Post-Transplant Glomerulonephritis

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- GN continues to be one of the main causes of **end-stage kidney disease** (ESKD) worldwide, with an incidence rating from 10.5% to 38.2% and a prevalence rating from 17.6% to 53.5%.
- Though recurrent GN was previously considered to be a minor contributor to graft loss, several studies have shown that about **10–20% of patients** with a glomerular disease develop **recurrence after renal transplantation** and 50% of them show a graft loss on long term follow up. On the other hand, propensity for GN to recur seems to depend on the graft survival increase

- The challenges in diagnosis of post transplantation GN are numerous and include
- (1) misdiagnosis or mislabeling of native kidney disease,
- (2) lack of a unified approach in using diagnostic tools for the diagnosis of recurrent GN, and
- (3) difficulties in differentiating GN from drug toxicity and alloantigen-dependant chronic immunologic damage to the transplant kidney

Classification of recurrent glomerular diseases

Clinical classification

1. True recurrence: Native and recurrent disease are the same confirmed by histology

2. Transplant glomerulopathy with unknown primary disease: Transplant renal biopsy confirming disease without histologic confirmation of native kidney disease.

3. De novo disease: Occurrence of new disease in the transplant kidney.

Histologic classification

- 1. Recurrence of primary glomerulonephritides (recurrent FSGS, MPGN, IgAN, MN)
- 2. Recurrence of secondary glomerulonephritides (SLE, Henoch Schönlein purpura, HUS/TTP, crescentic GN, anti-GBM disease)
- 3. Recurrence of metabolic or systemic disease (diabetic nephropathy, oxalosis, amyloidosis, Fabry disease, scleroderma, cystinosis, fibrillary GN)
- 4. De novo diseases (anti-GBM disease in Alport syndrome, MN in patients with polycystic kidney disease)

Limitations in the diagnosis of recurrent glomerulonephritides

Native kidney disease

- unknown in many patients with ESRD
- black patients are often labeled to have hypertensive nephrosclerosis
- difficulties in determining the cause of native kidney disease when presenting at a late stage
- difficulties in differentiating primary versus secondary FSGS

Limitations in the diagnosis of recurrent glomerulonephritides

Indication for posttransplantation renal biopsy

- lack of unified approach in diagnosing patients with posttransplantation proteinuria, hematuria, and renal dysfunction
- non-uniform indications for biopsy: protocol versus clinical renal disease
- immunofluorescence and electron microscopic examinations not routinely performed on all transplant biopsies

Limitations in the diagnosis of recurrent glomerulonephritides

Diagnosis of post-transplantation GN

- lack of histologic features of FSGS in early stage of recurrence
- difficulties in differentiating primary versus secondary FSGS
- difficulties in differentiating MPGN versus allograft glomerulopathy
- difficulties in differentiating primary versus secondary IgAN
- difficulties in differentiating the cause of HUS/TTP: primary/drug toxicity/humoral rejection

- prevalence of GN as the cause of ESRD is 10 and 25%,
- higher prevalence in children and white patients.
- children is related to lower prevalence of diabetes as the cause of ESRD in this population as opposed to adults.
- Lower prevalence of reported GN in black patients is possibly related to paucity of information on renal biopsy in this population as well as higher prevalence of hypertensive nephrosclerosis and diabetic nephropathy in this population.
- 8.4% of patients lost their grafts as a result of recurrent GN by 10 yr after transplantation

Causes of graft failure 10 years after transplantation

- Death with a functioning graft
- Chronic rejection (CR)
- Recurrent disease
- Acute rejection

Risk of recurrence

- type of glomerulonephritis. For example, lupus nephritis recurs in fewer than 10% of cases and graft loss is uncommon, in contrast C3 glomerulopathy recurs in more than 80% of patients and graft loss is frequent
- Time since transplantation may be related to the duration of the graft exposure to the nephritogenic factors responsible for GN
- The recipients of human leukocyte antigen (HLA)-identical transplants promote graft survival with an increased risk of recurrence

strategies to reduce the risk of recurrence

- Bilateral native nephrectomy to eliminate persistent antigenic stimulation (x)
- Induction of disease remission before transplantation (?)
- Longest time on dialysis pre-transplantation (?)
- Anti-GBM disease, where a negative serological test for at least 6 months before kidney transplantation might be associated with low risk of recurrence

Usually recur > 50 %	
- Adverse effects (graft loss > 5%)	• 1ry Hemolytic Uremic Syndrome (HUS). • 1ry oxalosis • Dense deposit disease • Collapsing FSGS
- Little or no adverse effects	• DM • Systemic light chain disease
Commonly recur (5- 50 %)	
Adverse effects	• FSGS • MPGN I. • Anti-Neutrophilic-CytoplasmicAntibody(ANCA) diseases (Wegner'sgranulomatosis–microscopic polyarteritis) • Progressive systemic sclerosis • Sickle cell nephropathy
Little or no adverse effects	• IgA nephropathy • Henoch-schönlein purpura • Amyloidosis

Rarely recur (< 5%) - Adverse effects - Little or no adverse effects	• Anti-GBM • SLE • Fabry's disease
Recurrence reported (too few cases)	• Thrombotic Thrombocytopenic Purpura (TTP) • Adenosine phosphoribosyl transferase deficiency • Familial fibronectin glomerulopathy • Lipoprotein glomerulopathy
Never recur 0 % - Unique complications	• Hereditary nephritis/Alport's syndrome (Anti-GBM disease) • Congenital nephrosis(nephrotic syndrome)
- No unique complication	• Poly Cystic Kidney Disease (PCKD). • Osteo-onchodysplasia (nail-patella) • Acquired cystic disease • 2ry HUS(infection) • 2ry focal segmental glomerulosclerosis • Familial focal segmental glomerulosclerosis • Post-infectious acute GN

Table 2 Limitation in the diagnosis of recurrent glomerulonephritis

Native kidney disease
Unknown in many patients with ESRD
Unknown cause of native kidney disease when presenting at a late stage
Difficulties in differentiating primary *versus* secondary FSGS
Donor kidney disease
Transmitted glomerulonephritis and glomerulopathy
Indication for renal graft biopsy
No uniform indication of biopsy for deteriorating graft:
Proteinuria, haematuria and renal dysfunction
Non-uniform indications for biopsy:
Protocol *versus* clinical renal disease
Lack of immunofluorescence and electron microscopic examinations:
Not routinely performed on all transplant biopsies
Diagnosis of post-transplantation GN
Lack of histologic features of FSGS in early stage of recurrence
Difficulties in differentiating primary *versus* secondary FSGS
difficulties in differentiating MPGN *versus* transplant glomerulopathy
Difficulties in differentiating primary *versus* secondary IgAN
Difficulties in differentiating the cause of HUS/TTP:
Primary *versus* drug toxicity *versus* humoral rejection

- 59% of biopsies with recurrent or de novo glomerulonephritis had superimposed pathologic findings of chronic allograft nephropathy

- Implantation baseline graft biopsy often shows transmitted subclinical glomerulonephritis. Transmitted mesangial IgA deposition compatible with IgA nephropathy is frequently noted in Japanese living related donors

Second litreature

- De novo GN appear to have poorer prognosis than the recurrent type
- recurrent GN is considered to be the third most common cause for graft loss 10 years after kidney transplantation
- The risk of graft loss from recurrence was found to be increased from 0.6% during the first year post-transplant to 8.4% after 10 year of follow up
- Isografts (identical twins) have the highest recurrence rate

Type of glomerulonephritis	Clinical recurrence rate (% of recipients)	Rate of graft loss
FSGS	20–40	20
Membranous GN	10–30	50
MPGN type I	20–33	High
MPGN type II	67–100	34–66
Anti-GBM nephritis	<5	Can occur
ANCA-positive crescentic GN	0–20	8
IgA Nephropathy	7–30	3–16
Iopathic D– HUS	33–82	90

- Only 1ry **focal segmental glomerulosclerosis and MPGN** recur with sufficient frequency and aggressiveness to affect graft survival
- Diabetic glomerulopathy also may recur but with variable clinical effects, Eighty to 100 percent of diabetic transplant recipients develop histological changes of recurrent diabetic nephropathy **(DN).** The time of development of nephropathy may be as little as six years post-transplantation
- Recurrent GN is diagnosed by exclusion of donor-transmitted disease and de novo GN

- the clinical course and severity of recurrent glomerular disease often copies that of the patient's original disease, except for patients with **vasculitis and lupus nephritis**; these conditions usually controlled by transplantation immunosuppression.
- Focal segmental glomerulosclerosis (20%-50% recurrence rate) and dense deposit disease (50%-90% recurrence rates) have the worst prognosis and together constitute 55%-60% of all recurrent GN
- Membranous GN recurs in 29%- 50%, MPGN type I recurs in 20%-33%, and IgA nephropathy recurs in 58%, although with limited early (but increased later) clinical impact
- Diabetic glomerulopathy also may recur but with variable clinical effects, Eighty to 100 percent of diabetic transplant recipients develop histological changes of recurrent diabetic nephropathy (DN). The time of development of nephropathy may be as little as six years post-transplantation. However, the incidence of DN as a cause of graft failure is poorly studied and has been thought to be rare

Minimal change glomerulonephritis

- **Fourteen cases** of renal transplant recipients developing nephrotic syndrome with minimal glomerular abnormalities have been reported although the cases do not represent true recurrence of a disease
- The prognosis is variable and follow-up often very short but in some reports there is progression to renal failure
- It is notable that **re-biopsy** in two patients showed focal segmental glomerulosclerosis (**FSGS**)
- Not all of the reports included venography or other imaging to exclude renal vein thrombosis and drug-associated effects are impossible to rule out.

Focal and Segmental Glomerulosclerosis (FSGS)

- FSGS recurs after transplantation in approximately 20 to 30% of cases.
- Primary, familial, and secondary forms
- De novo FSGS has also recently been related to sirolimus therapy in some transplant patients
- **primary** FSGS(pediatric patients and young adults), as high as 50%
- **Familial FSGS** has been linked to genes encoding various podocyte-related proteins, including **podocin, a-actinin 4, and nephrin**, do not recur after transplantation. The defect is intrinsic and specific to the kidney

- The proteinuria almost always occurred early, in 14 out of 18 occasions in this report within the first month
- Familial focal and segmental glomerulosclerosis, although rare, is important to recognize, as it is a different syndrome to idiopathic FSGS of childhood
- Patients presented on average in their third or fourth decade,
- ‚good outcome after transplantation has been reported by others. Adults with '**secondary**' FSGS, for example due to **renal artery stenosis** or some other long standing conditions that lead to renal insufficiency, would not be expected to be at risk of recurrent disease in a renal transplant

- early in the post-transplantation period with heavy proteinuria and progressive renal insufficiency and graft failure
- **younger age,**
- **rapid progression to ESRD from the onset of proteinuria**,
- **collapsing variant of FSGS**
- **previous transplant failure** as a result of recurrent FSGS (the second one up to 80%)
- such as younger age of the recipients, rapid progression to ESRD, **mesangial proliferation** in the native kidney biopsy (reflecting a more severe form of disease) and steroid resistance, older donor, pre-transplant bilateral nephrectomy (native kidney seems to be absorber of permeability factors), and recurrence of FSGS in a previous allograft
- the duration of dialysis and the **type of post-transplant immunosuppression** seem to be risk factors of recurrence
- t use of **anti-thymocyte globulin (ATG)** is associated with a higher risk of recurrence

- There are two clinical manifestations of recurrent FSGS: an **early** recurrence characterized by a **massive proteinuria** within 48–72 h after transplantation and a **late recurrence**, characterized by a progressive development of the **nephrotic syndrome** within months or years after surgery

- **Early recurrence**, immediately or few days after surgery, histological lesions by light microscopy are generally not present and segmentally sclerotic lesions may occur only later. In fact, the diffuse effacement of foot processes by **electron microscopy** is the only initial histologic finding of early recurrent FSGS if ultrastructural examination is performed.
- In transplanted patients the differential diagnosis between recurrence and FSGS caused by **Calcineurin-inhibitors (CNI**) or other causes such as **obesity and hypertension**, is difficult, especially in the advanced phase, but in the latter case the diffuse effacement of foot processes is less obvious

- The frequent occurrence of proteinuria within a **few hours or days** after transplantation suggests that podocyte injury is probably caused by a circulating **permeability factor**
- Some proteins such as **suPAR**, **cardiotrophin-like cytokine-1 (CLCF-1)**, **apolipoprotein A-1**
- The average time of onset of recurrence is **2 weeks in children** and **7.5 months in adult** patients . However, often these patients may have an early recurrence with a proteinuria usually in a nephrotic range, within a few hours of surgery
- Besides, in patients who have had recurrent FSGS in the first transplantation, the risk of recurrence in the second graft is exponentially greater

IgA Nephropathy (IgAN)

- Morphologic recurrence of IgAN after transplantation is seen in from **20 to 60%** of patients in retrospective analyses
- Diagnosis of de novo IgAN is complicated by the fact that IgA deposition can be present in the donated kidney
- Progression of IgAN in the transplanted kidney is generally slow, but graft failure certainly can occur on long-term follow-up
- Allograft loss as a result of recurrence varies from 45 to 70% of patients with documented recurrence followed long term
- Recurrence **more often occurs 3 years** after transplantation, reducing the graft survival only in the long term

- Correlation for an adverse outcome between the number of **crescents** in the native biopsy and both the renal native survival and the risk of recurrence post transplantation, increasing the probability of allograft rejection
- many patients with recurrent IgA do not have clinical signs and the diagnosis can be histological only with **mesangial IgA deposits** with or without mesangial proliferation. In a minority of cases cellular, fibro-cellular, or fibrous crescents are described at the graft biopsy and they are associated with a significantly worse graft survival
- **Oxford classification** criteria have been successfully applied to recurrent IgAN and provide useful prognostic information for graft failure

Risk factors for IgAN recurrence

- **time-dependent,** progressively increasing after transplantation
- **Younger age** at renal transplantation
- recipients of zero-HLA mismatched live-related donor kidney
- **steroid-avoidance** or early steroid-withdrawal immunosuppressive regimens
- **male** gender
- **rapidly progressive** course of the original disease before transplantation
- degree of **proteinuria**
- **HLA-B35/DR4**
- higher levels of **circulating Gd-IgA1 and IgA-IgG** immune complexes
- Several molecules, such as **soluble CD89**, may be related to an increased risk of disease progression and of recurrence after transplantation

Membranous Nephropathy (MN)

- MN recurs in from **10 to 30%** of renal allografts
- As proteinuria is approximately **10 months**
- graft loss at **10 yr in 12.5%** of 81 allografts in patients with MN as their native disease
- early after transplantation
- **Massive proteinuria** progress rapidly toward graft failure
- **Hepatitis B and C** and autoimmune diseases such as SLE
- primary MN
- Detection of **antiphospholipase A2 receptor antibody** in the recipient may be a sensitive predictor of recurrence of membranous nephropathy.

- Approximately **70%** of patients with **idiopathic membranous** nephropathy have shown to have **circulating anti-PLA2R antibodies**, noticeably **IgG4** type. Therefore, there is a direct relationship between the circulating levels of anti-PLA2R autoantibody and the risk of recurrence after kidney transplantation

Membrano-Proliferative Glomerulonephritis (MPGN), type I

- MPGN type I recurs in from **20 to 30%** of allografts, esp in **children**
- **overestimate**, since similar histologic changes can occur as part of chronic **transplant rejection**
- Patients with recurrent disease may remain **asymptomatic**, although the majority of patients with recurrent MPGN tend to present with **proteinuria, hematuria and hypertension.**
- **Hypocomplementemia** may be associated with recurrent disease, however, disease recurrence can occur in the absence of this finding.

Membrano-Proliferative Glomerulonephritis (MPGN), type II

- MPGN type II (**dense-deposit disease**) recurs in **50 to 100%** of allografts and is even more likely to lead to graft loss
- **one year following** transplantation with **non-nephrotic range proteinuria**
- The **age** of the patient
- Presence of **crescents**
- **Graft loss** due to recurrent disease is thought to occur in only **10 to 20** percent of cases, although some centers have reported rates as high as 30 to 50 percent

C3 Glomerulopathy

- Risk factors : presence of **monoclonal paraprotein**, **lower serum complement** level, human leukocyte **antigen B8, DR3, B49, and DR4**, **higher proteinuria** and the presence of **crescents in the native kidney** biopsy, instead C3NeFs levels seem to be not related to the risk of recurrence and the degree of disease activity
- **Clinical presentation** of recurrent C3 glomerulopathy includes proteinuria, hematuria, and higher serum creatinine, although DDD usually recurs later than C3GN and presents clinically only with allograft dysfunction. However, patients with DDD commonly have low serum levels of C3 and C3NeF in circulation

Hemolytic Uremic Syndrome (HUS)

- (1) HUS/TTP with specific **etiology**
- (2) HUS/TTP with **unclear etiology**, including those associated with **calcineurin inhibitor therapy**
- **non–infection**-related HUS and found a **60% recurrence** rate, with graft failure in **90% of those with recurrence**.

- Previously renal transplantation was **contraindicated** in the patients with **aHUS**. Indeed, rate of recurrent aHUS after renal transplantation is really significant, about 75–80%. aHUS may be associated with genetic acquired or idiopathic forms. Mutations of the type "loss of function" have been identified, in genes that encode complement regulatory proteins such as complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (CMP, CD46), and thrombomodulin (THBD) and mutation of the type "gain of function" in genes that encode C3 and complement factor B (CFB)

- Furthermore, the rate of recurrent aHUS after renal transplantation is closely related to the specific mutated factor, **membrane-bound** or **circulating**. Patients with mutation of membrane-bound factors, for example **MCP**, have an extremely low risk of developing recurrence, depending on donor genome. On the other hand, patients with mutation of circulating factors, for example CFH and CFI, have a higher risk of developing recurrence leading to graft loss in 80–90% of cases

- Patients with post-transplant aHUS usually present with macroangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, similar to non-kidney transplant patients. Typical laboratory abnormalities include an increased serum creatinine, evidence of hemolysis (such as increased reticulocyte count, schistocytes on peripheral smear, and increased serum lactate dehydrogenase), and a low platelet count. Histologic injuries on biopsy include vessel wall thickening (mainly arterioles or capillaries), intraluminal platelet thrombosis and obstruction of the vessel luminal, endothelial cell swelling and detachment from the basement membrane, glomerular ischemia, and onion-skin hypertrophy of the arteriolar walls. Differential diagnosis with acute antibody-mediated rejection is often difficult. Nevertheless, in the latter case C4d staining of peritubular capillaries and circulating donor specific antibodies are found

Systemic disease

- Differ on the basis of the specific disease.
- Recurrent **lupus nephritis** can be seen in 2 to 10% of allografts

- **Wegener's granulomatosis**, recurrence rate of 17%
- **ANCA positivity** at the time of transplantation was not a risk factor for recurrence.
- **Anti-GBM** disease may also recur after transplantation, although morphologic detection of linear GBM staining is much more common than allograft dysfunction
- De novo anti-GBM disease after transplantation can occur in those with **Alport syndrome** as a result of development of anti-GBM antibody in patients with genetic deficiency of type IV collagen proteins in their native kidneys
- A highly sensitive detection method for **free light chains and kappa/lambda** ratio is beneficial in early diagnosis of the recurrent light chain deposition disease and/or AL-amyloidosis

RPGN

- Pauci-Immune Crescentic GN, SLE, anti-GBM may recur later after renal transplantation and rarely lead to allograft failure.
- Pauci-immune Crescentic GN is the most common cause of rapidly progressive glomerulonephritis, followed by anti-glomerular basement membrane (anti-GBM) disease and immune-complex glomerulonephritis and it is generally associated with circulating antineutrophil cytoplasmic antibodies (ANCA)
- Patients with **ANCA associated** vasculitis should be in clinical remission for at least 12 months, however, persistent ANCA positivity is not a contraindication to transplantation
- In patients with Pauci-Immune Crescentic GN rate of recurrence is about 17% and incidence of allograft loss is about 7.7%.
- In patients with SLE rate of recurrence is about 30% and allograft loss is uncommon. Clinical manifestation of recurrent lupus nephritic (LN) is generally modest proteinuria, microhematuria, cutaneous rash, and arthralgias
- Biopsy highlights in most cases mesangial lesions or atypical pauci-immune proliferative GN. The risk factors associated with recurrent LN are black non-Hispanic ancestry, female gender, and young age. Patients with antiphospholipid (aPL) autoantibodies and those receiving the kidney from living donors also have a higher risk of recurrence

- The presence of a high titre of circulating anti-glomerular basement membrane (**GBM)** antibodies at the time of transplantation increases the risk of recurrence in the allograft in Goodpasture syndrome. In contrast, clinical recurrence is extremely rare if the antibody is **undetectable** over the **6 months prior to transplantation**.
- The prevalence of recurrent **lupus nephritis** is very low. The vast majority of recipients with ESRD due to lupus nephritis has lost serological activity of systemic lupus erythematosus, and seems to be in a burn-out state. As a result, the recurrence rate of lupus nephritis is extremely low.

Table 3 Possible factors influence the recurrence of glomerulonephritis

Focal segmental glomerulosclerosis
Age of onset
Interval to end-stage renal disease
History of graft loss due to recurrent FSGS
Circulating permeability factors
Circulating urokinase receptor
Membranous glomerulonephritis
Anti-phospholipase A2 receptor antibody
Anti-glomerular basement membrane (GBM) antibody glomerulonephritis
High titre of a-GBM antibody
Light chain deposition disease
AL-amyloidosis
Paraproteinaemic glomerulopathy
Free light chain detection, kappa/lambda ratio
Atypical HUS
Low ADMTS13 activity
Mutation of complement regulatory factor I, H
Some of MPGN-II (DDD)
Mutation of complement regulatory factor I, H, C3 NeF

De Novo Glomerulonephritis

- membranous nephropathy,
- anti-GBM in Alport's syndrome and
- recurrent nephrotic syndrome in congenital nephrosis. A fourth common de novo GN,
- focal segmental glomerulosclerosis, is believed to be related to hyper filtration injury or marked compromise as a result of calcineurin inhibitor toxicity

Membranous Nephropathy

- De novo MN is typically a late complication affecting about **1%-2%** grafts.
- The risk factors for de novo MN include **time after transplantation**, **de novo MN in a first graft, HCV infection**
- Light microscopy usually shows mild glomerular basement membrane changes. **Mesangeal hypercellularity** is found in about 33% of biopsies.
- In most cases, MN in the transplant is a de novo disease, occurring in patients who had a different primary renal disorder
- The cumulative incidence of this complication is approximately 1.5 to 2 percent, but the frequency rises with time, reaching 5.3 percent at eight years in one report

Anti-Glomerular Basement Membrane glomerulo-nephritis (Anti-GBM)

- Patients with **Alport's syndrome** or **hereditary nephritis** commonly develop anti-GBM alloantibody because they genetically lack self tolerance to GBM collagen components, however GN develops in few cases only and de novo **crescentic and necrotizing GN** 2ry to anti-GBM post transplantation is uncommon, seen in only 5% of adult male recipients with Alport's syndrome
- The **overall 5-year graft survival** is equal to that of recipients without Alport's syndrome

Recommendations

- 1- **Native kidney biopsies** should help to clarify the true incidence of recurrent disease. Extra efforts may be necessary in certain populations, such as black patients, indigent patients, and those without adequate access to health care to avoid labeling bias with the far less helpful diagnoses of "chronic renal failure or ESRD of unknown etiology."
- 2- **Urinalysis or a simple dipstick** check of the urine for protein and blood should be performed on all transplant patients at every visit. There is already evidence in some recurrent diseases (e.g., FSGS) that earlier diagnosis and intervention will lead to remissions of recurrent GN and improved allograft survival.
- 3- **Transplant biopsy**. In all patients with GN as their diagnosis in their native kidneys, full evaluation of the biopsy including **IF and EM** is warranted.
- 4- Studies of **genetic variants of the disease** (e.g., podocin and α-actinin defects in FSGS), morphologic patterns (e.g., collapsing FSGS, crescentic IgA), and links to basic science (analysis of undergalactosylated IgA) whenever possible.
- 5- Therapeutic interventions should be studied in a collaborative manner for each disease entity to provide more than just anecdotal information on therapy of recurrent disease.

Conclusion

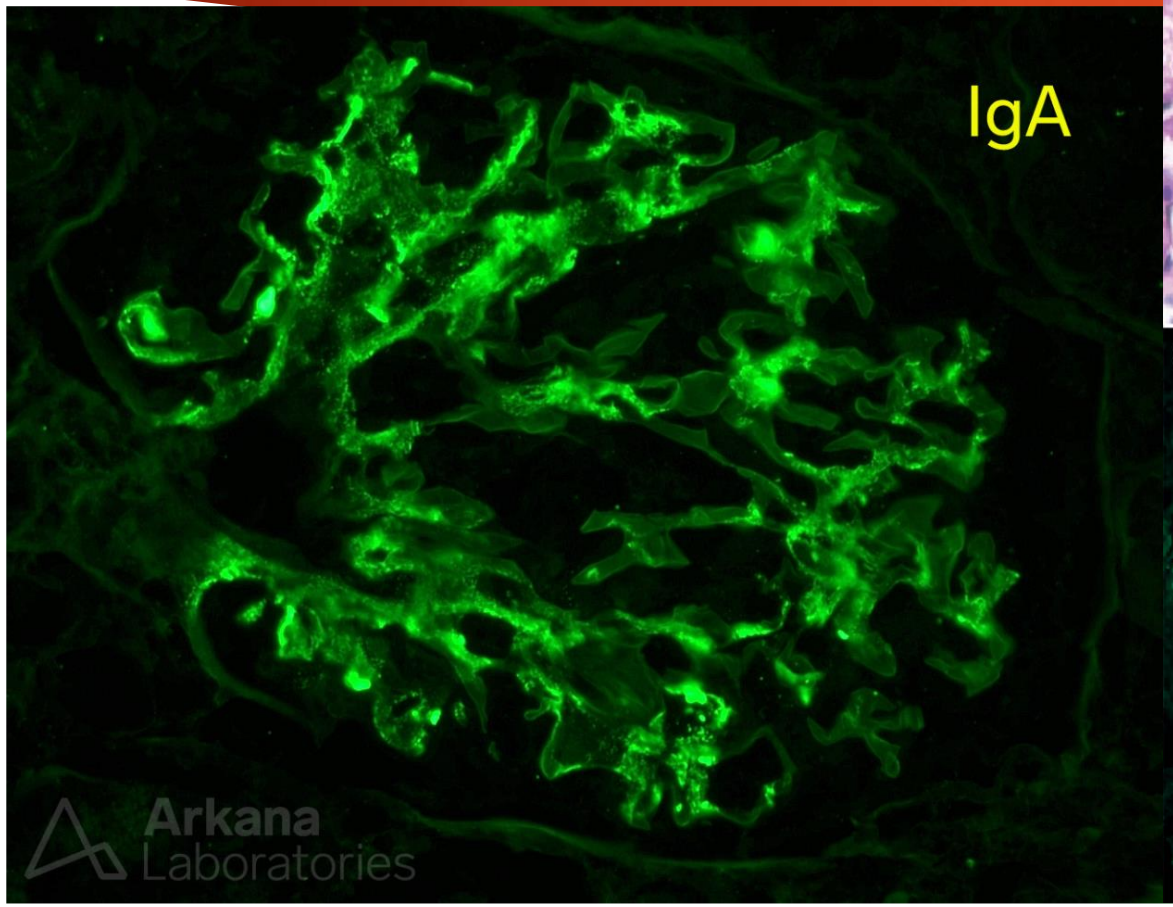
- Recurrent and De novo GN occur earlier than transplant Glomerulopathy and recurrent GN is the earliest glomerular lesion observed in the **first 3 months** post transplantation.
- **FSGS is the most common** type of PTGN and **MPGN** represents the second common type.
- **Pre-transplant glomerulonephritis**, donor **age 31-40 years** old, and **Sirolimus protocol** are risk factors for developing PTGN.
- Difference in blood group between the donor and recipient carries a favorable significant delay in the development of PTGN.
- The risk factors associated with graft loss in PTGN are; recipient age between **40 and 50 years, induction therapy with polyclonal antibody (ATG), incidence and number of acute rejection episodes, and development of chronic rejection.**

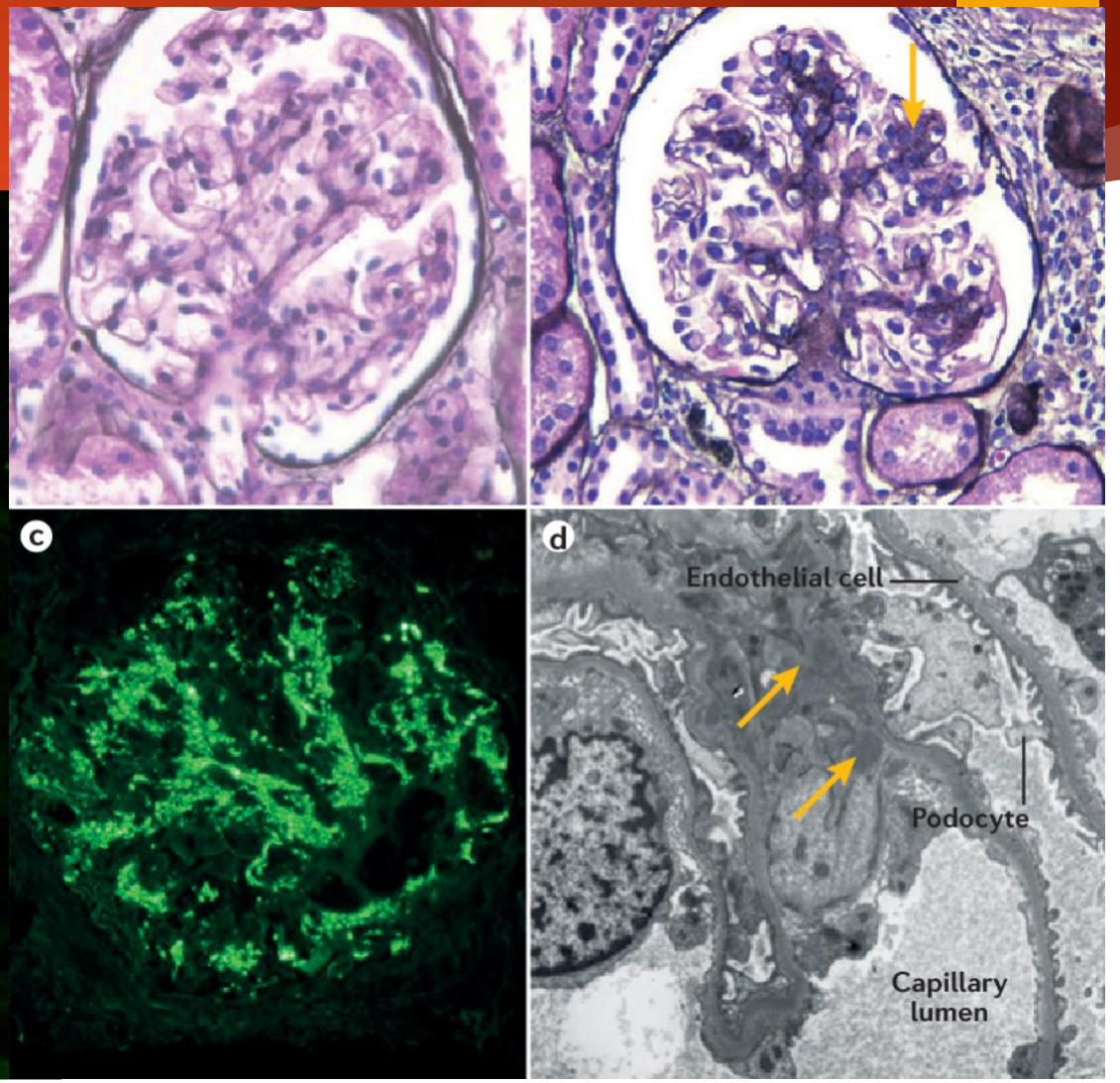
- Significant drop of **graft survival** is observed in recipients who developed PTGN after the **first 2** years pos-transplant.
- The graft survival in the recipients with Recurrent GN is significantly lower than the graft survival of recipients who developed De novo GN and Transplant glomerulopathy.
- **De novo GN** has an independent negative impact on the long term graft loss.
- **Middle aged donor** grafts, patient receive their grafts from **their off springs**, and **different blood groups between** recipients and donors have favorable significant effect on graft survival.
- The patient survival in the recipients with PTGN is comparable to those without PTGN in the first 5 years post transplantation. Thereafter, significant drop of patient survival is observed in the group of recipients who suffered from De novo GN and Transplant Glomerulopathy.

SIGNIFICANCE OF PROTOCOL BIOPSY FOR EARLY DIAGNOSIS OF RECURRENT GLOMERULONEPHRITIS

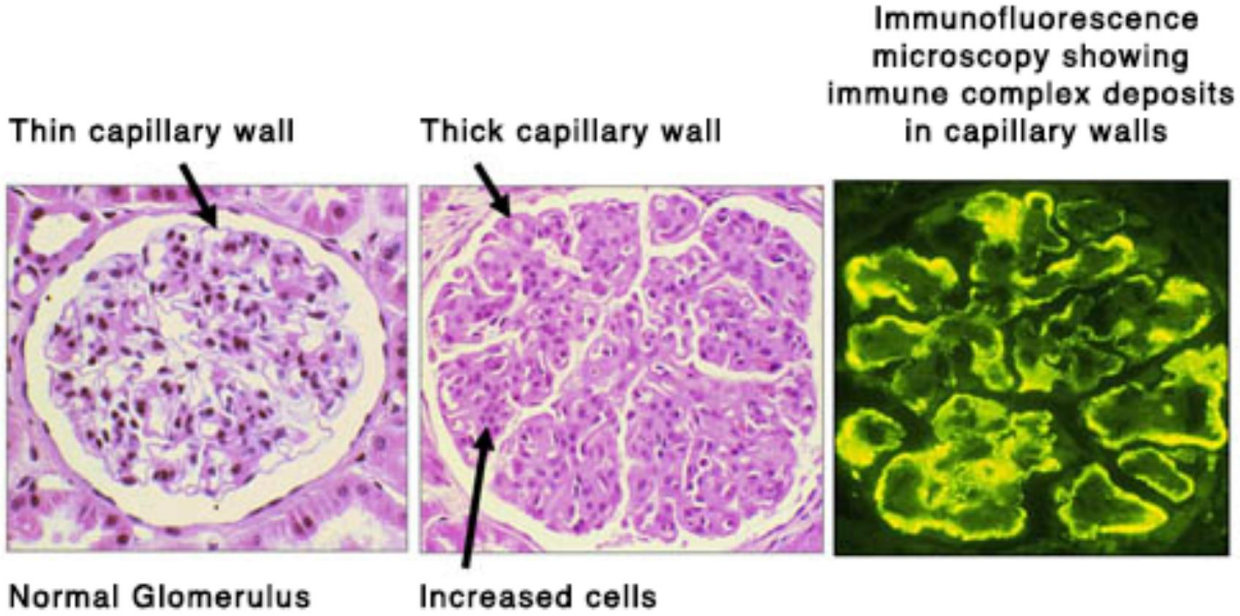
- Protocol biopsy is widely accepted in Japan. An implantation baseline biopsy during the kidney transplant **operation and a biopsy at discharge of post-transplant (po-) 2 to 3 week, po-3 to 6 month, po-12 month and po-3 year** are performed as standard protocol biopsies in many kidney transplant centers
- Transmitted subclinical glomerulonephritis is noted in approximately **15%** of Japanese donors.
- **IgA nephropathy** accounts for over 90% of transmitted glomerulonephritis. The follow-up protocol biopsy shows early disappearance of IgA deposition within **the first 3 months after** transplantation in many recipients.
- On the contrary, early recurrence of IgA nephropathy develops within **1 to 2 months' post-transplant** in a small number of recipients with IgA nephropathy.
- In the overlapping period between transmission and early recurrence, it would be impossible to correctly detect recurrence of IgA nephropathy.
- Recurrence of IgA nephropathy is usually confirmed at the protocol biopsy performed 3 months post transplant or later, and deteriorated graft function is absent at the protocol biopsy.
- The majority of recurrent IgA nephropathy cases involve **only histological** recurrence **without proteinuria and microscopic hematuria.**

IgA nephropathy

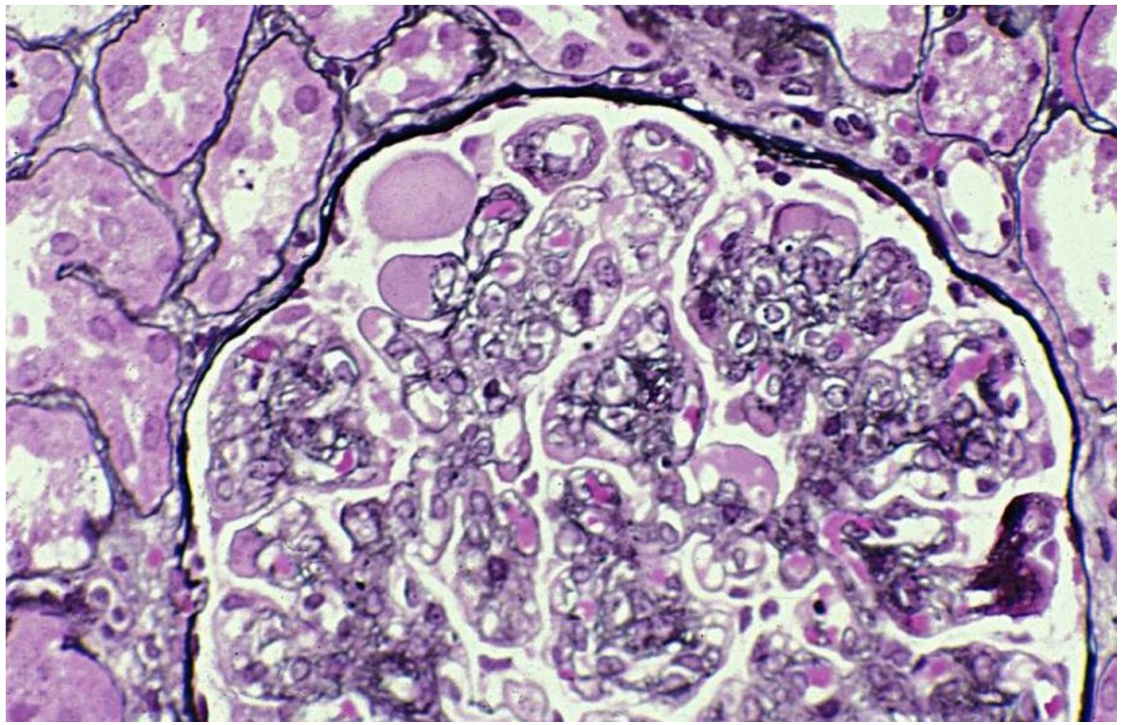




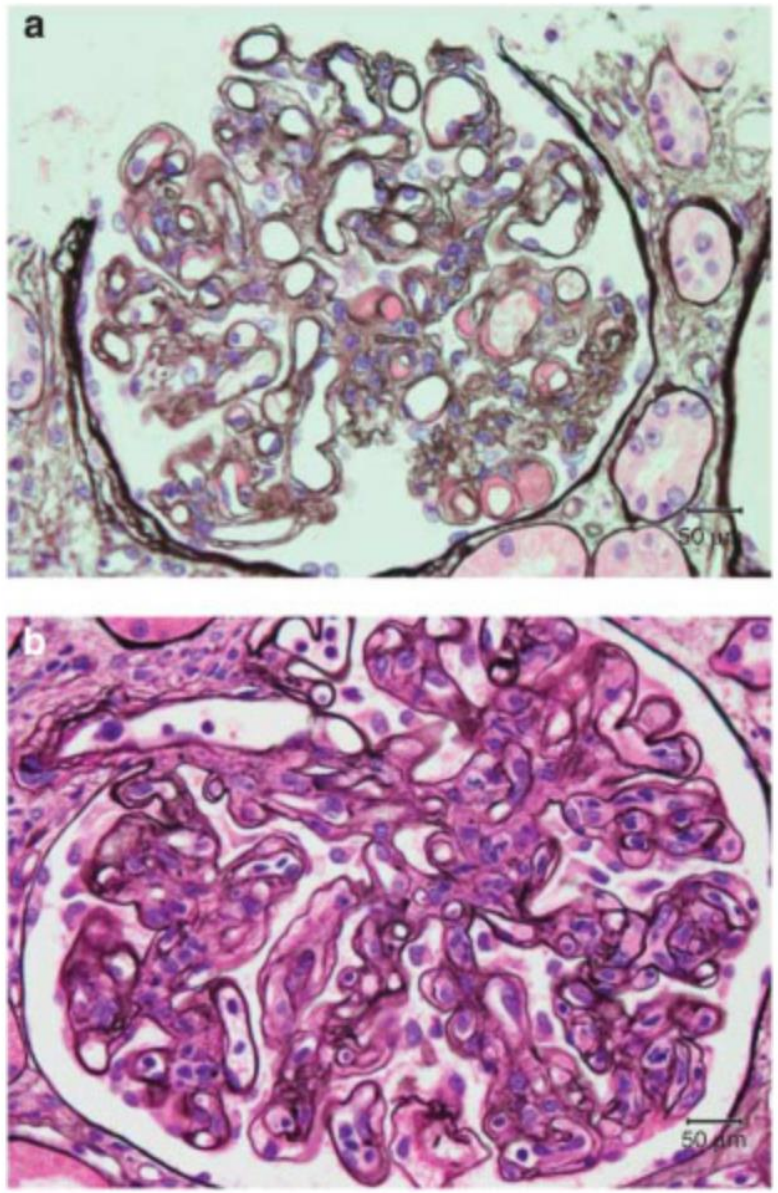
MPGN


Thin capillary wall
Thick capillary wall
Immunofluorescence microscopy showing immune complex deposits in capillary walls
Normal Glomerulus
Increased cells

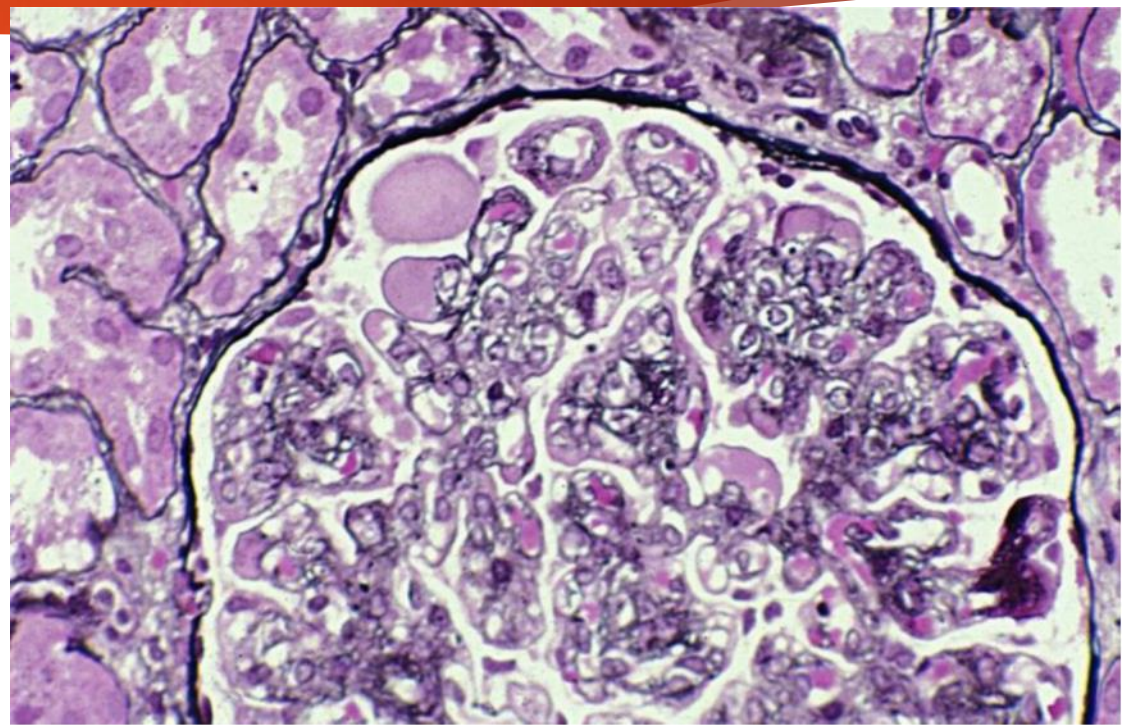
MPGN



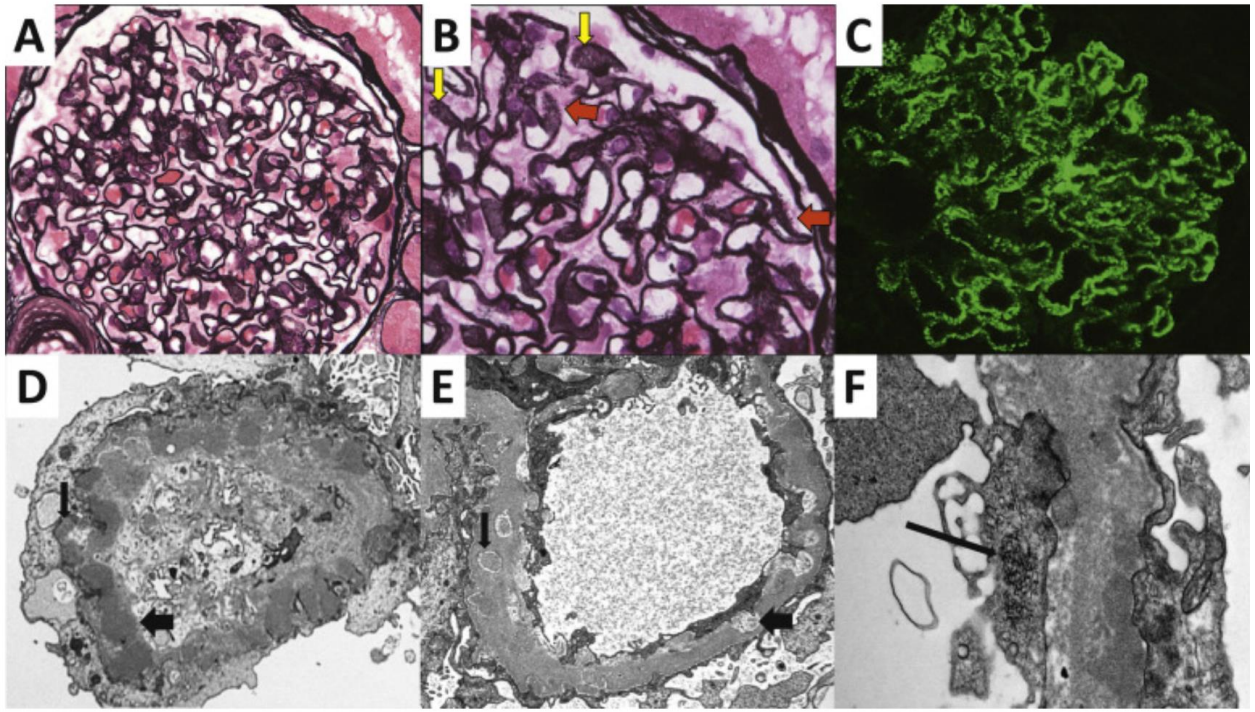
Transplant glomerulopathy



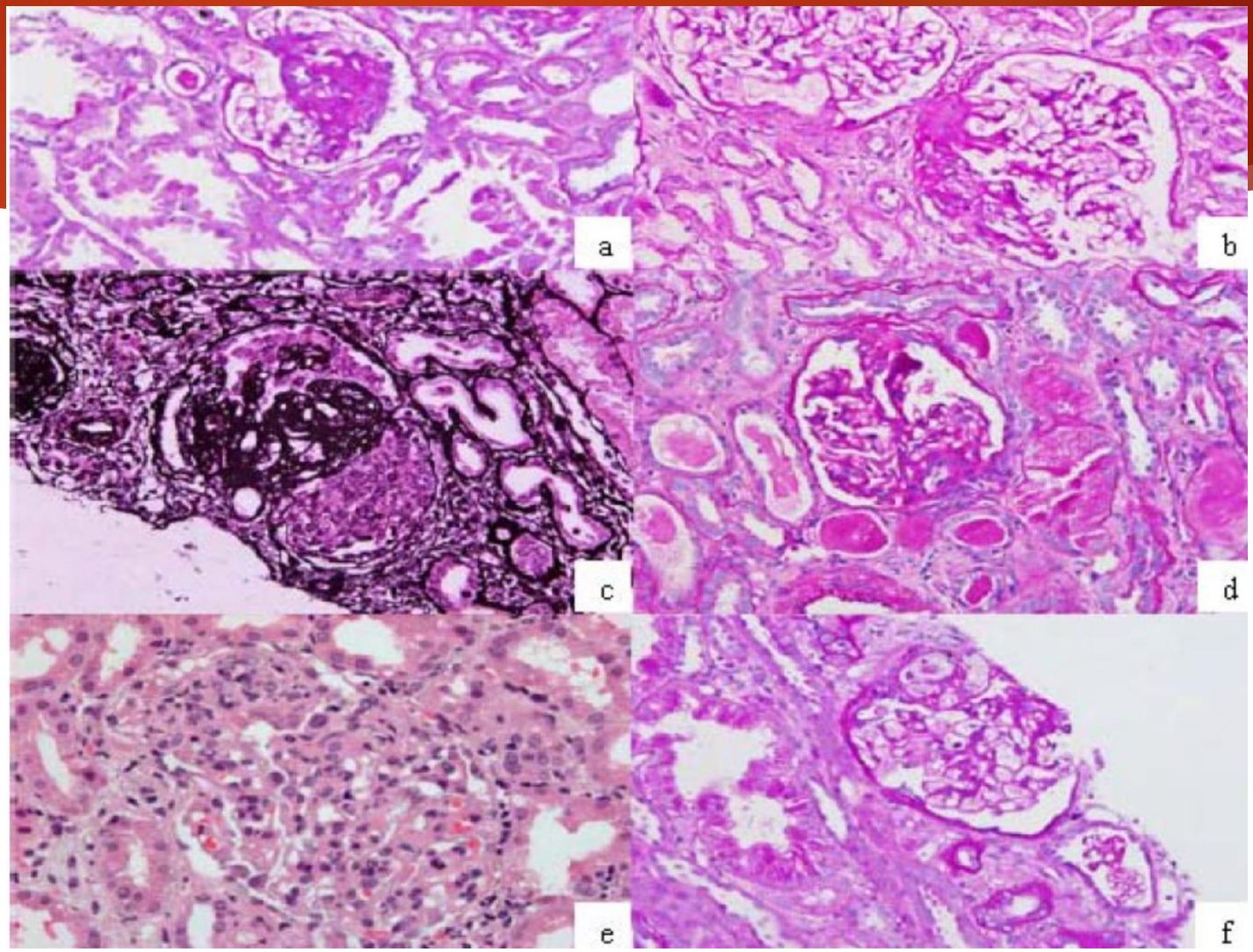
MPGN



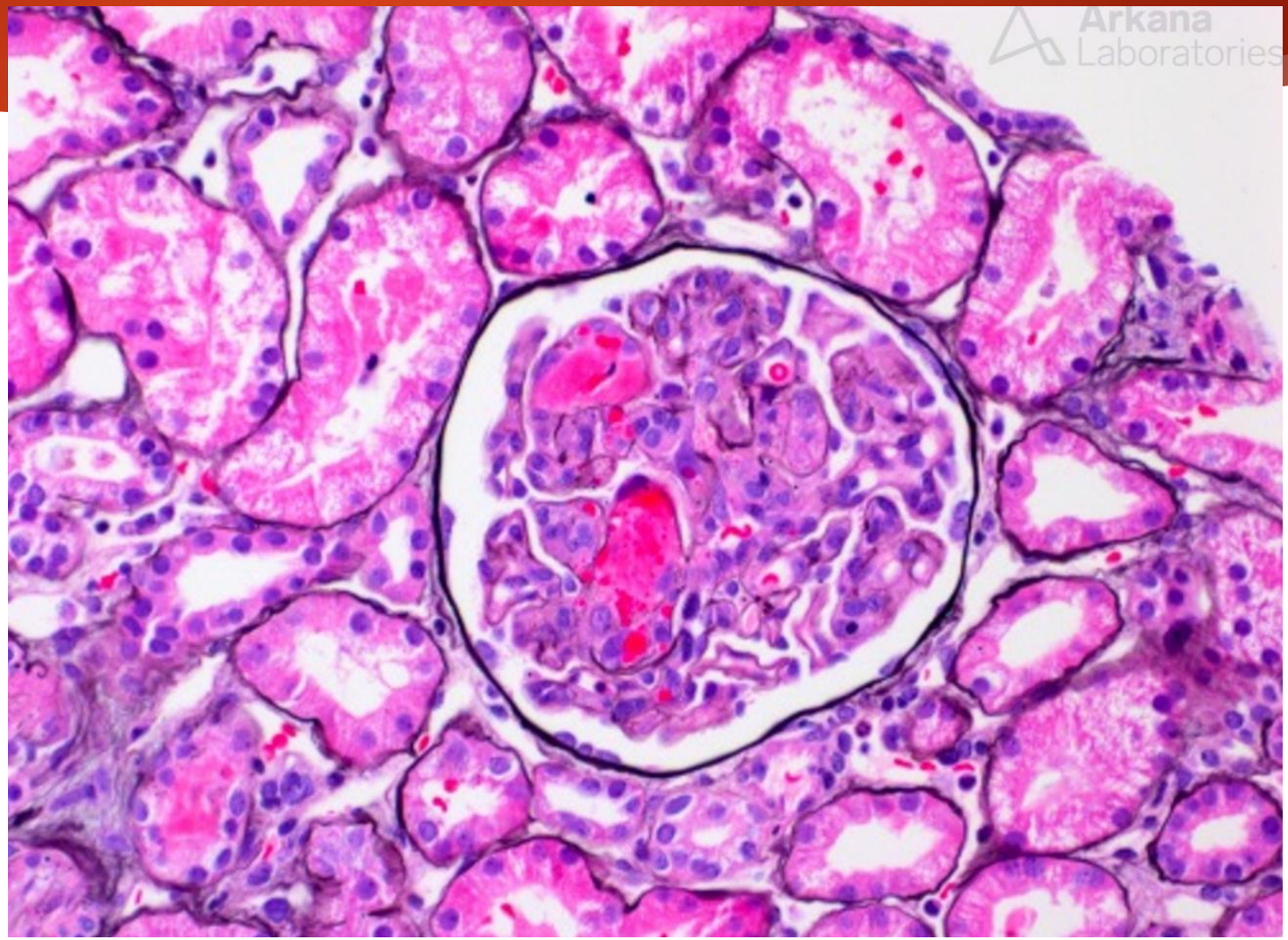
MGN



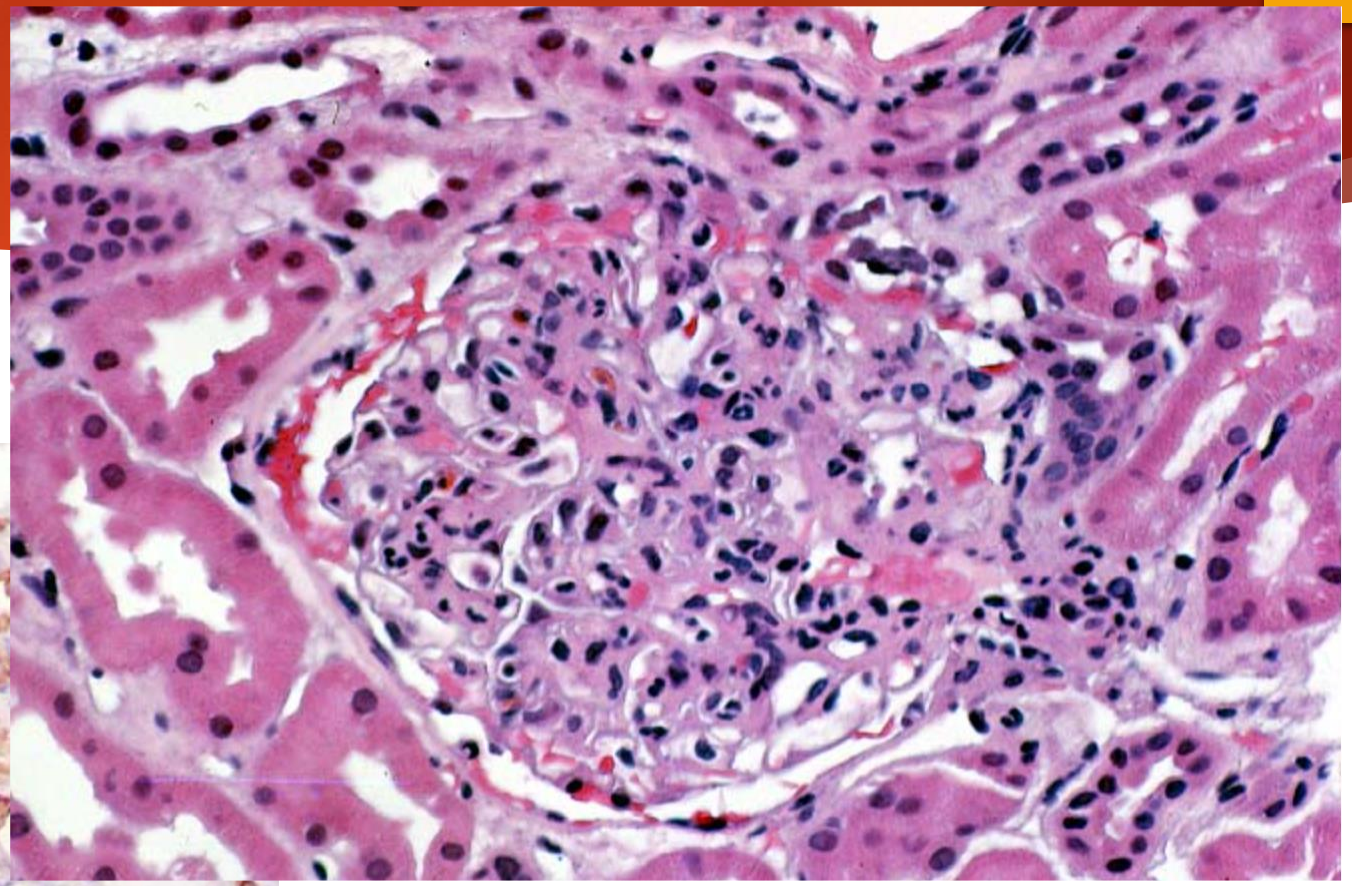
FSGS

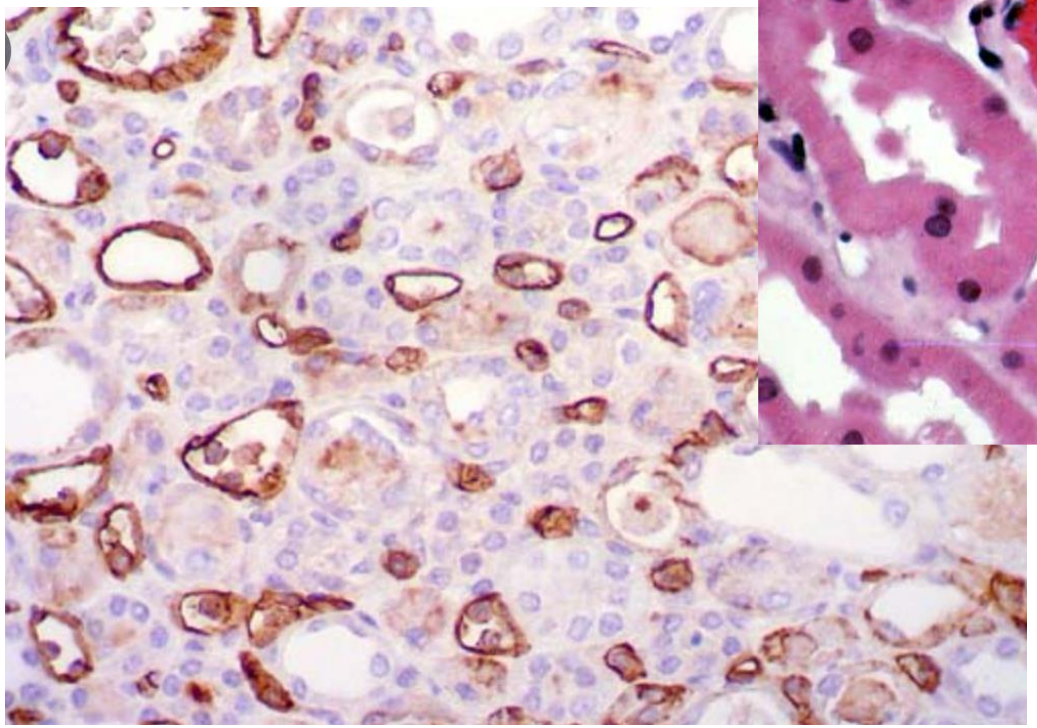


HUS

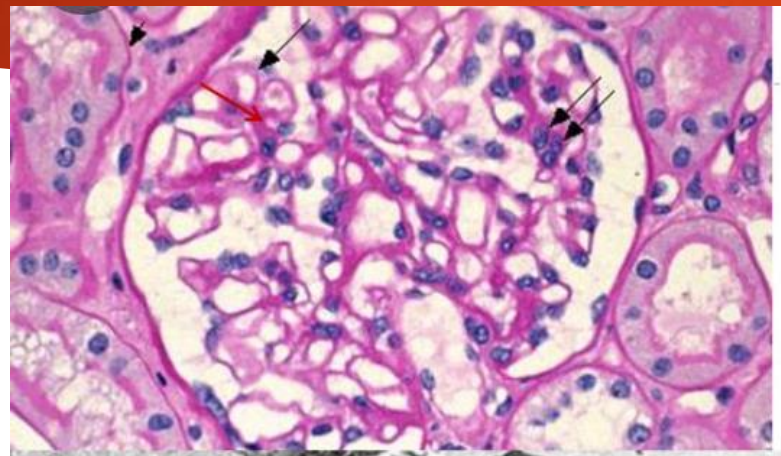


C4d in Ab mediated rejection





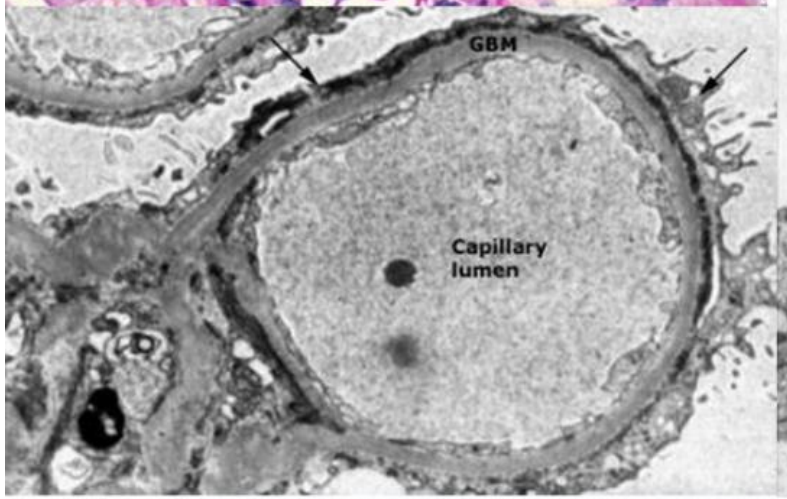
MCD



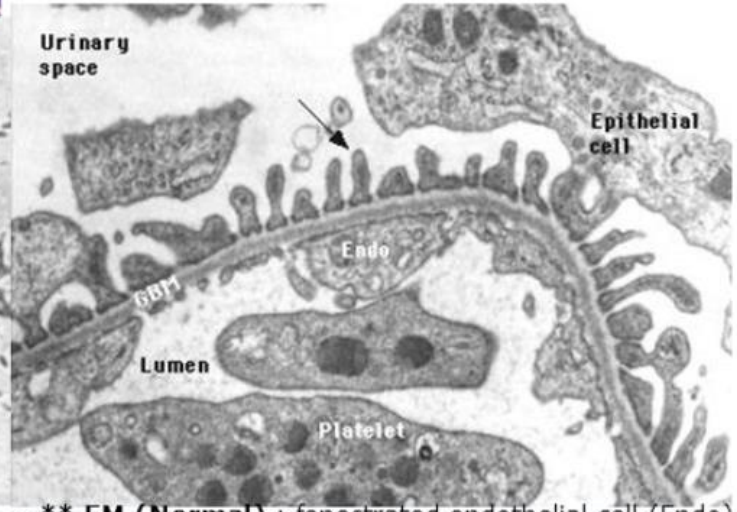
: normal appearing glomeruli

1. thickness of the glomerular capillary wall
   → similar to that of TBM (normal)
2. expansion nor hypercellularity
   in the mesangial areas
   in the central or stalk regions of the tuft

** **Immunofluorescence microscopy**
: absence of complement or immunoglobulin deposits



** **EM (MCD) :** normal GBM, no immune deposits
widespread fusion of the epithelial cell foot processes
→ excess albumin load into the urinary space



** **EM (Normal)** : fenestrated endothelial cell (Endo),
glomerular basement membrane (GBM)
epithelial cells with interdigitating foot processes