IgG_4 concentration	
Normal or not checked	0
>Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
≥>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual and submandibular glands	

No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney	
Not checked or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+10
Retroperitoneum	
Not checked or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8
Step 4: Total inclusion points	
A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20	



IgG4-RD

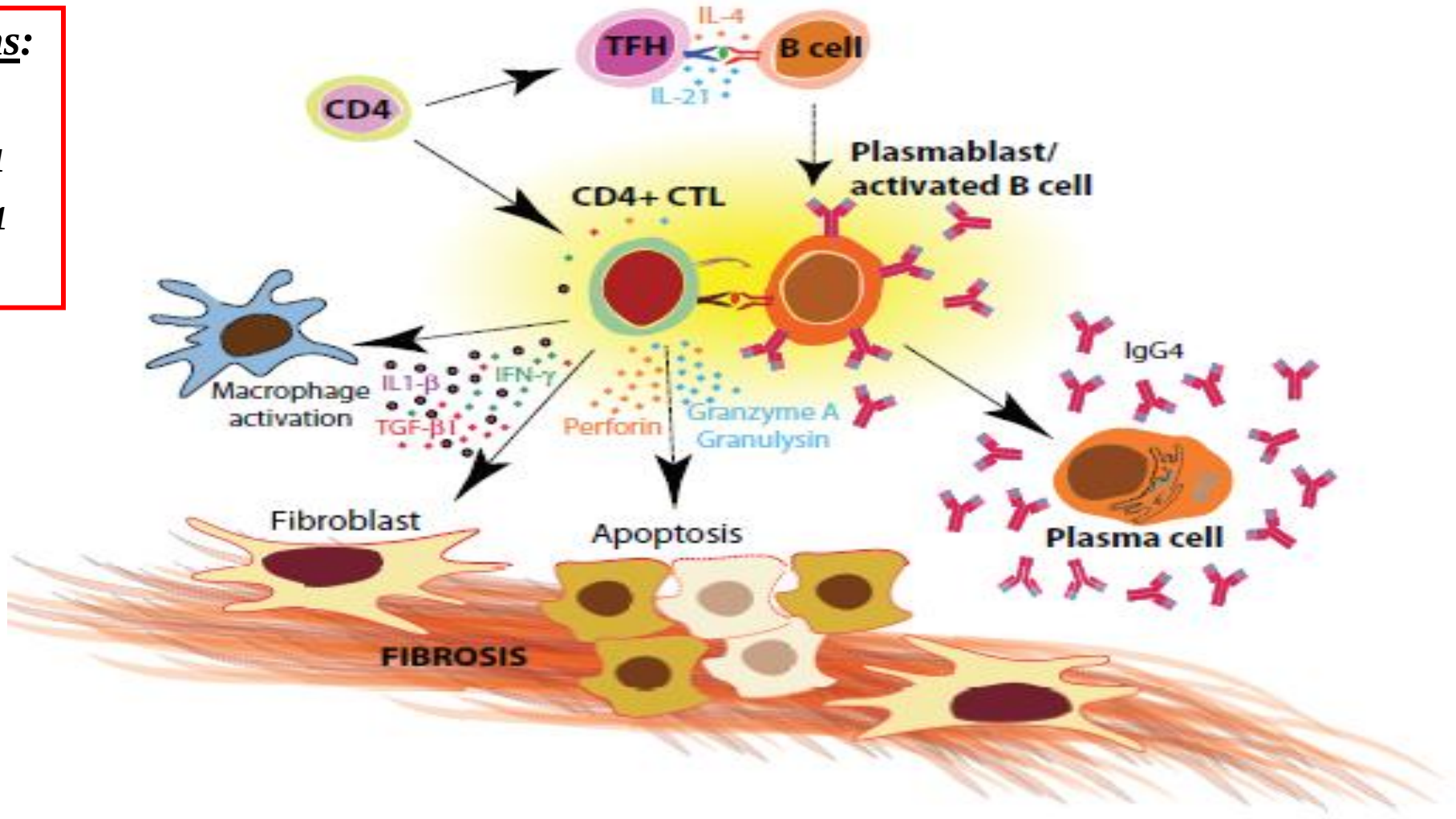


- IgG4-Related Diseases
- IgG4-Related Kidney Disease
- Clinical Features
- Laboratory Features
- Imaging Features
- Pathological Features
- **Pathophysiological Mechanisms**
- Treatment

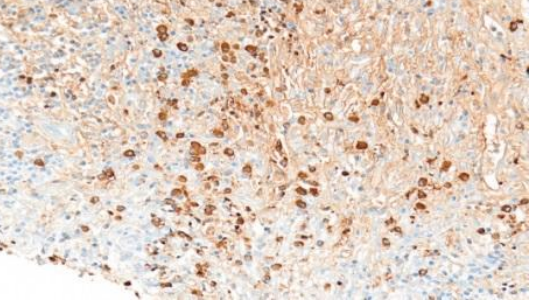
Pathophysiological mechanisms

Self-antigens:

- ***Galectin-3***
- ***Annexin-A11***
- ***Laminin-511***
- ***Prohibitin***



Autoimmunity (2017) **50**: 19-24



IgG4-RD

- IgG4-Related Diseases
- IgG4-Related Kidney Disease
- Clinical Features
- Laboratory Features
- Imaging Features
- Pathological Features
- Pathophysiological Mechanisms
- **Treatment**

First-line treatment: steroids !

Table 2. Treatment and follow-up of IgG4-TIN

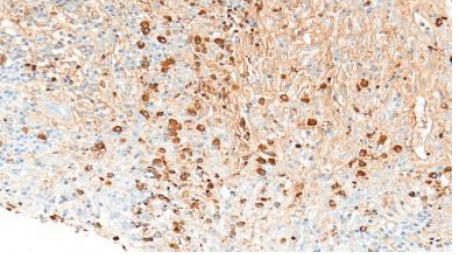
Pt No.	Treatment	SCr at Bx	f/u SCr	Response	Length of f/u (months)
1	Pred	3.2 to 3.8	2.2	Yes; initial response and then relapse with steroid withdrawal	10
2	None	1.6	1.6	NA; stable incr SCr	9
3	Pred	1.9	1.6	Yes	5
5	None	1.7	1.6	NA; stable incr SCr	1
6	Pred	2.5	2.8	No	6
7	Pred	3.0	1.5	Yes	12
8	Pred	4.2	1.5	Yes	6
9	Pred	2.0	1.5	Yes	3.5
10	Pred/MMF/dialysis	5.7	2.9	Yes	5
11	Pred/MMF	1.1	1	Stable normal SCr	6
12	Pred	3.4	2.1	Yes	19
13	Pred	3.8	1.4	Yes	3
14	Pred	6.3	1.2	Yes	2
15	Pred/dialysis	5.4	ESRD	No	1
16	Pred	8.5	2.3	Yes	3
18	Pred	0.9	1.1	Stable Scr	14
19	Pred/MMF	2.6	1	Yes	36
20	Surgery only	1.4	1	Yes	84
21	Pred	2.8	1.3	Yes	13
22	Pred	3.3	1.5	Yes	4
23	None	4.4	4.4	NA; stable incr SCr	17
24	Pred	5.7	3.3	Yes	6
27	Pred	3.2	1.5	Yes	1
30	Pred	6.6	2.5	Yes	1.1
31	None	0.9 to 1.1	1.8	NA; incr SCr	20
33	None	0.9 to 1.1	1.2 to 1.8	NA; incr SCr	64
34	Pred	3.0	1.0 to 2.9	Yes; initial response and then relapse with steroid withdrawal	40

f/u, follow-up; Pred, prednisone; MMF, mycophenolate mofetil; Bx, biopsy; SCr, serum creatinine; Incr, increased.

JASN (2011) **22**: 1343-1352, *Lancet* (2015) **385:** 1460-1471, *Arthritis Rheumatol* (2015) **67**: 1688-1699

Treatment: YES, steroids! But …

- Good response in inflammatory stage
- Importance of fibrosis extension
- Recurrent or refractory cases common
- Adverse effects

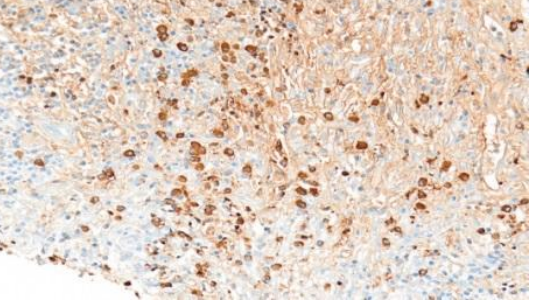


IgG4-Related Diseases

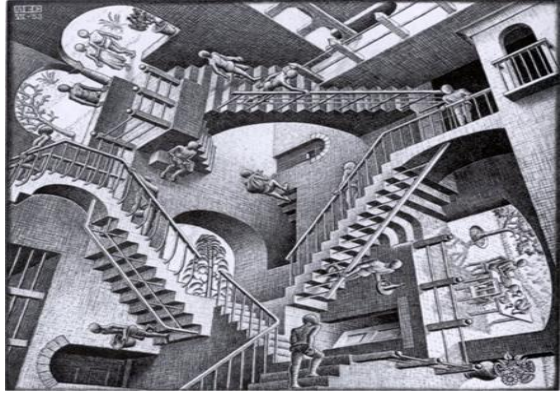
Question 4

What is your second-line treatment in relapsing IgG4-RD?

- A second course of steroids
- Anti-CD20 agents
- DMARDS



Treatment



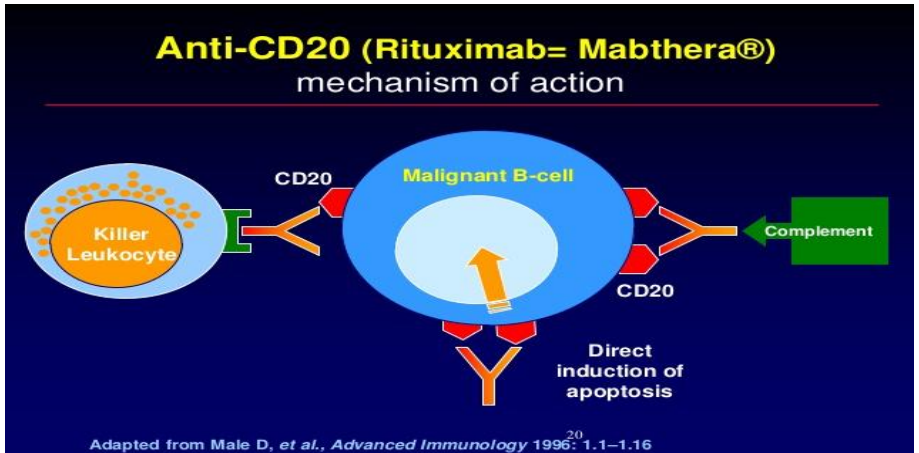
SO WHAT … ?

- **Azathioprine**
- **Mycophenolate mofetil**
- **Methotrexate**
- **Cyclophosphamide**
- ***Rituximab***

EXTENDED REPORT

Rituximab for IgG4-related disease: a prospective, open-label trial

Mollie N Carruthers,[1] Mark D Topazian,[2] Arezou Khosroshahi,[3] Thomas E Witzig,[4] Zachary S Wallace,[1] Philip A Hart,[2] Vikram Deshpande,[5] Thomas C Smyrk,[6] Suresh Chari,[2] John H Stone[1]

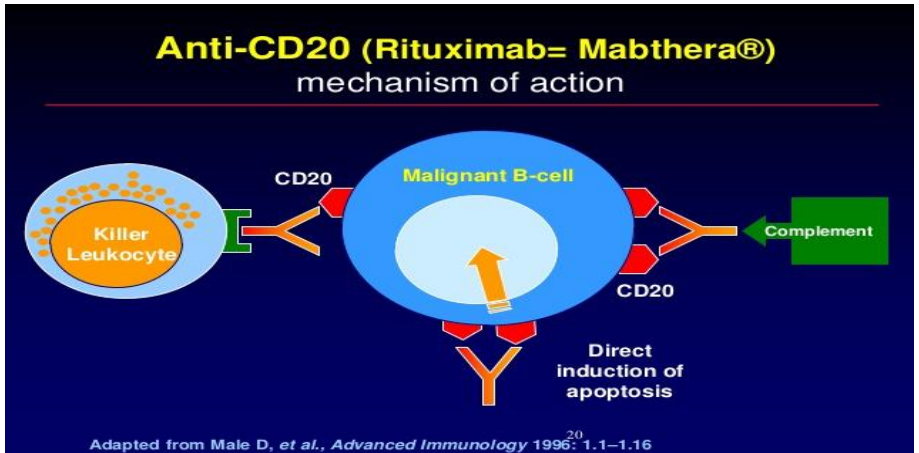


Ann Rheum Dis (2015) **74:** 1171-1177

Original article

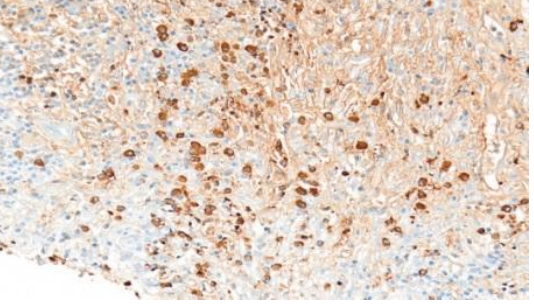
Predictors of disease relapse in IgG4-related disease following rituximab

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]

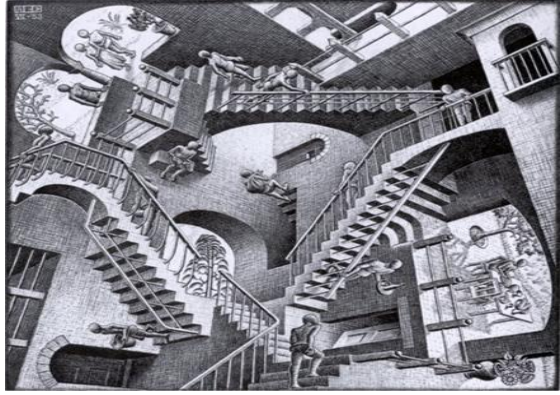


37% relapse !

Rheumatology (2016) **55:** 1000-1008



Treatment: our experience …



J Nephrol (2016) 29:487–493
DOI 10.1007/s40620-016-0279-4

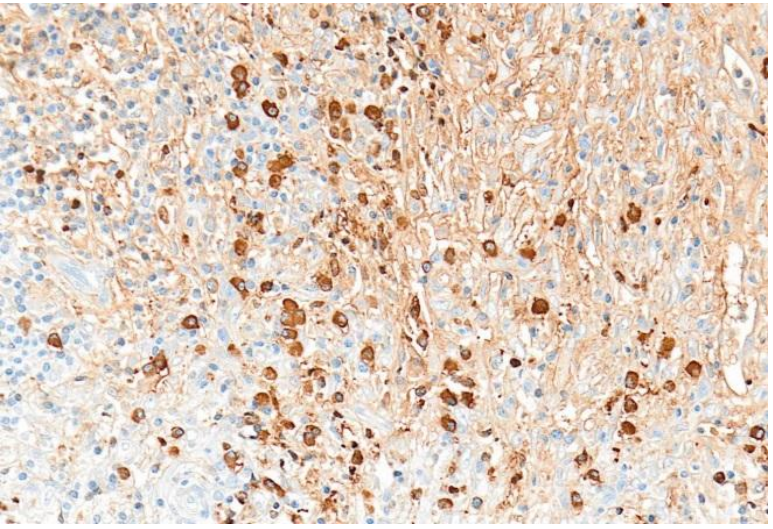
REVIEW

IgG4-related nephropathy

Giacomo Quattrocchio[1,2] · Dario Roccatello[1,3,4]

IgG4-related kidney disease: the effects of a Rituximab-based immunosuppressive therapy

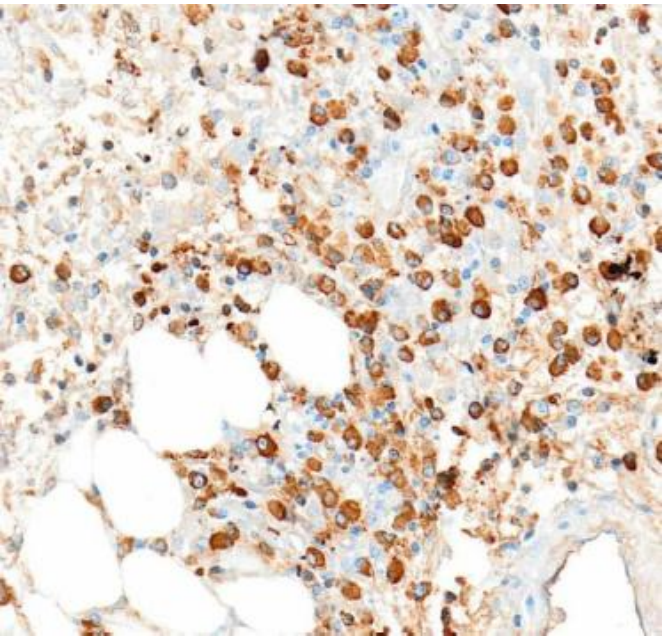
Giacomo Quattrocchio[1], Antonella Barreca[2], Andrea Demarchi[3], Laura Solfietti[4], Giulietta Beltrame[1], Roberta Fenoglio[1], Michela Ferro[1], Paola Mesiano[1], Stefano Murgia[1], Giulio Del Vecchio[1], Carlo Massara[1], Cristiana Rollino[1] and Dario Roccatello[1,4]



Oncotarget (2018) **9:** 21337-21347

Long-term effects of intensive B cell depletion therapy in severe cases of IgG4-related disease with renal involvement

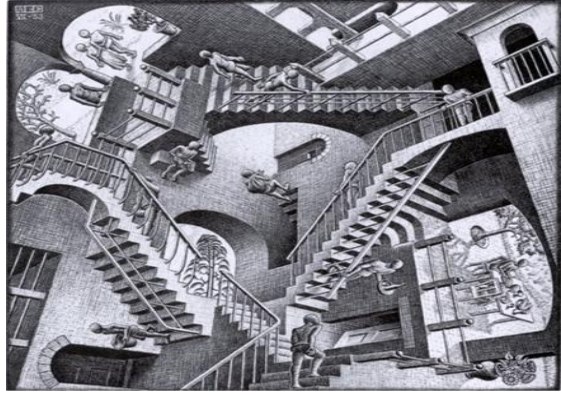
Giacomo Quattrocchio [1] · Antonella Barreca [2] · Andrea Demarchi [3] · Roberta Fenoglio [1] · Michela Ferro [1] · Giulio Del Vecchio [1] · Carlo Massara [1] · Cristiana Rollino [1] · Savino Sciascia [1] · Dario Roccatello [1]



Immunol Res (2020) **68:** 340-352

Two is better than one !!

IgG4-RKD



Intensive short-term treatment with rituximab, cyclophosphamide and methylprednisolone pulses induces remission in severe cases of SLE with nephritis and avoids further immunosuppressive maintenance therapy

Dario Roccatello, Savino Sciascia, Daniela Rossi, Mirella Alpa, Carla Naretto, Simone Baldovino, Elisa Menegatti, Rita La Grotta and Vittorio Modena

NDT (2011) **26**: 3987-3992

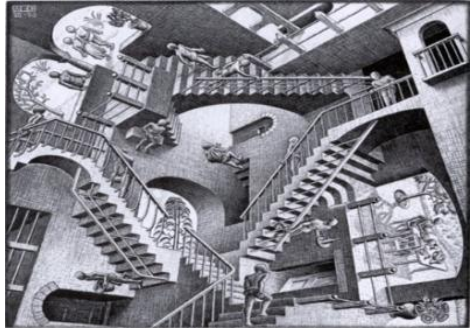
A Prospective Study on Long-Term Clinical Outcomes of Patients With Lupus Nephritis Treated With an Intensified B-Cell Depletion Protocol Without Maintenance Therapy

Dario Roccatello[1], Savino Sciascia[1], Carla Naretto[1], Mirella Alpa[1], Roberta Fenoglio[1], Michela Ferro[1], Giacomo Quattrocchio[1], Elena Rubini[1], Elnaz Rahbani[1] and Daniela Rossi[1]

Kidney Int Rep (2021) **6**: 1081-1087

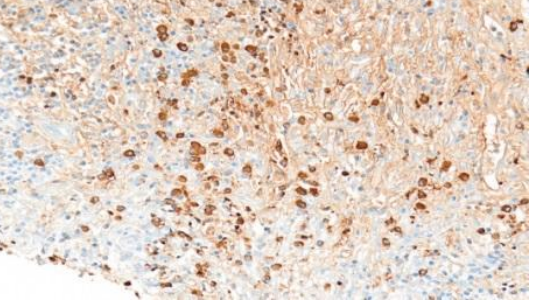
Intensified immunosuppressive treatment

Rituximab, cyclophosphamide, steroids



Rituximab	2° day	8° day	15° day	22° day
	200 mg/m2	375 mg/m2	375 mg/m2	375 mg/m2
Cyclophosphamide	4° day	17° day		
	750 mg	750 mg		
i.v. Methylprednisolone	1° day	4° day	8° day	
	15 mg/Kg	15 mg/Kg	15 mg/Kg	
Oral Prednisone	days 1-15	50 mg		
	days 16-30	37,5 mg		
	days 31-45	25 mg		
	days 46-52	20 mg		
	days 53-59	15 mg		
	days 60-66	10 mg		
	Since day 67	5 mg		

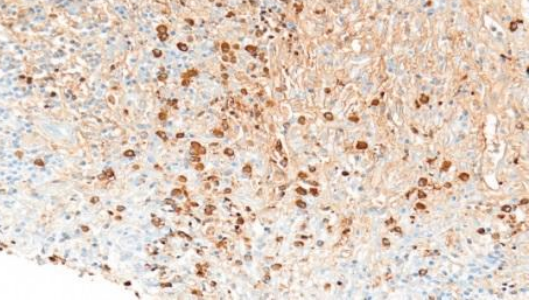
❖ **Rituximab 375 mg/m2 after 1 and 2 months following the last weekly infusion**



IgG4-RKD patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yr)	74	70	82	54	73
Sex	Male	Male	Male	Male	Female
IgG4-RKD	TIN	TIN	TIN	RPF	RPF

Immunol Res (2020) **68:** 340-352



IgG4-RKD patients
follow up at 48 months

- Substantial, persistent increase in eGFR

- Definite improvement in immunologic, radiologic and/or histological parameters

Immunol Res (2020) **68:** 340-352

IgG4-RKD patients: *Lab*

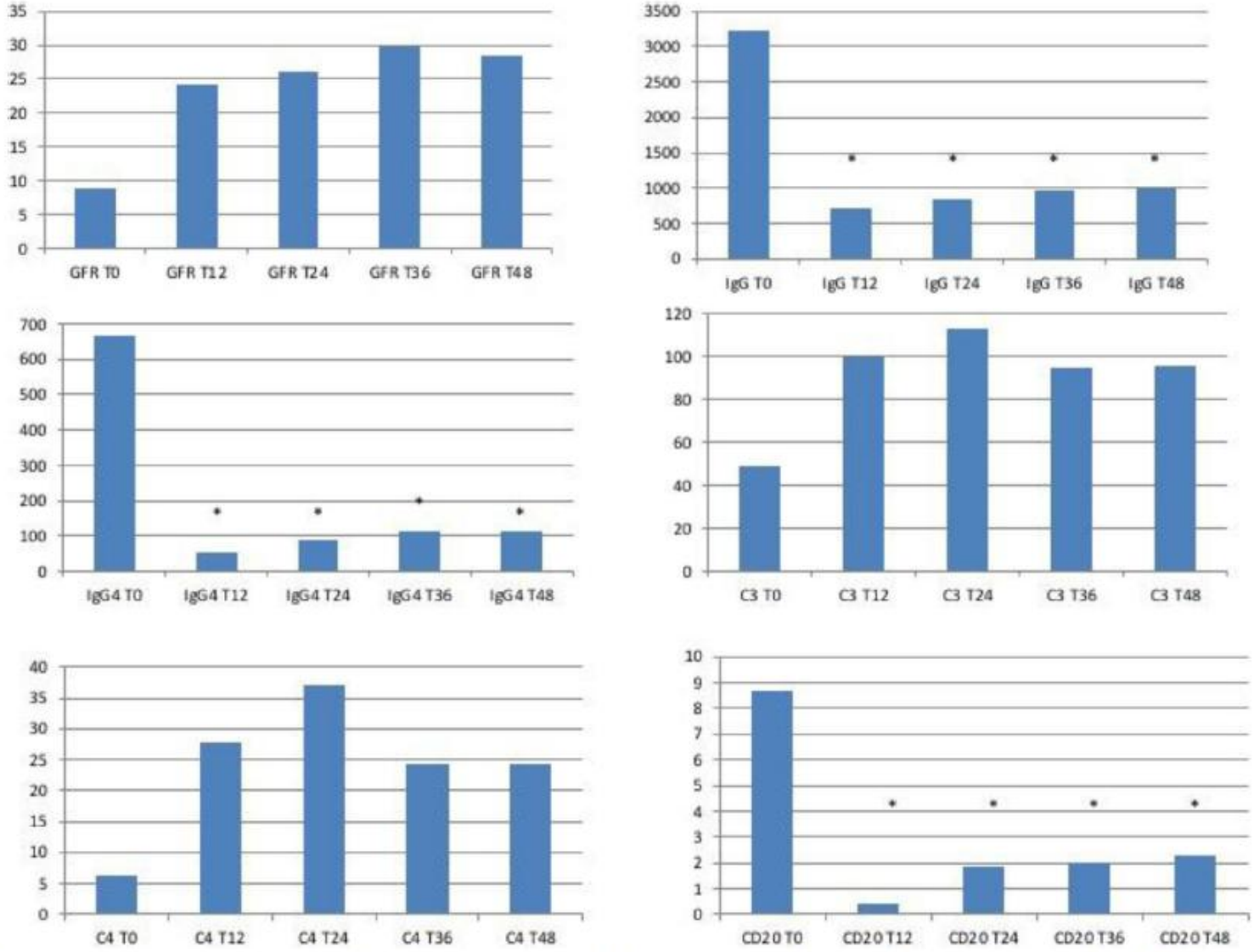
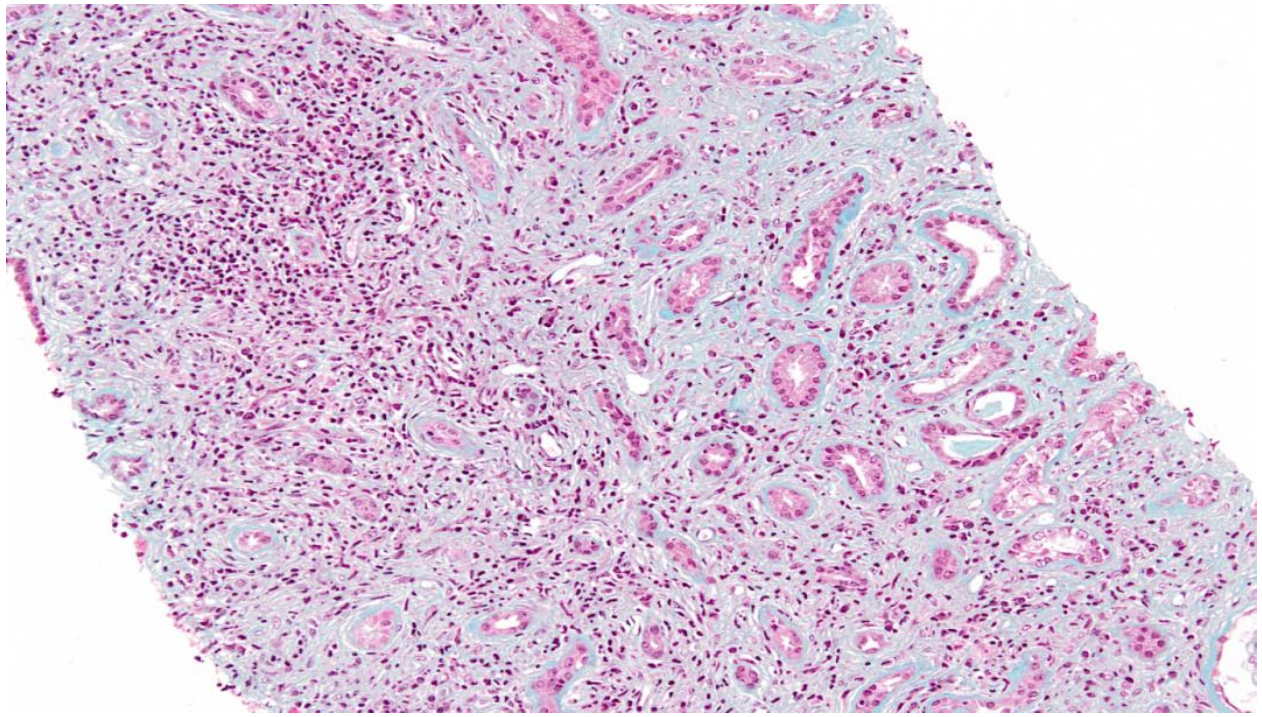


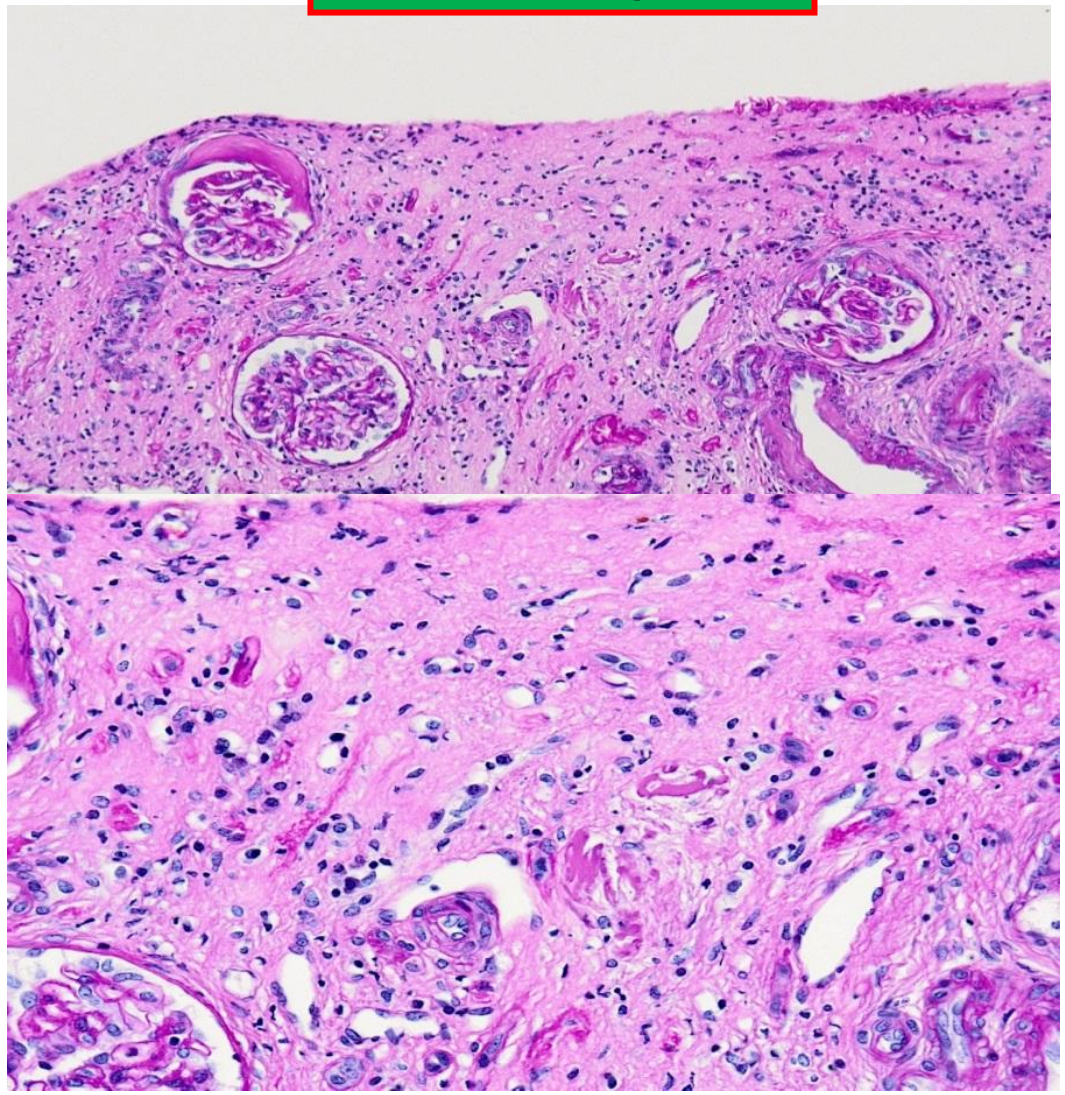
Fig. 1 Laboratory parameters. GFR, IgG, IgG4, C3, C4, % of CD20+ at T0 and yearly up to 4 years of follow-up. eGFR, glomerular filtration rate (ml/min); CD20+ are expressed as % of total lymphocytes; T, time as expressed in months

IgG4-RKD patients: *Histology*

Before Tx



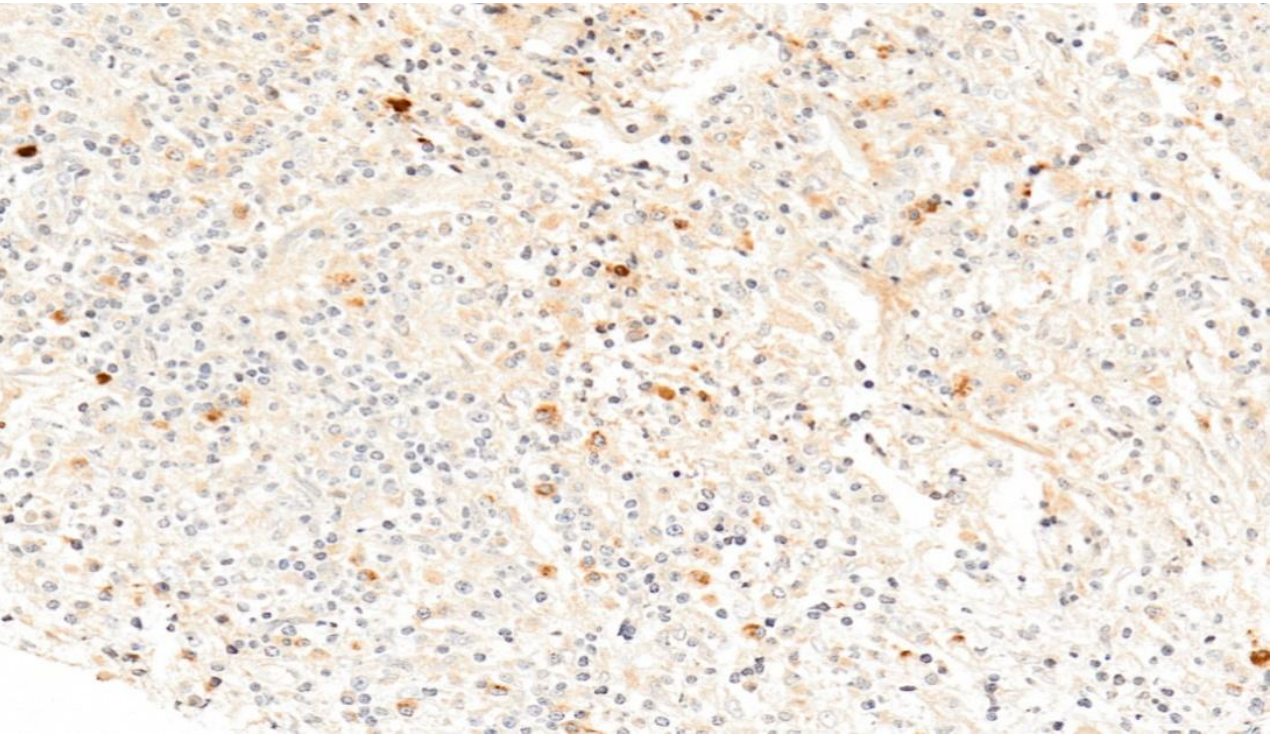
After 1 year



CELLULAR INFILTRATE AND FIBROSIS

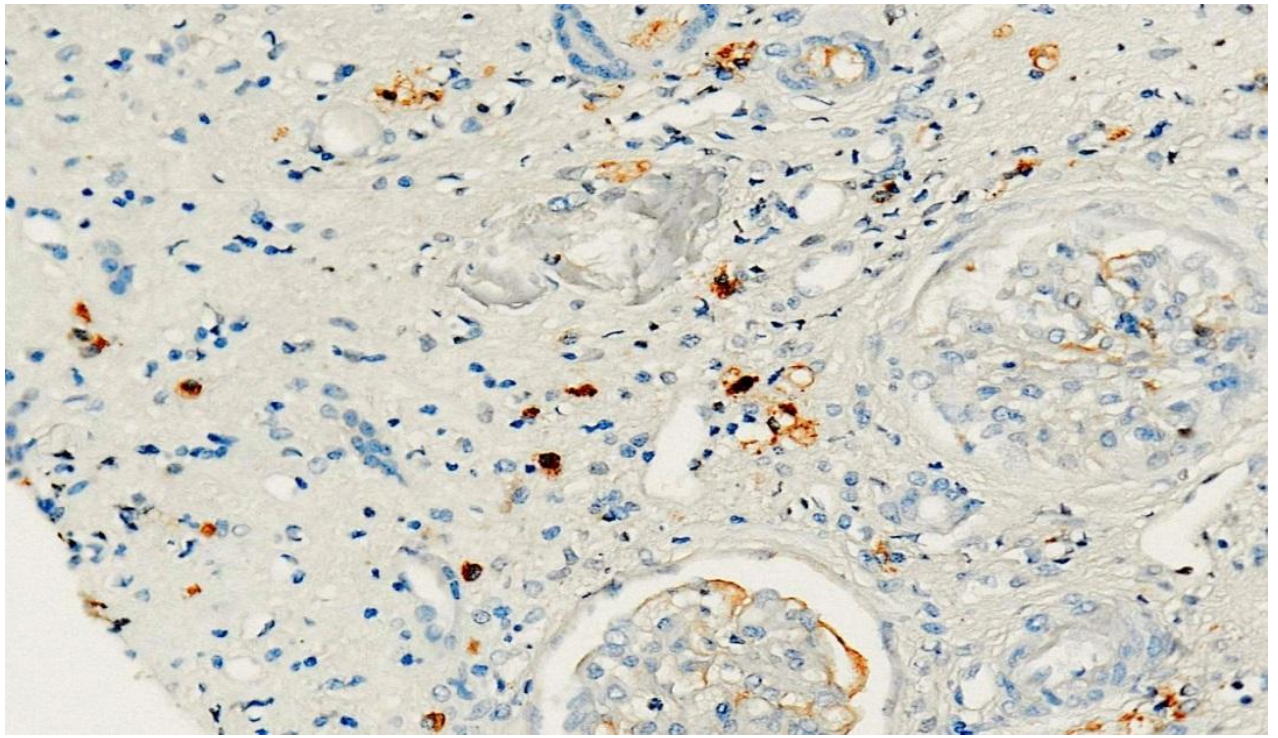
IgG4-RKD patients: *Histology*

Before Tx



IgG4+/IgG+ plasma cells 40%

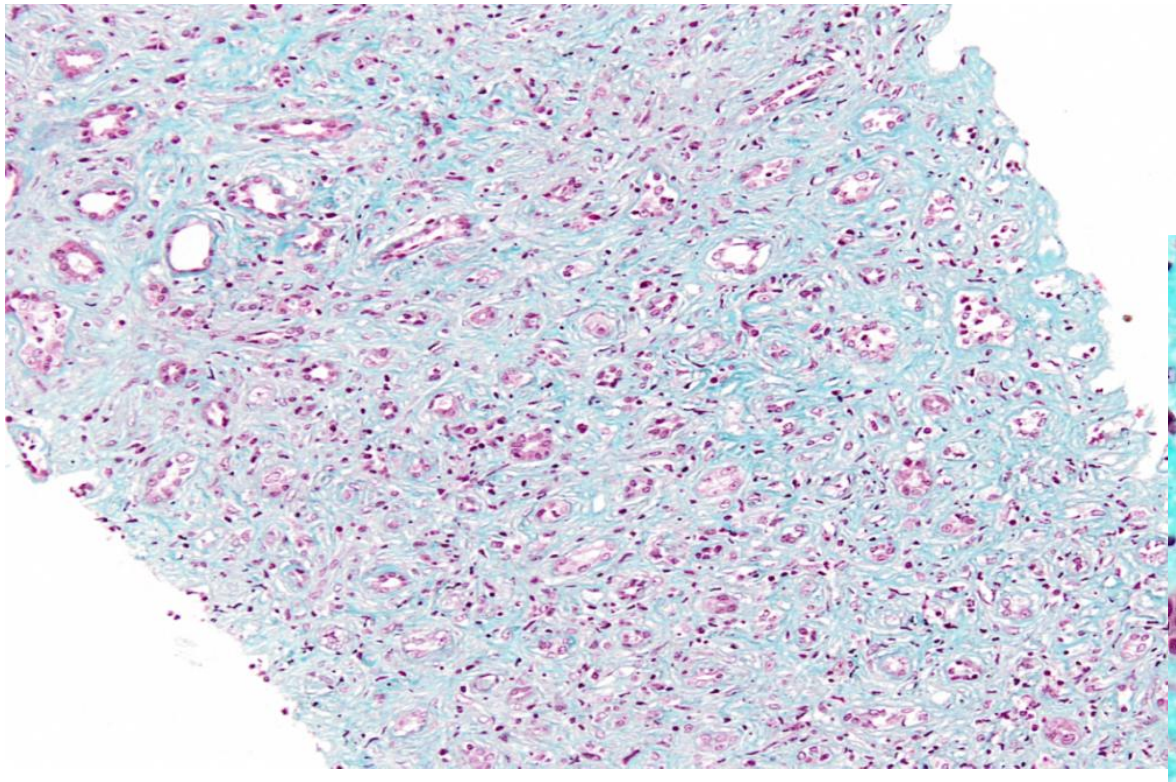
After 1 year



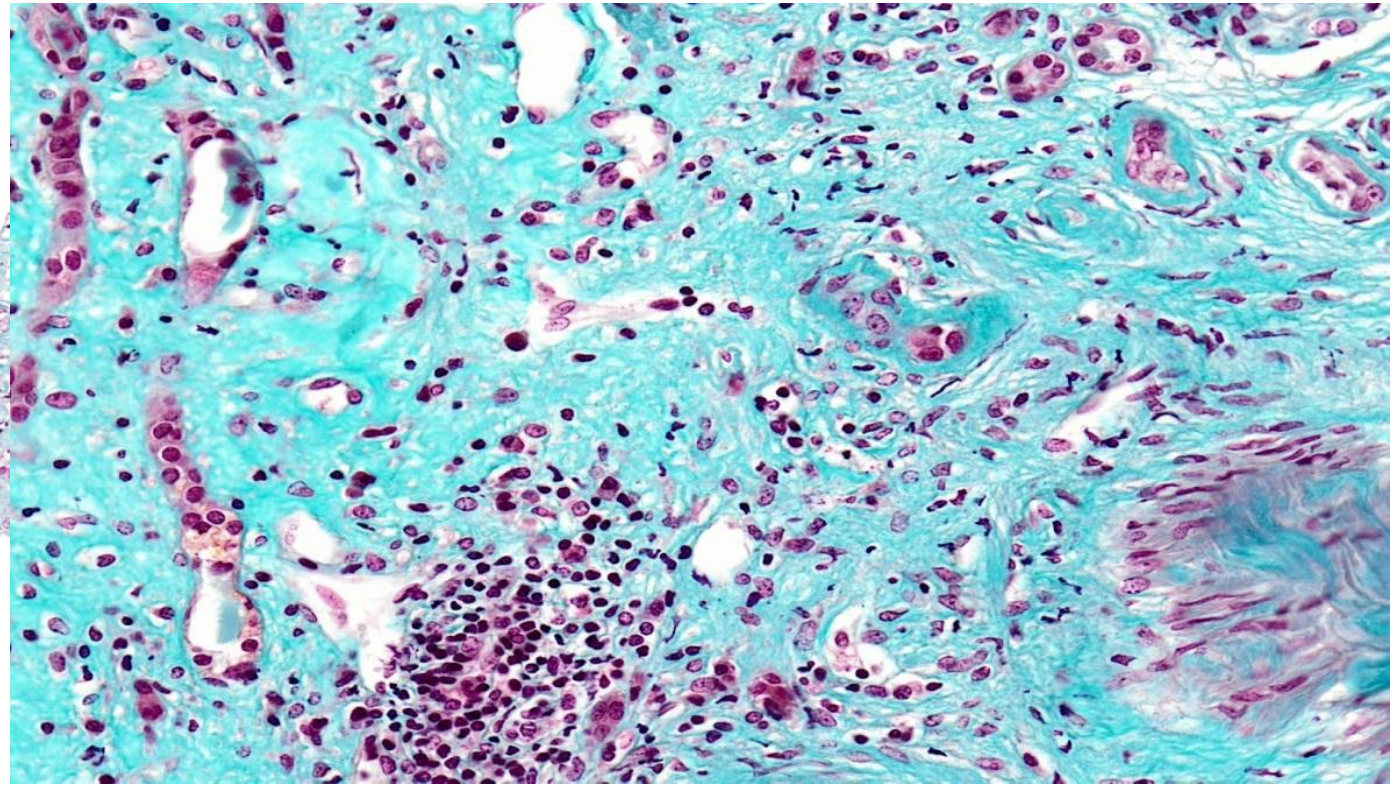
IgG4+/IgG+ plasma cells 4%

IgG4-RKD patients: *Histology*

Before Tx



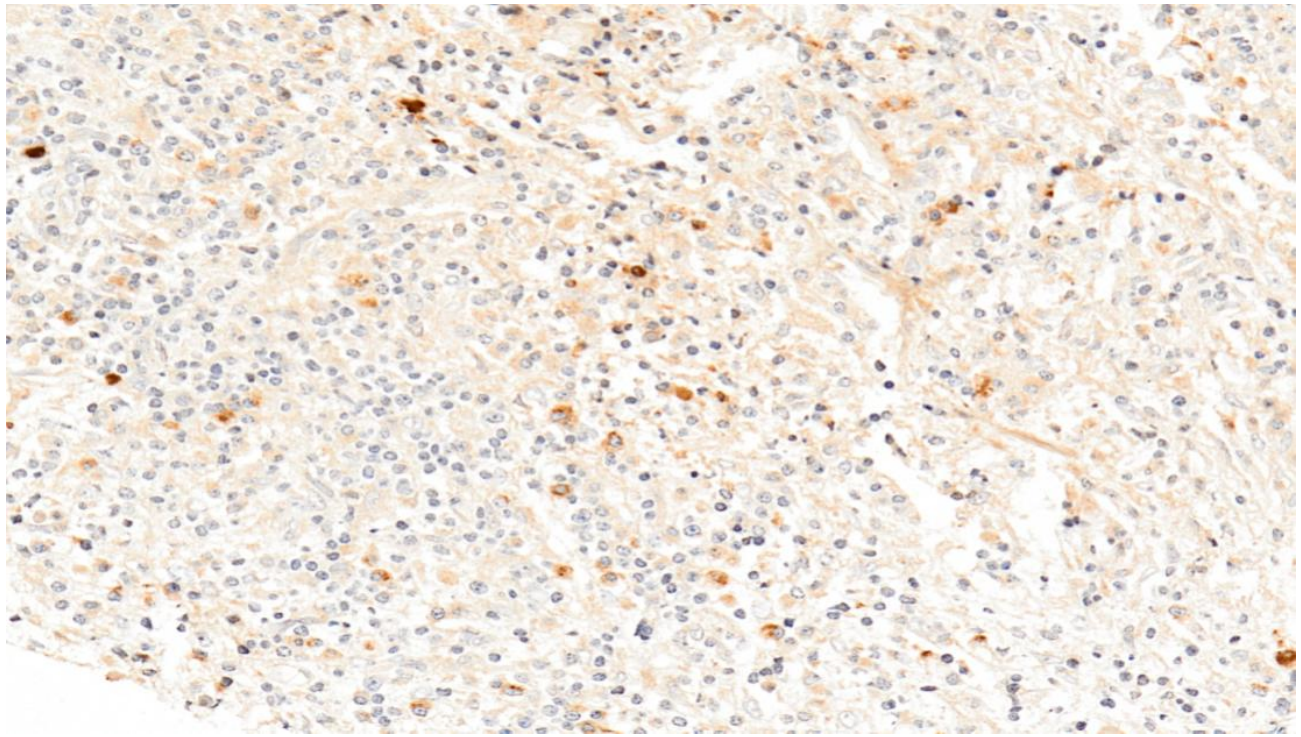
After 1 year



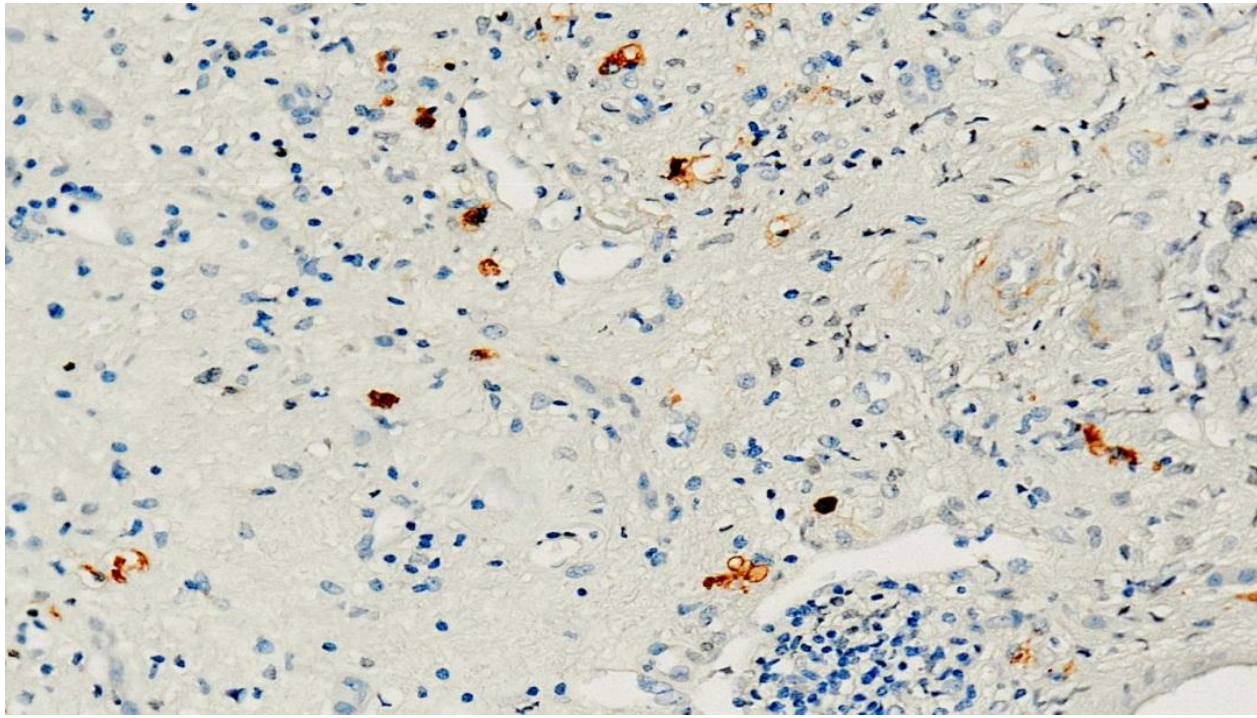
CELLULAR INFILTRATE AND FIBROSIS

IgG4-RKD patients: *Histology*

Before Tx



After 1 year

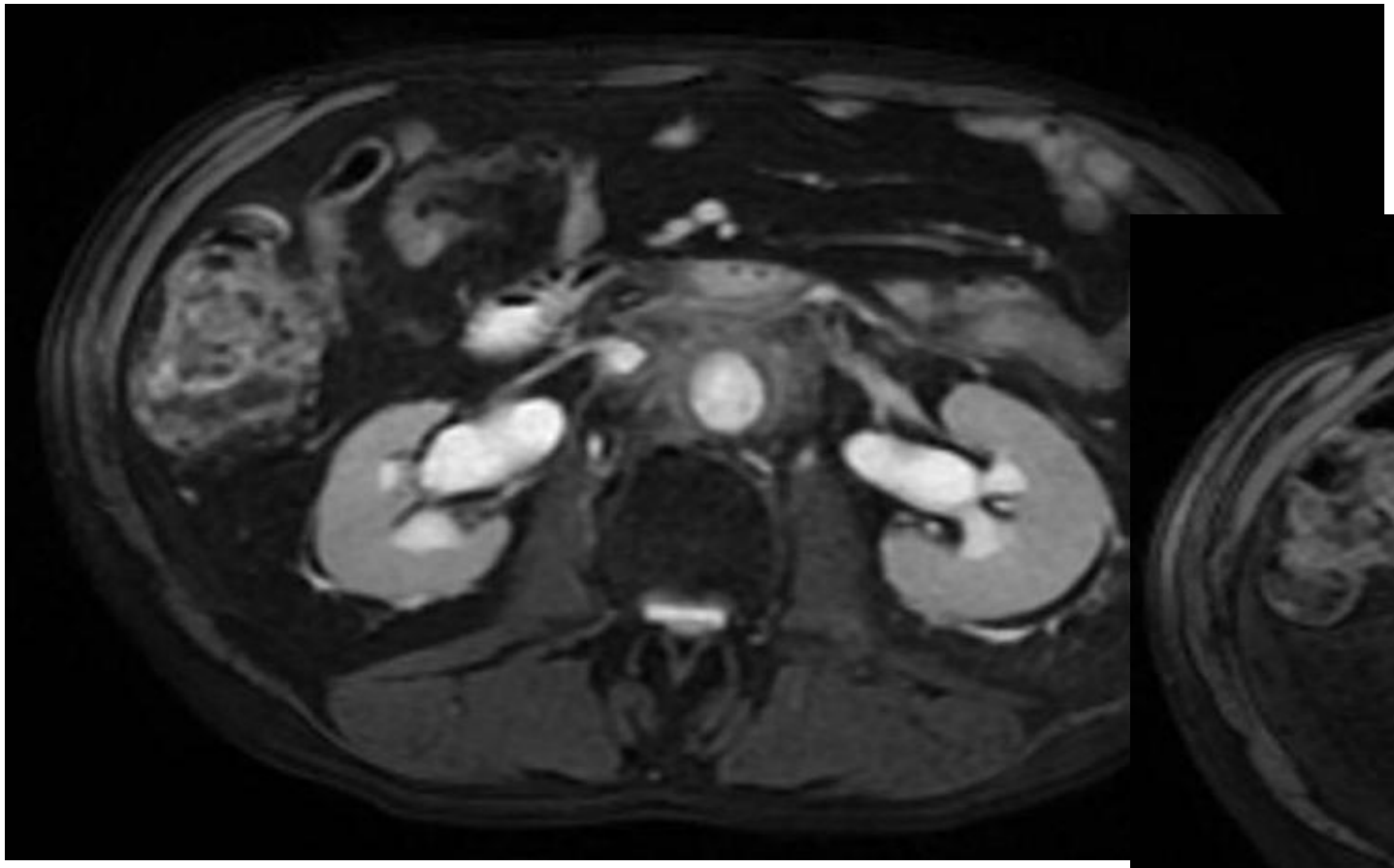


IgG4+/IgG+ plasma cells 60%

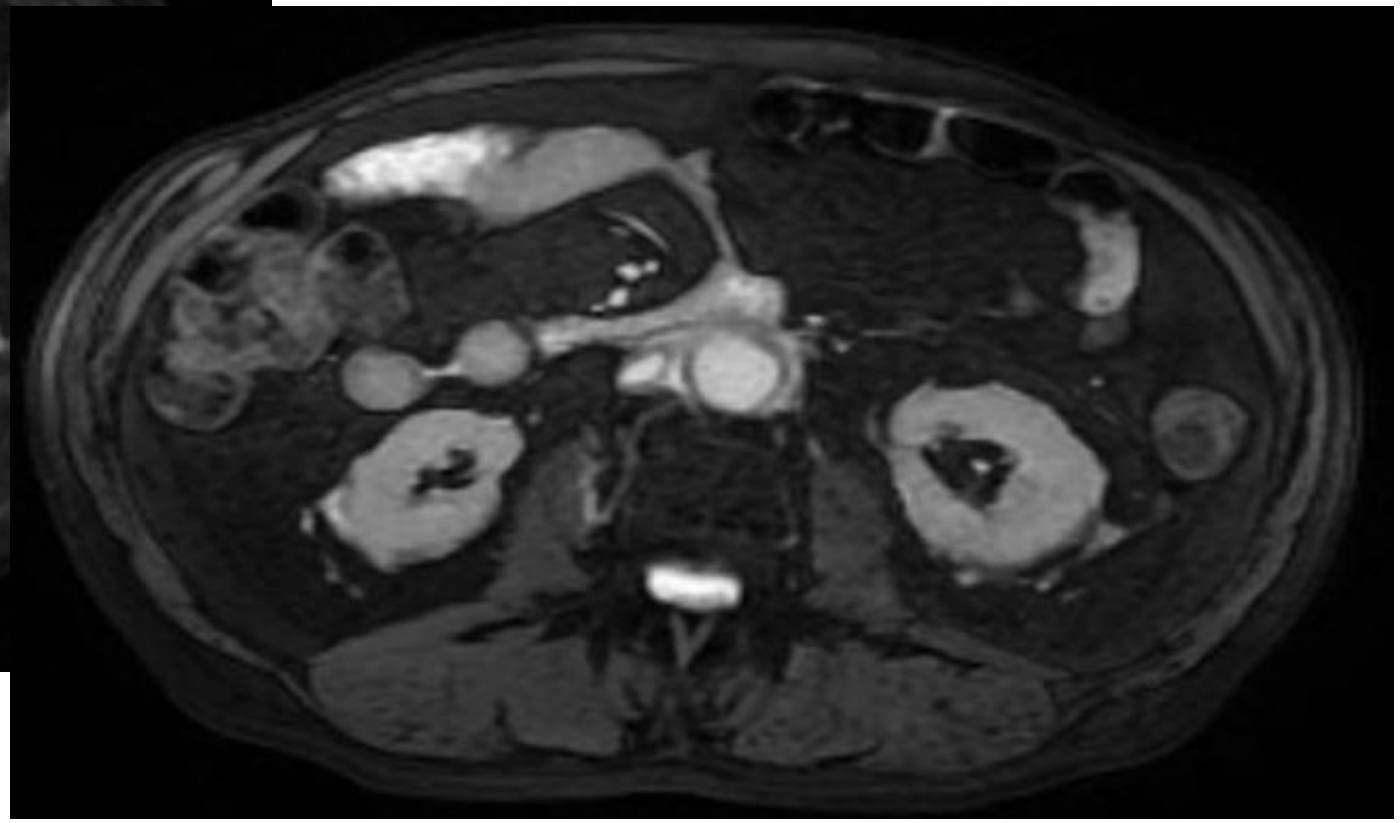
IgG4+/IgG+ plasma cells 2%

IgG4-RKD patients: *Radiology*

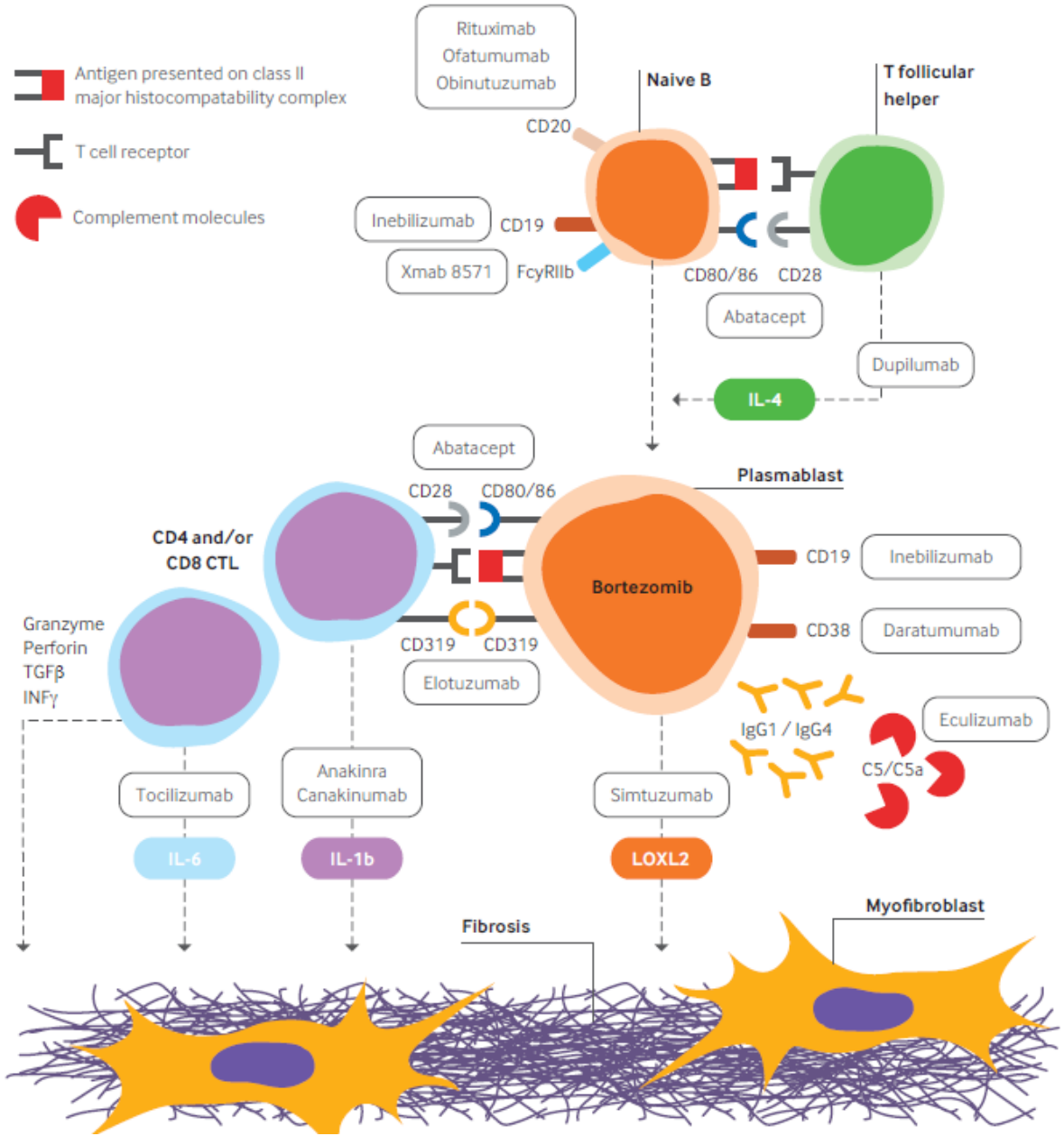
Before Tx



After 5 months



IgG4-RD: *pathogenetic mechanisms*



BMJ 2020

IgG4-RD: *potential targeted therapies*

Table 3 | Established, emerging, and novel potential biological therapies for IgG4 related disease

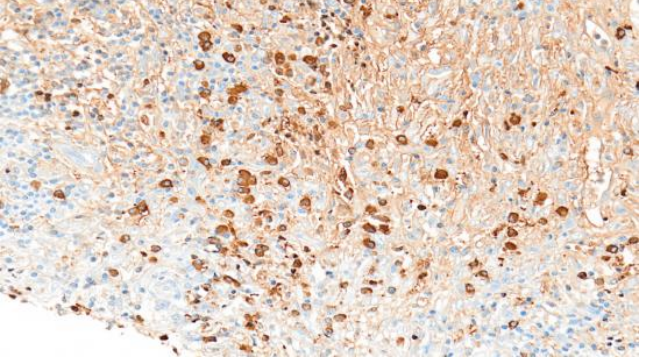
Target	Mechanism of action	Biological agent	Development stage	Trial status
B cells[41 120 134-136 154-159]	B cell depletion mediated by targeting CD20+ cells	Rituximab	Open label, prospective clinical trial	Completed
		Ofatumumab	-	-
		Obinutuzumab	-	-
	B cell depletion mediated by targeting CD19+ cells	Inebilizumab	Phase IIb, prospective, randomized, blinded trial	Starting
	Plasmablast and plasma cell depletion by targeting CD38+ cells	Daratumumab; isatuximab	-	-
	Autoreactive plasma cell depletion by targeting proteasome degradation	Bortezomib	Case report	-
	B cell inhibition mediated by co-ligation of CD19 and FcγRIIb	XmAb5871	Open label, prospective clinical trial	Completed
T cells[158]	Prevention of CD28 mediated T cell activation by targeting CD80 and CD86 co-stimulatory molecules on antigen presenting cells	Abatacept	Open label, prospective clinical trial; case report	Enrolling
B and T cells[43 158]	Depletion of plasmablasts, CD4+ CTLs, and CD8+ CTLs mediated by targeting CD319/SLAMF7	Elotuzumab	-	-
Complement[83]	Inhibition of complement activation by targeting C5 and C5a/C5aR pathways	Eculizumab; avacopan	-	-
Cytokines[43 66 142-145 160 161]	Interleukin 1 blockade	Anakinra; canakinumab	-	-
	Interleukin 6 blockade	Tocilizumab	-	-
	Interleukin 4 and interleukin 13 blockade	Dupilumab	Case report	-
	Tumor necrosis factor α	Infliximab	Case report	-
Fibrosis[41]	Disrupting extracellular matrix by targeting LOXL2	Simtuzumab	-	-

CTL=cytotoxic T lymphocyte; LOXL2= lysyl oxidase homologue 2.

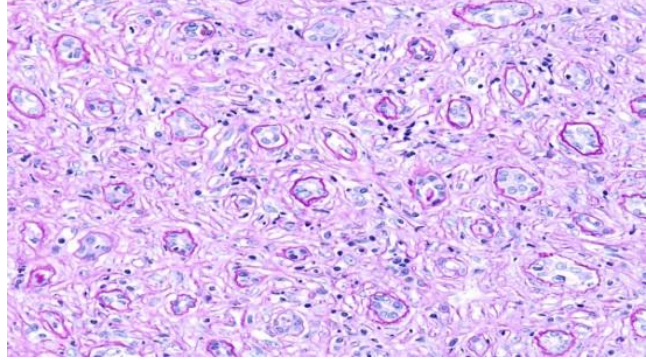
BMJ 2020

TAKE HOME MESSAGES

1. *IgG4-RDs are rare, protean conditions*
2. *Awareness of this diseases is necessary for an early diagnosis*
3. *In IgG4-RKD Acute/Progressive renal failure and/or proteinuria and/or radiologic lesions are «red flags»*
4. *Treatment is still «a work in progress»*
5. *Our intensified immunosuppressive protocol seems to be effective and relatively safe*

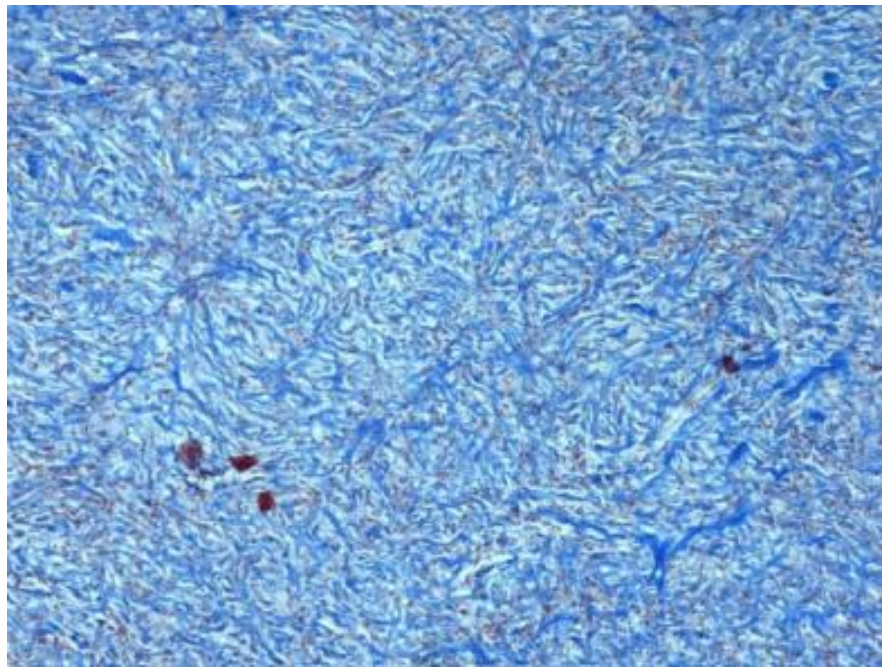


IgG4-RDs



A black crow flying through ~~the dark night~~

A black crow flying through <u>a bright light</u>



Thank you for your attention!

Next Webinars

ERA/ERKNet Advanced Webinars on Rare Kidney Disorders

Date: **30 Nov 2021**

Speaker: **Giacomo Quattrocchio**

Topic: **IgG4 related diseases**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **07 Dec 2021**

Speaker: **Joseph Flynn**

Topic: **Hypertension**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **18 Jan 2022**

Speaker: **Michal Maternik**

Topic: **PUV**

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