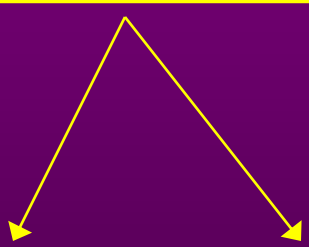
RECURRENT AND DE NOVO RENAL DISEASES IN THE ALLOGRAFT

HISTOPATHOLOGIC DISORDERS AFFECTING THE ALLOGRAFT OTHER THAN REJECTION

RECURRENT DISEASE



Glomerular **Non-glomerular**

DE NOVO DISEASE

Glomerular

TRANSPLANT GLOMERULOPATHY

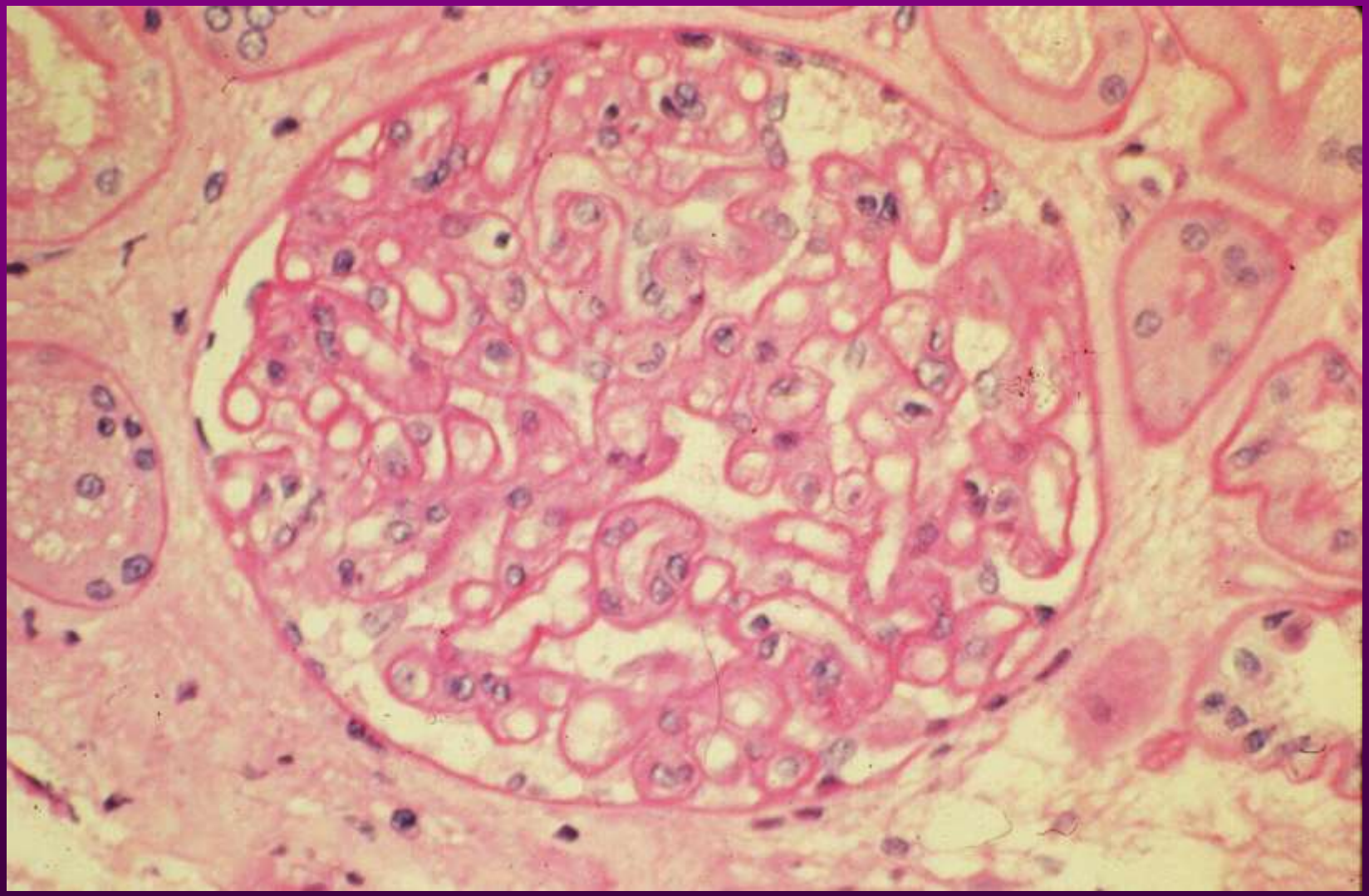
Chronic Rejection

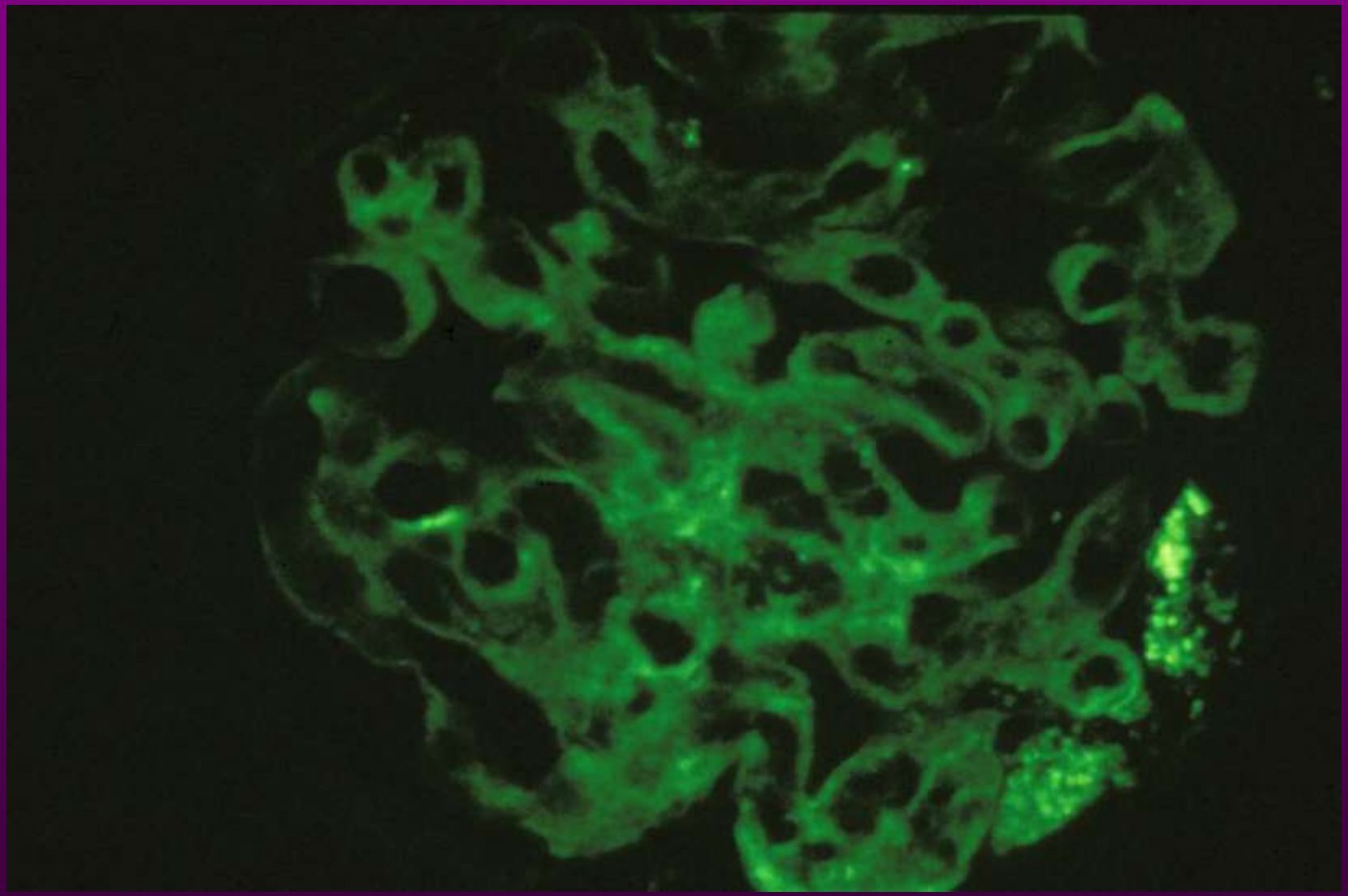
TRANSPLANT GLOMERULOPATHY

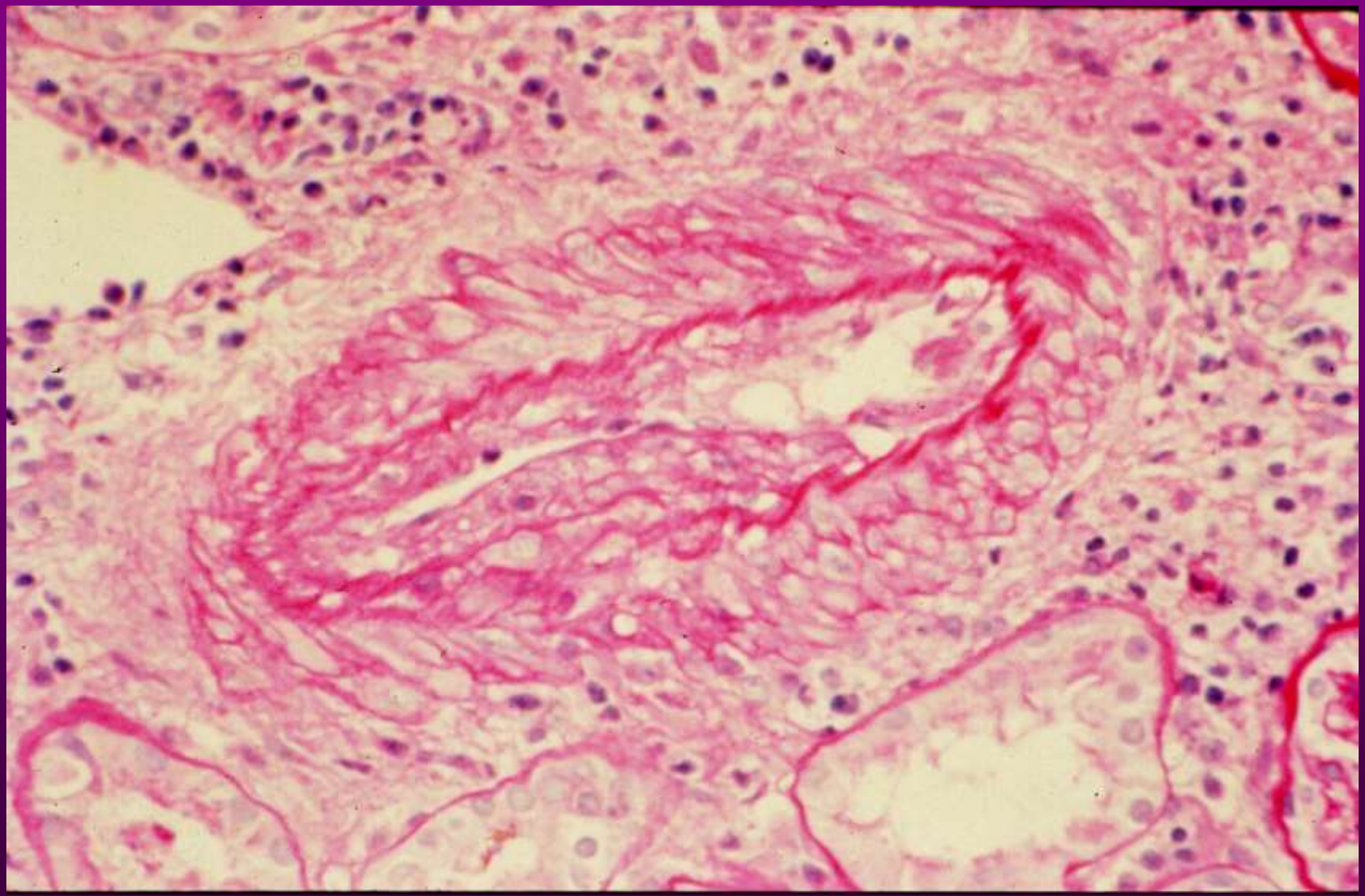
Pathogenesis: consequence of chronic rejection; inverse relation with donor an recipient compatibility; repetitive episodes of endothelia injury

Histology: endothelia and mesangial cell swelling; GBM reduplication; myointimal proliferation progressing to fibrosis leading to obliterative arteriopathy; IF- capillary wall lgM and C3; EM- subendothelial deposits, effacement of foot processes

Clinical: onset of nephrotic syndrome ~ 9 mos (1-48 mos) post-tx; 2 year graft survival of 67%







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RECURRENCE OF DISEASE AFTER TRANSPLANTATION

Mathew TM; Am J Kid Dis 12:85; 1988

1. Overall incidence of recurrent disease ~ 10-20%
2. Recurrent disease accounts for < 2% of graft loss
3. Most frequent cause of recurrent disease is recurrent GN
4. GN recurs in 6-9 % of transplanted patients

GLOMERULONEPHRITIS IN RENAL ALLOGRAFTS: RESULTS OF 18 YEARS OF TRANSPLANTATIONS

Honkanen E et al; Clin Neph 21:210, 1984

Analyzed 1282 renal allograft recipients – found 13 cases of allograft GN of which 4 were recurrent GN – for a recurrence rate of < 1%

EVALUATION OF RECURRENT GLOMERULONEPHRITIS IN KIDNEY ALLOGRAFTS

Morzy;cka M et al; Am J Med 72:588, 1982

In patients with glomerulonephritis as their original disease, they found a 17.9% recurrence rate of glomerular disease

GLOMERULAR LESIONS IN THE TRANSPLANTED KIDNEY IN CHILDREN

Habib R et al; Am J Kid Dis 10:198, 1987

40/436 patients – 9% incidence of recurrent GN

40/120 patients – 33% recurrence rate of glomerular disease in patients whose original disease was a glomerulopathy

PROBLEMS WITH INTERPRETATION OF DATA

1. Nature of recipient's original disease must be well documented
2. Indications for allograft biopsy – usually based on an abnormality (renal dysfunction, abnormal U/A)
3. Recurrence - ? Histological or clinical
4. Interpretation of biopsy – differentiate recurrent changes from rejection or those already present in the grafted kidney

PATHOGENESIS OF RECURRENT DISEASE

Nephritogenic factors:

1. Anti-GBM disease – circulating anti-GBM Abs
2. Recurrent FSGS – serum from patient → injected into rats resulted in increased urinary protein excretion

High recurrence rates in isografts and well-matched living related allografts

RECURRENT DISEASES OF THE ALLOGRAFT

GLOMERULAR

PRIMARY

- FSGS
- Membranous Nephropathy
- MPGN I
- MPGN II
- lgA Nephropathy
- Anti-GBM

SECONDARY

- HSP
- HUS
- SLE
- DM
- Amyloidosis
- Wegener's
- Cryoglobulinemia (EMC)
- Monoclonal Gammopathy

NON-GLOMERULAR

- Oxalosis
- Fabry's Disease
- Cystinosis
- Sickle cell nephropathy
- Scleroderma
- Alport's Syndrome

RECURRENT FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

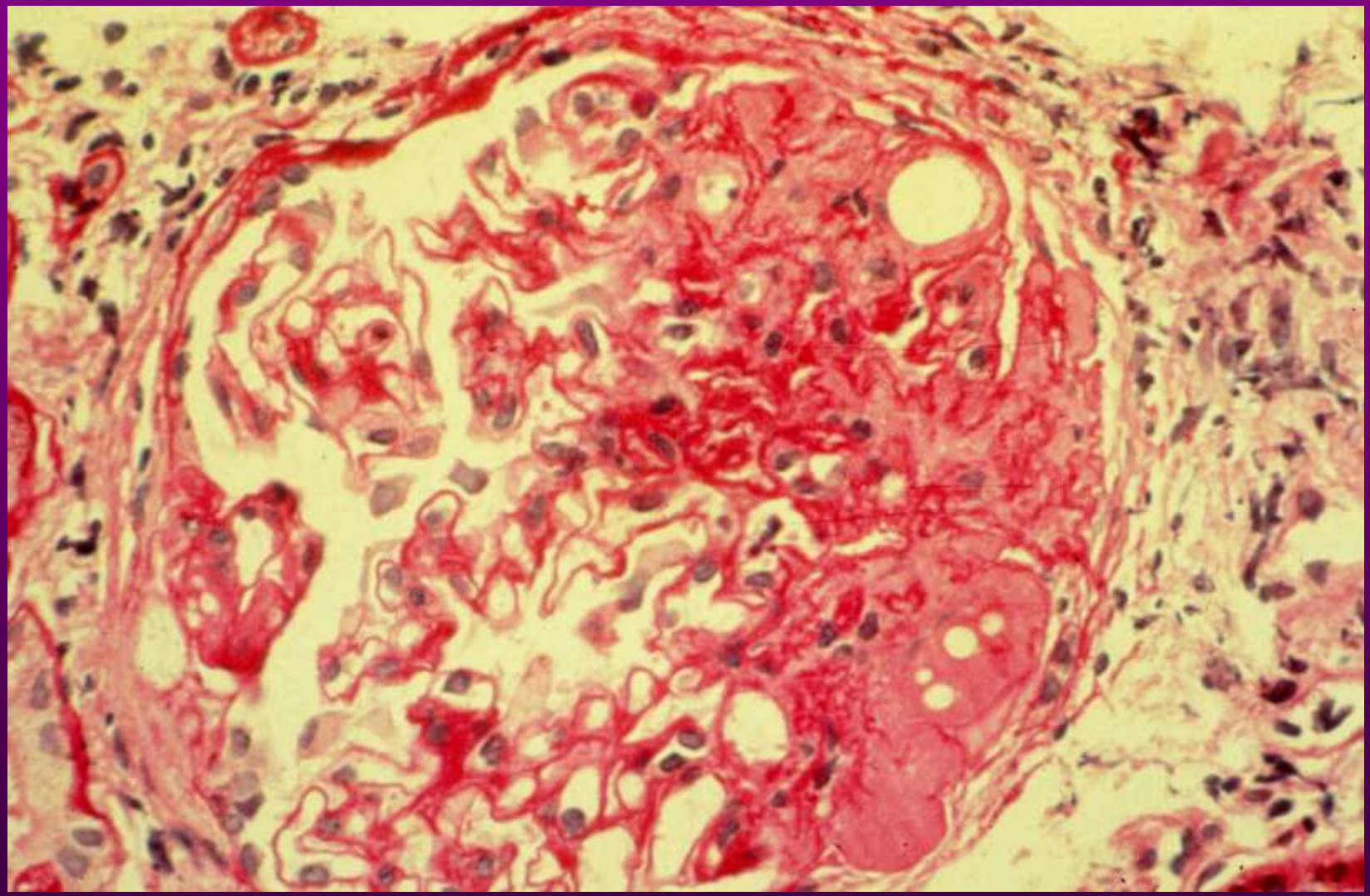
Recurrence rate: 20%

High risk group (recurrence rate of 50%)

- diagnosis to ESRD < 3 years
- younger patient (< 20 years of age)

Once recurrence in the first graft, subsequent graft with ~ 75% rate of recurrence

Histology: mesangial proliferation in the native kidney correlates with graft loss

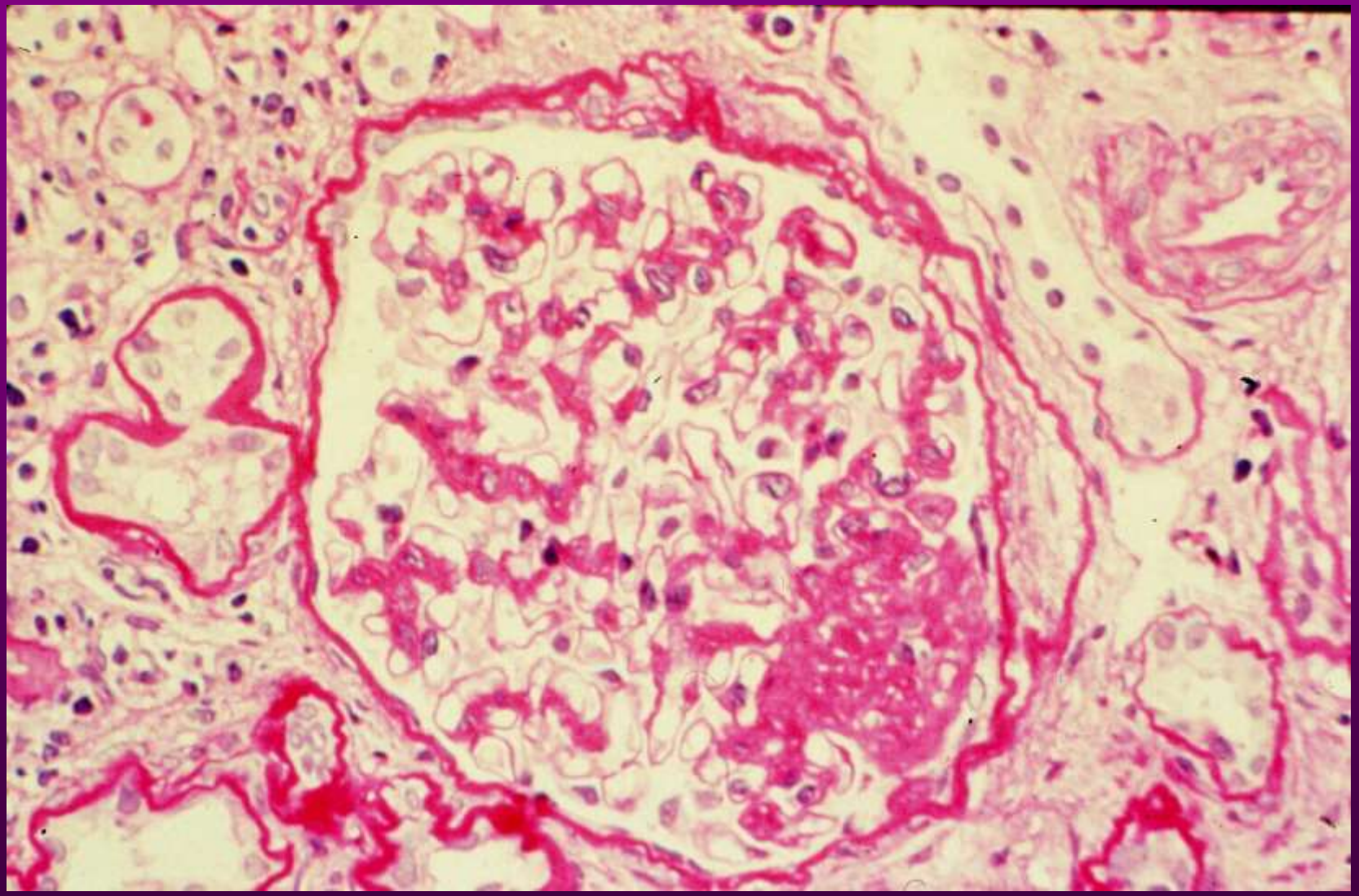


RECURRENT FSGS

Clinical – most present with nephrotic range proteinuria; graft loss seen in 10-80% (highest in those with recurrence in earlier transplant);

Treatment – plasmapheresis, plasma exchange,MMF, high dose prograf

Recommendations – living related transplants are those at high risk for recurrence or those with prior history of recurrence; wait 1-2 years between transplants; counseling for LRD

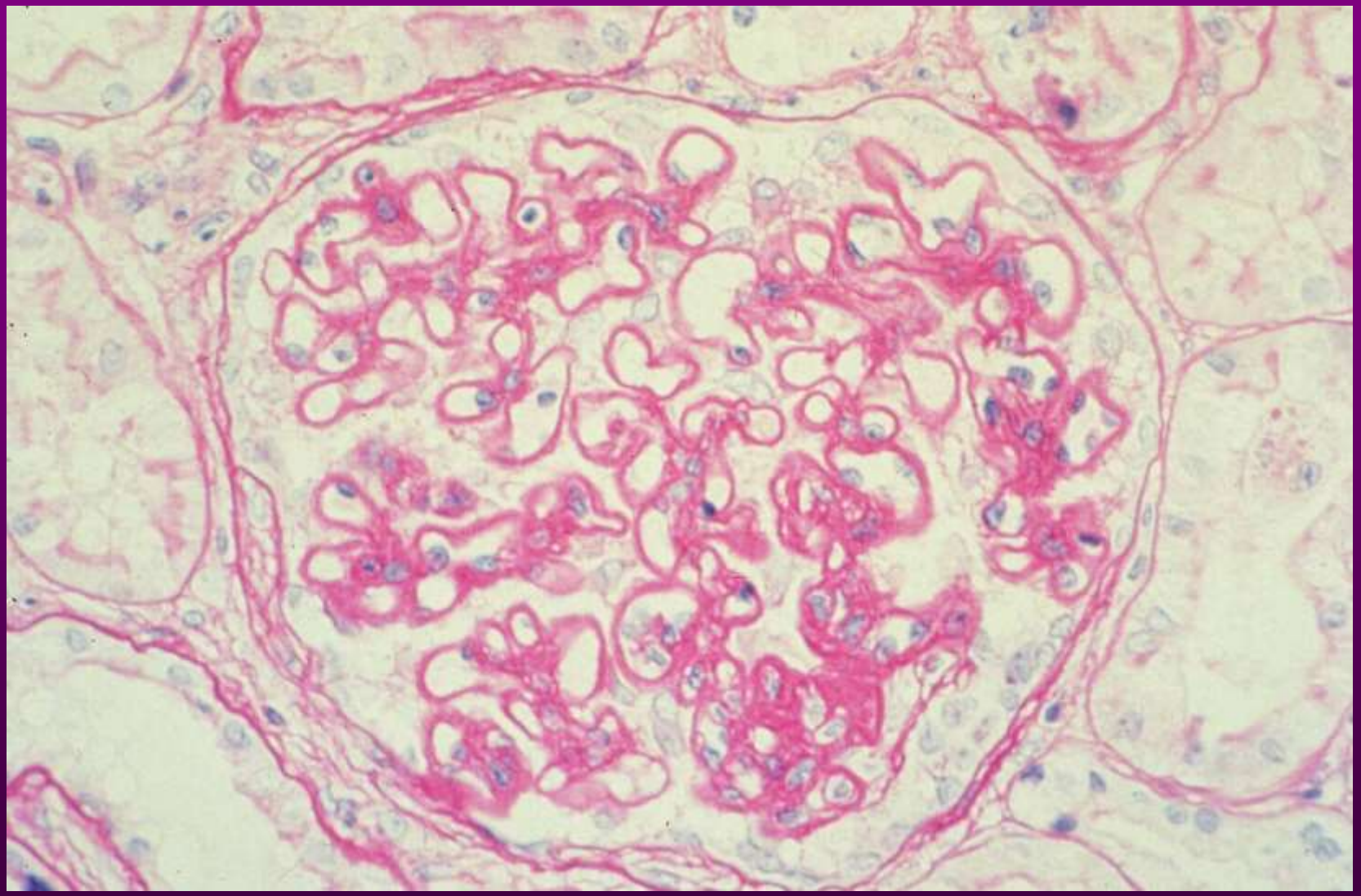


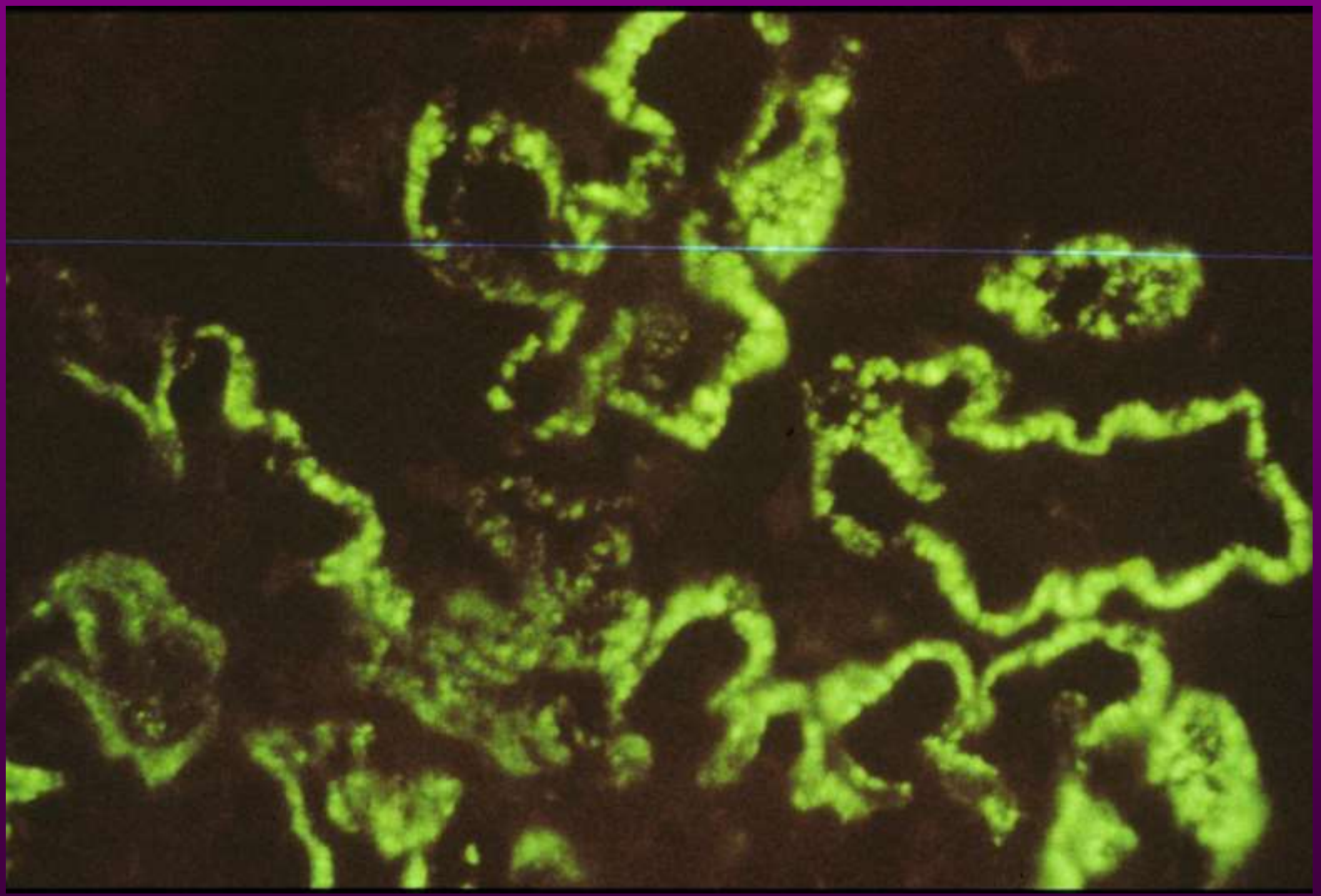
RECURRENT MEMBRANOUS NEPHROPATHY

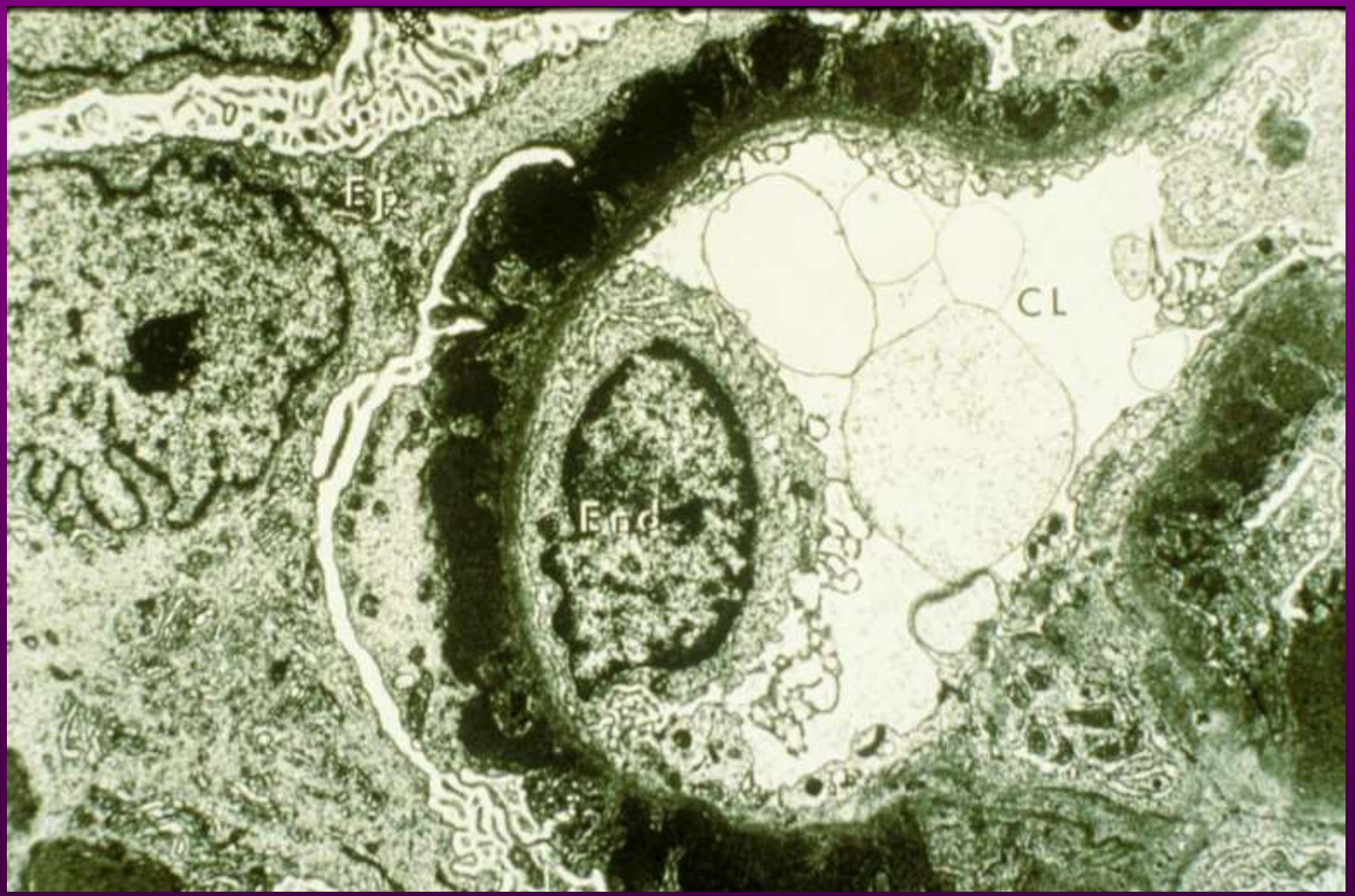
Recurrence rate - ~3-7% (up to 57%); accounts for < 25% of post-transplant membranous nephropathy

Clinical – most present early post transplant with nephrotic range proteinuria; graft loss – rare to 30% (± rejection); HLA-identical grafts at higher risk for recurrence

Treatment – no benefit with additional steroids



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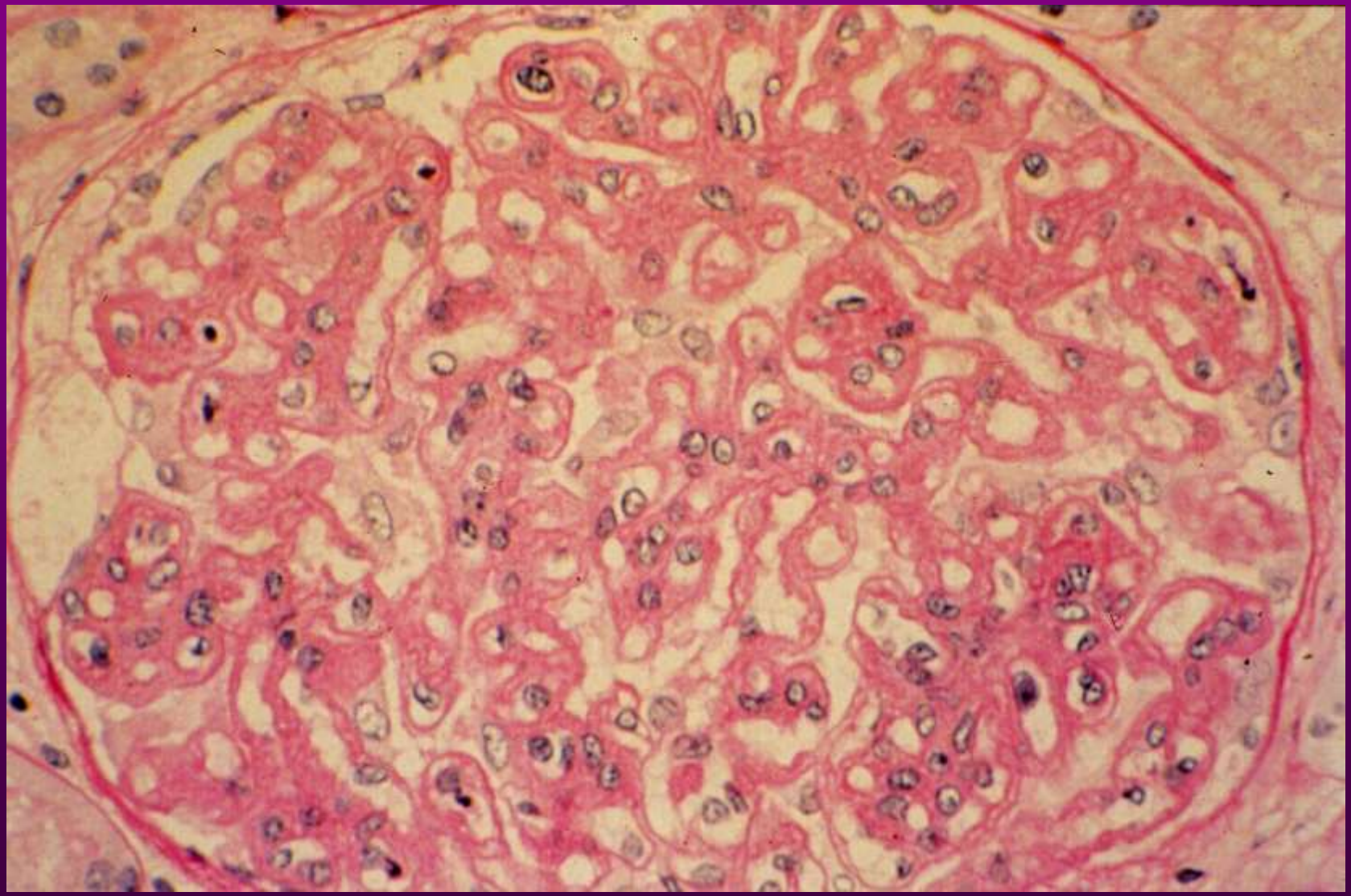
RECURRENT MPGN – TYPE I

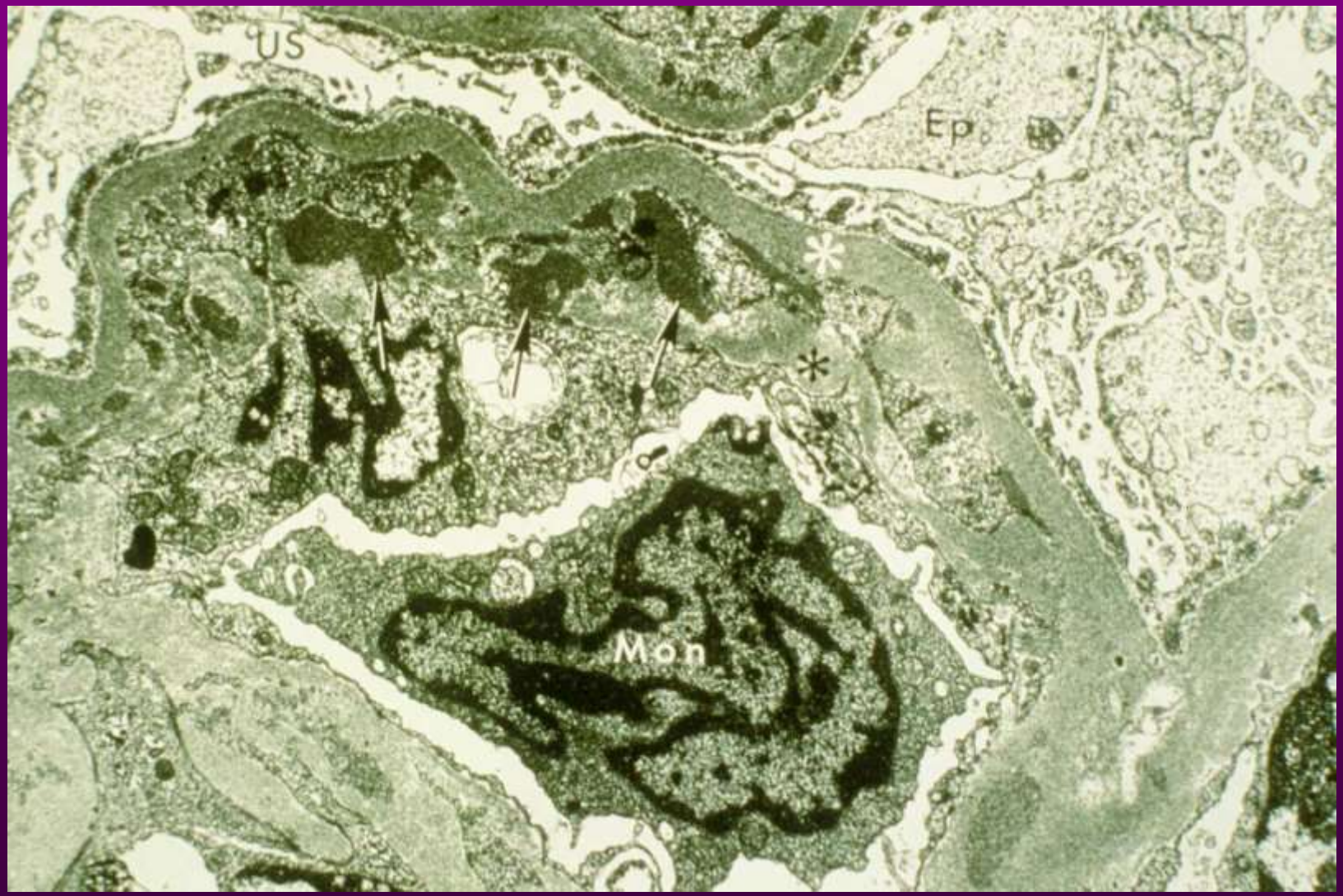
Recurrence rate - ~20-30%

Histology- presence of subendothelial deposits and glomerular crescents may differentiate this from transplant glomerulopathy

Clinical – proteinuria, hematuria; serum C3 levels not helpful in diagnosis or prognosis; graft loss in 28-42%

Treatment – anti-platelet (ASA, dipyridamole), plasma exchange (?)

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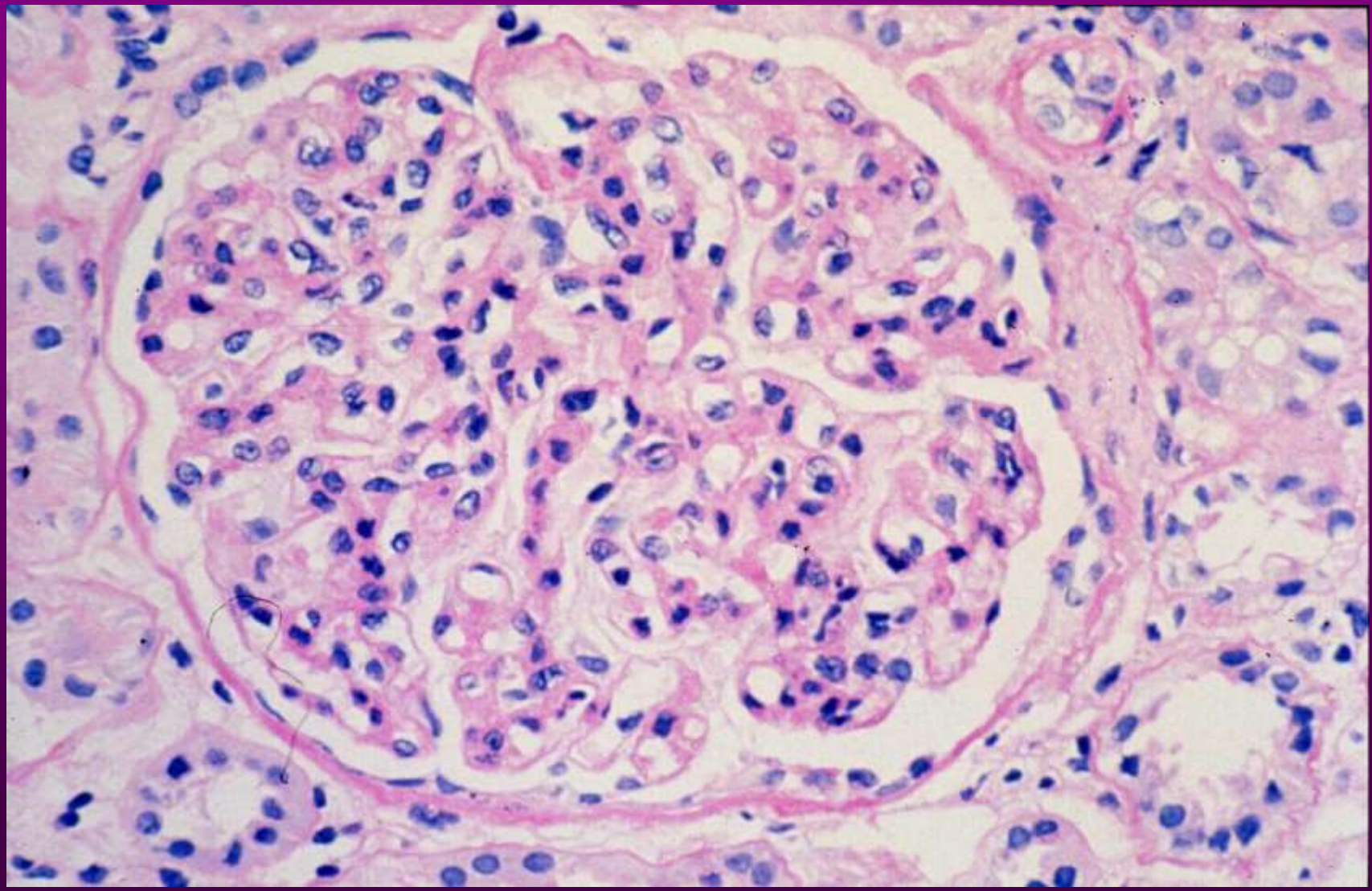
RECURRENT MPGN TYPE II

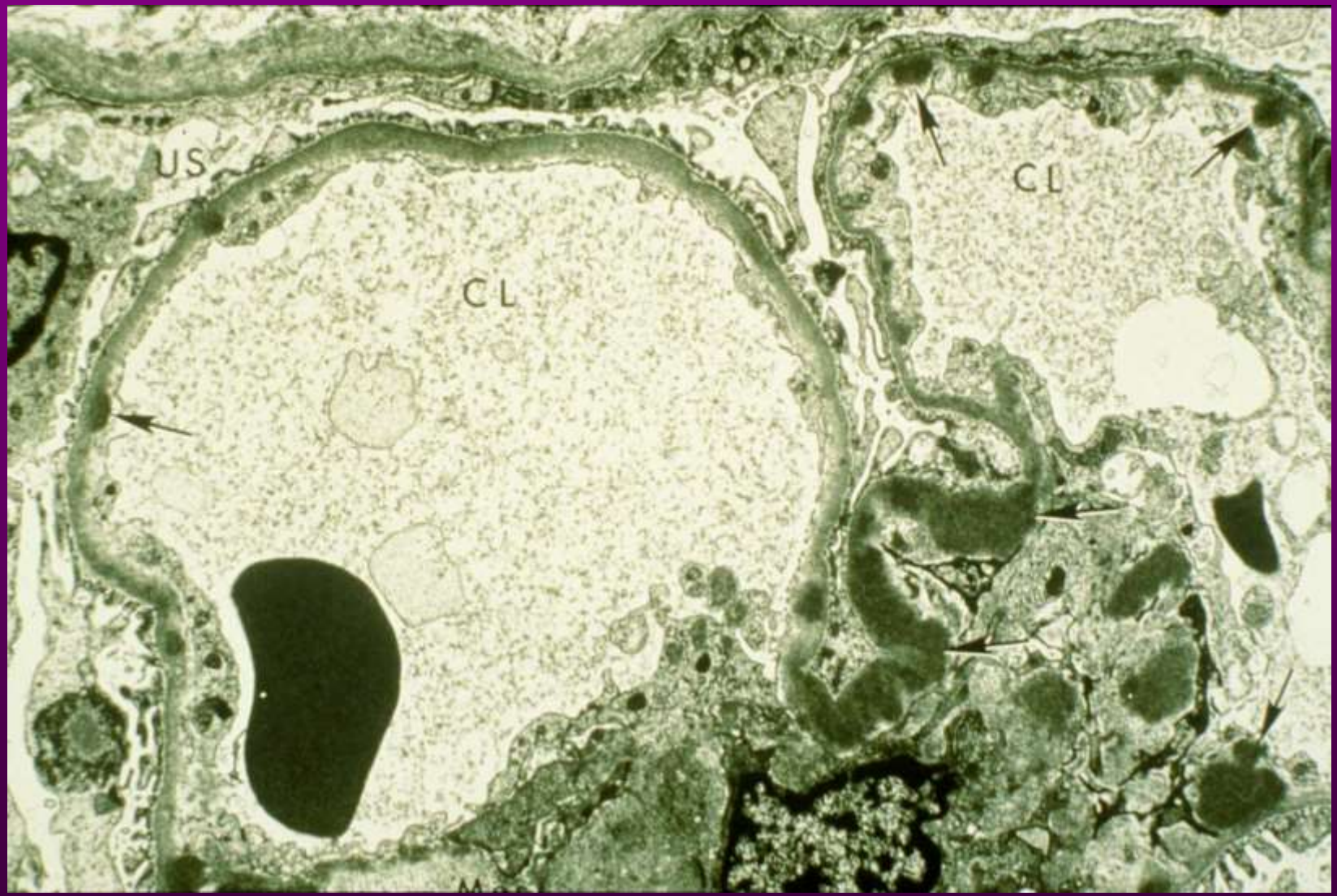
Recurrence rate – 50-100%

Histology – subendothelial dense deposits

Clinical – proteinuria, hematuria; graft loss 10-20%, up to 50% (risk factors – male sex, RPGN, recurrent nephrotic syndrome)

Treatment – plasma exchange (?)

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Clinical – proteinuria, hematuria; graft loss 10-20%, up to 50% (risk factors – male sex, RPGN, recurrent nephrotic syndrome)

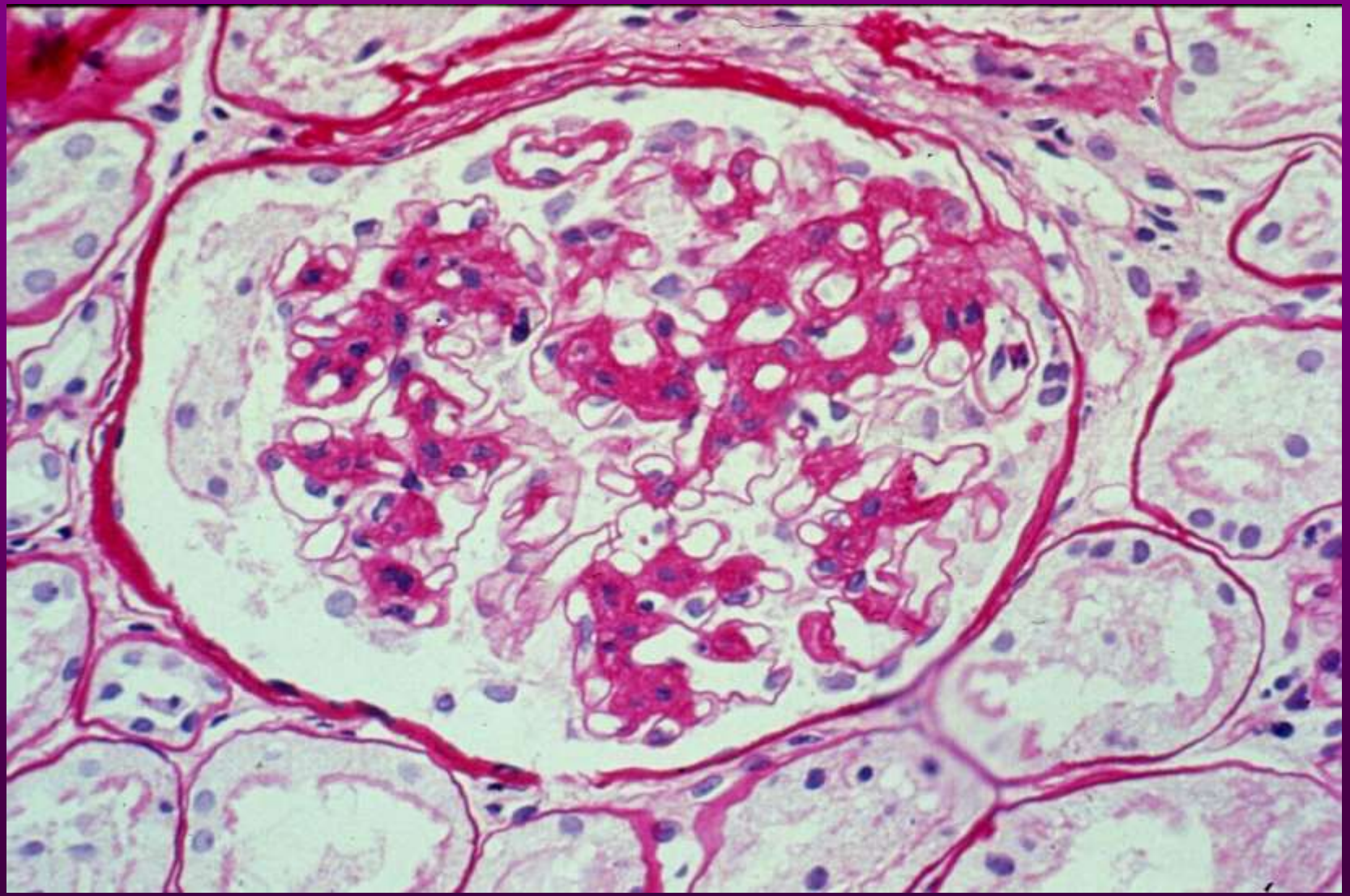
Treatment – plasma exchange (?)

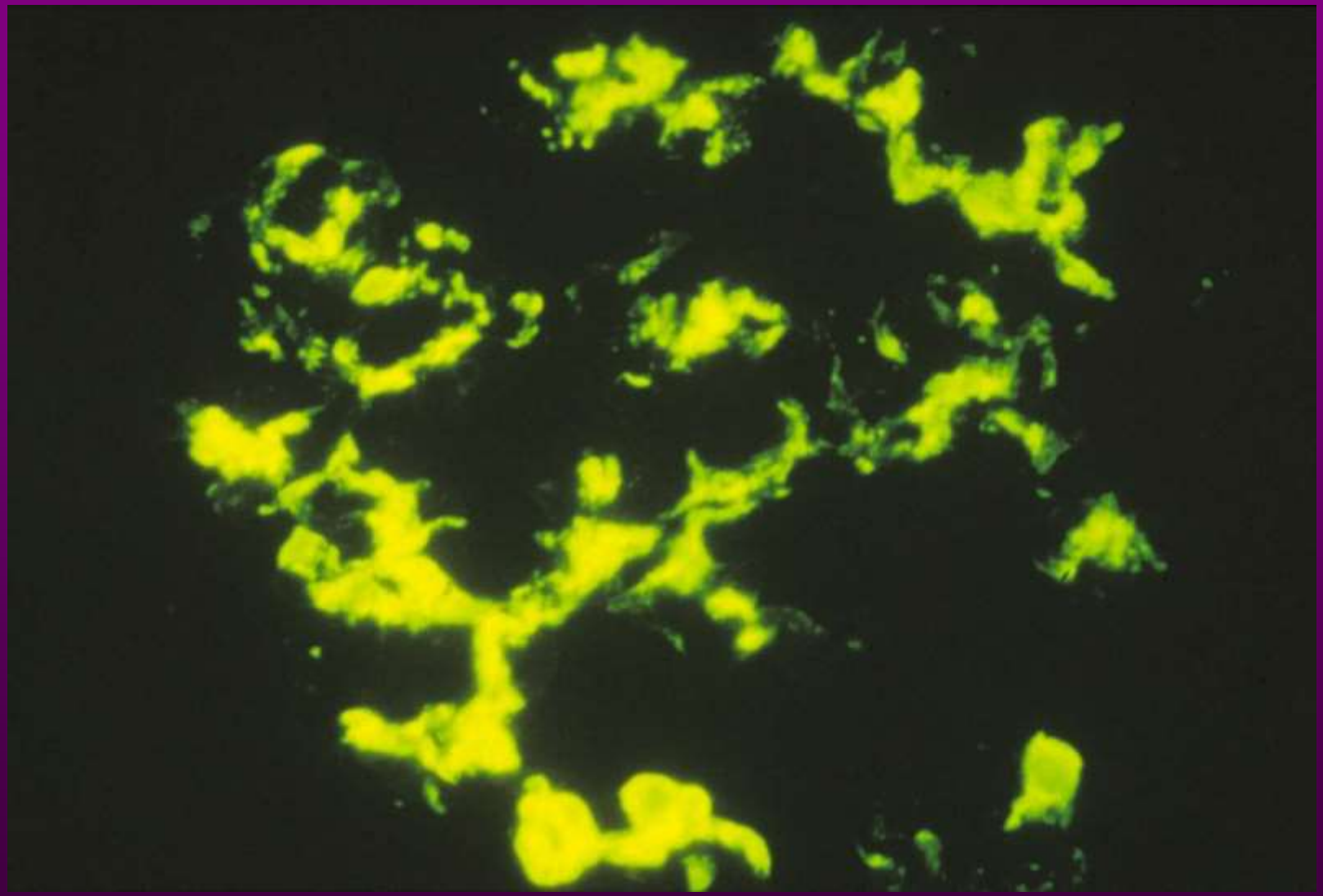
RECURRENT lgA NEPHROPATHY

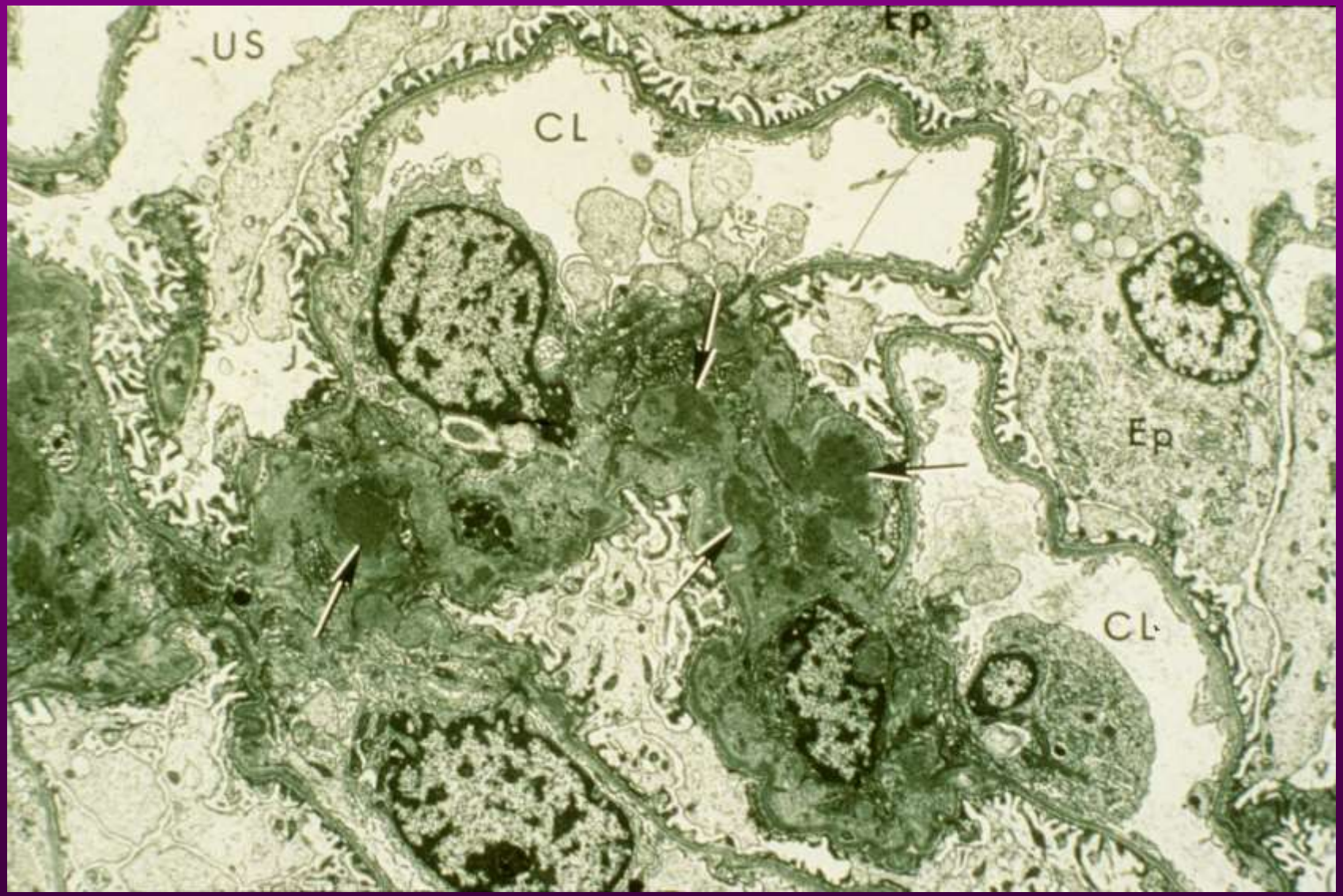
Recurrence rate - ~50% (range 20-75%)

Histology – prominent mesangial lgA staining

Clinical – hematuria, proteinuria; recurrence more common in LRA (83%)/HLA B35, DR4; lgA rheumatoid factors may be elevated; graft loss is minimal (<10%)



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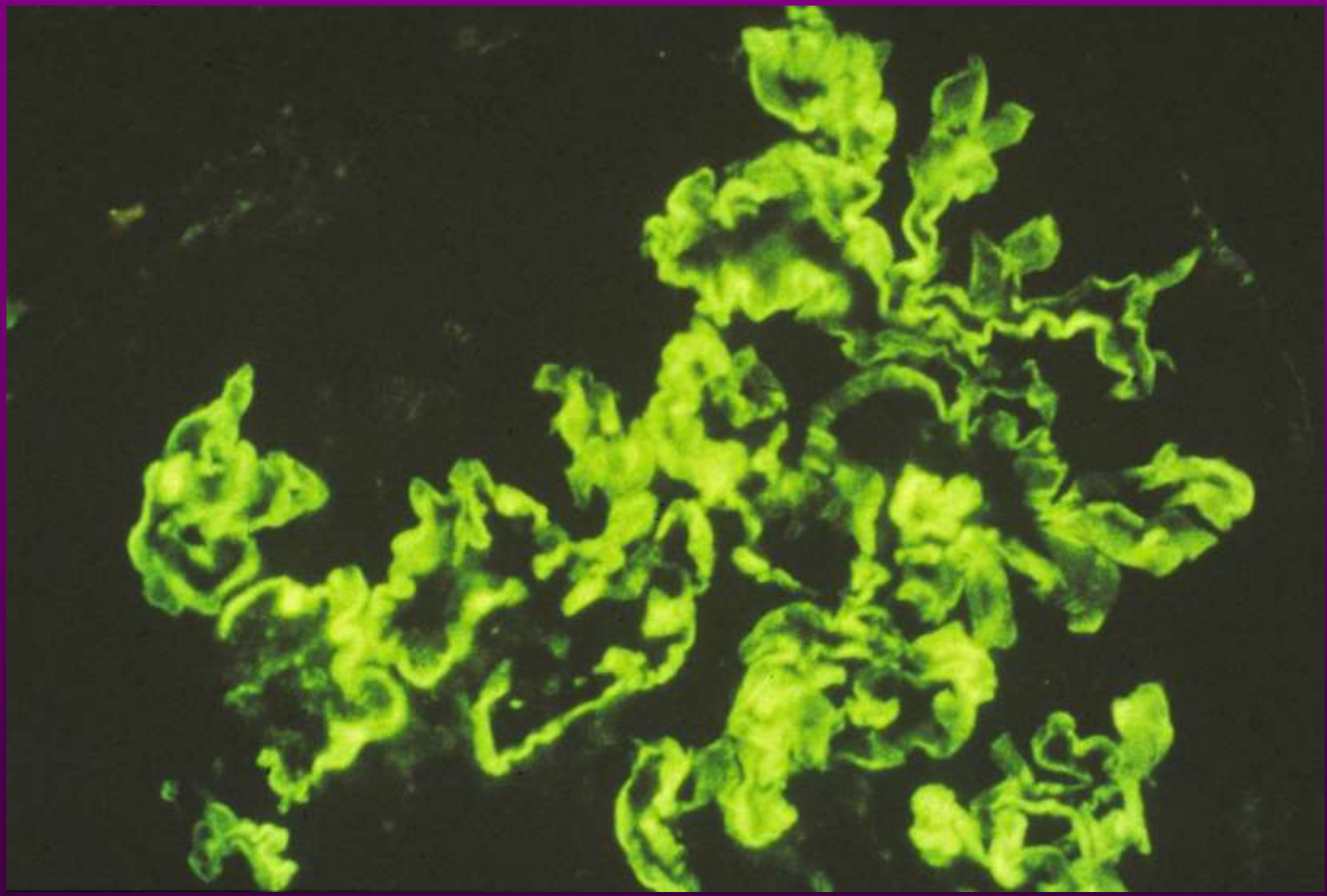
RECURRENT ANTI-GBM NEPHRITIS

Recurrence rate – clinical recurrence (nephritis) ~25%; histologic recurrence ~50%

Clinical – hematuria/proteinuria; some will resolve spontaneously; graft loss is rare

Recommendation: wait 6-12 months after loss of serum anti-GBM antibodies prior to transplantation



RECURRENT HENOCH-SCHOENLEIN PURPURA

Recurrence rate – clinical recurrence <10%; histologic recurrence (mesangial lgA) ~30%

Clinical – hematuria/proteinuria ± purpura; those with recurrence of purpura and renal involvement had active disease within 8-18 mos of tx; graft loss may approach 40-75% if both renal and skin involved

Recommendation – wait at least 6-12 mos, up to 2 years after disappearance of purpura before tx

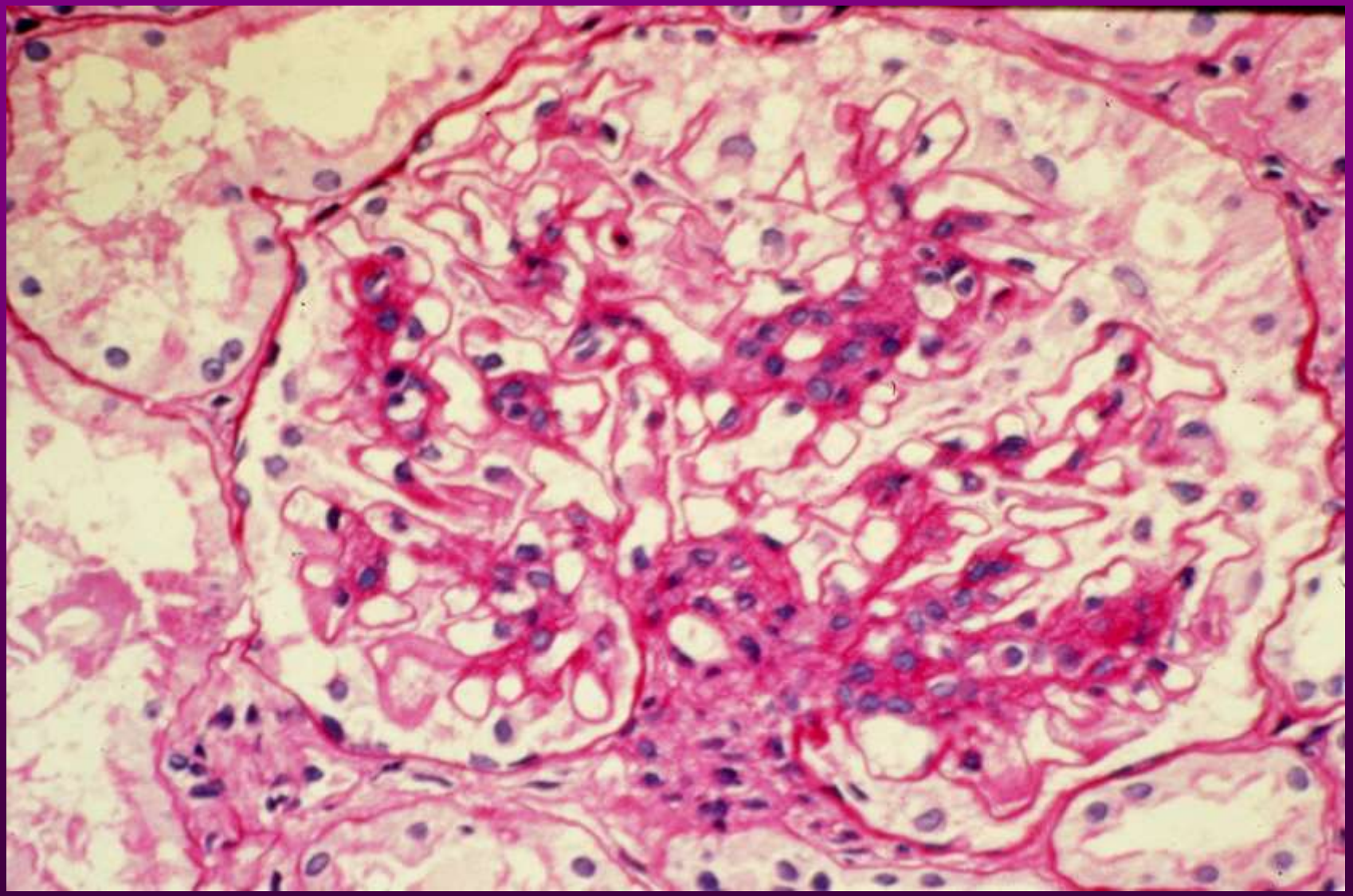
RECURRENT LUPUS NEPHRITIS

Recurrence rate – old view <1%; 5 cases documented; recent understanding 25% (Goral et al 2003)

Clinical – malar rash, Raynaud's, proteinuria (1-3gms), hematuria, pyuria; elevated anti-DNA titers and depressed complement levels; graft loss – none

Treatment – high dose steroids, chlorambucil, plasmapheresis

Recommendation – clinical and serologic quiescence prior to transplantation



RECURRENT HEMOLYTIC UREMIC SYNDROME

HUS associated with viral infections, pregnancy, oral contraceptives, chemoRx, CsA, malignant HTN, PSS< irradiation nephritis, severe acute vascular rejection, prograf

Recurrence rate - ~25-50%

Pathogenesis – lack of plasma factors leading to endothelial prostacyclin synthesis; CsA effect on prostaglandin synthesis

Histology – microvascular thrombosis

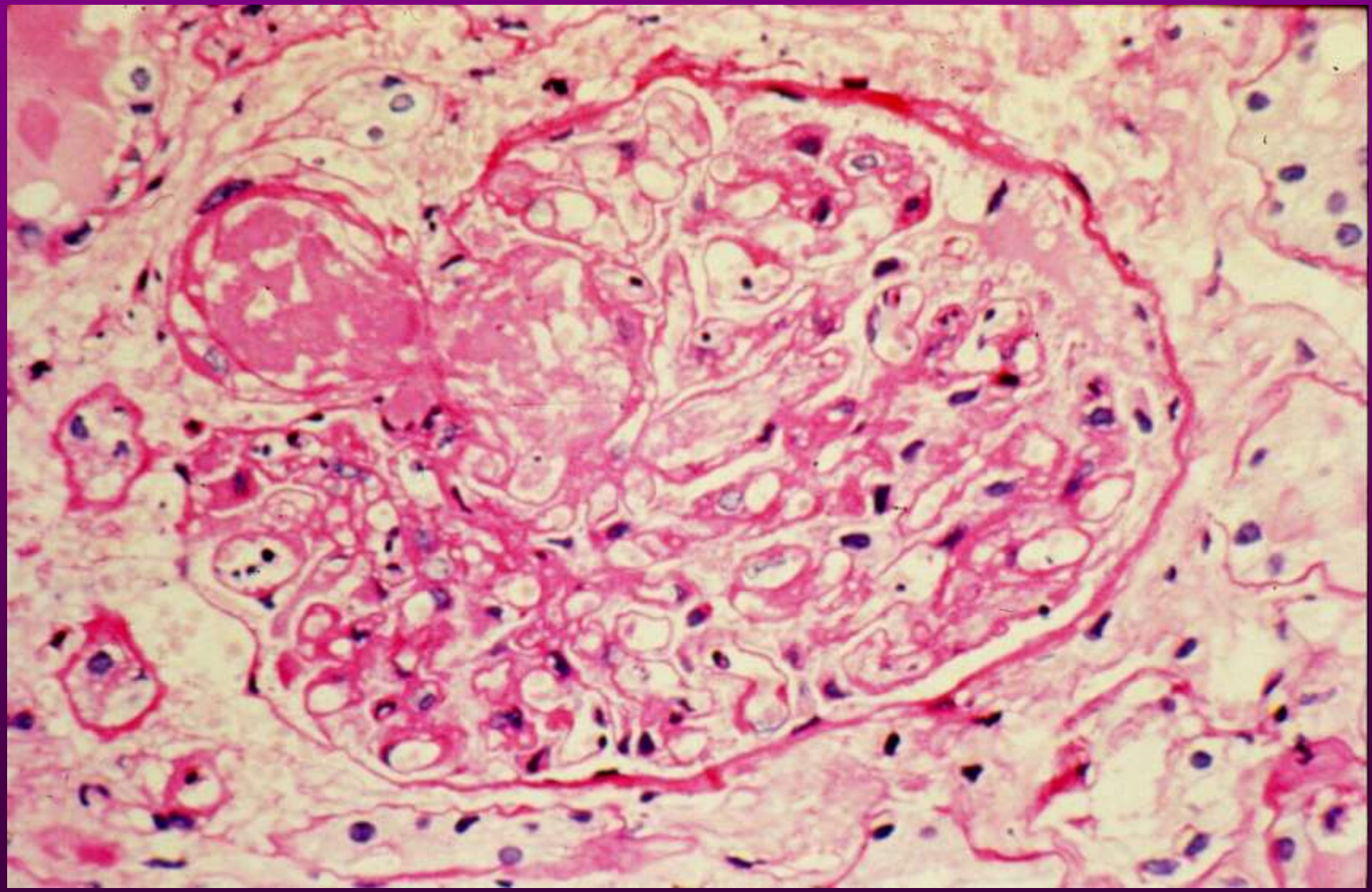
RECURRENT HUS

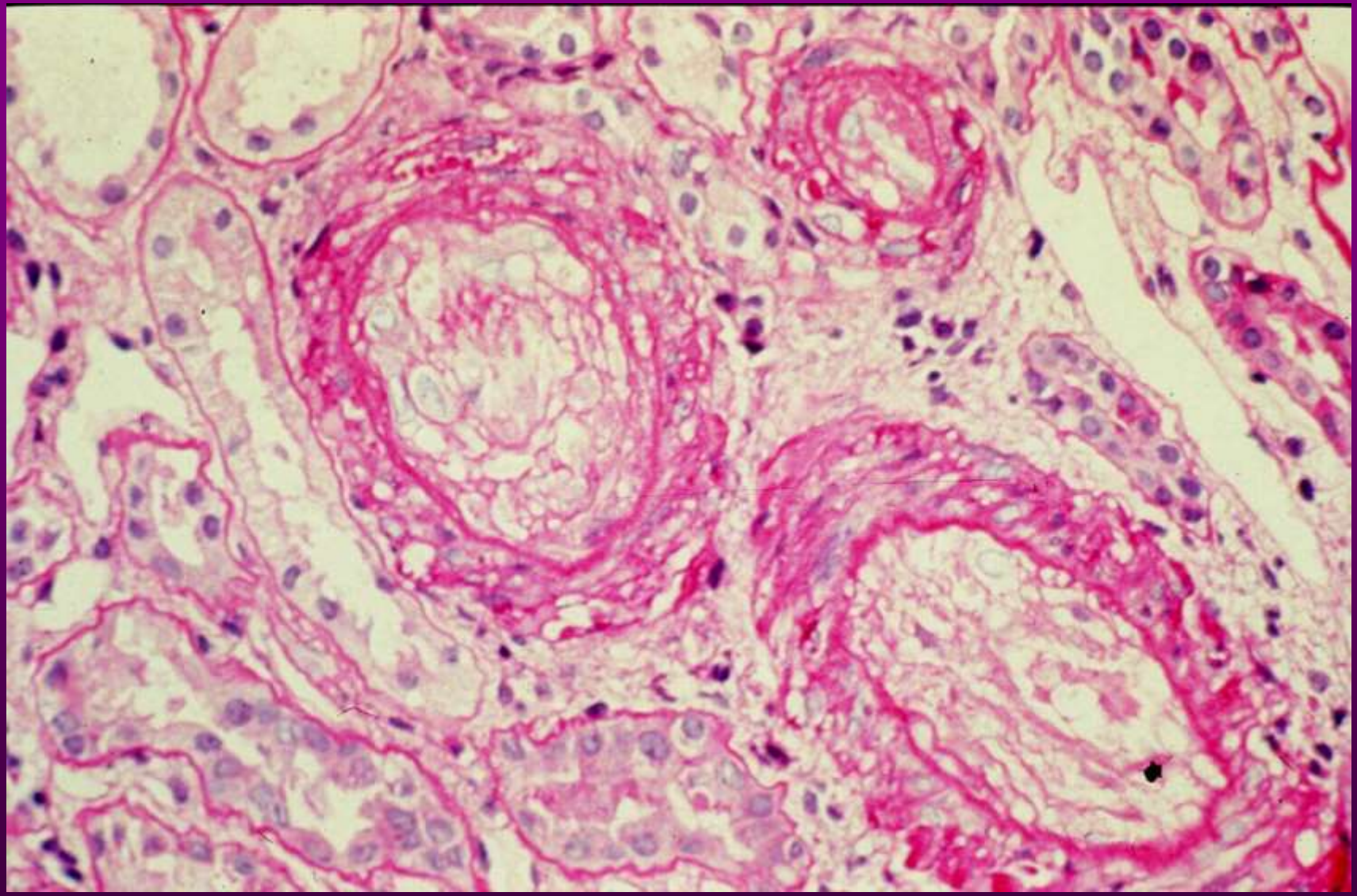
Clinical – microangiopathis hemolytic anemia, thrombocytopenia, acute renal failure; graft loss – 10-40%

Treatment –

1. **Prophylactic – low dose salicylate, dipyridamole**
2. **Acute – plasma infusions, plasma exchange**

Recommendations – avoid CsA, ALG and living related transplants



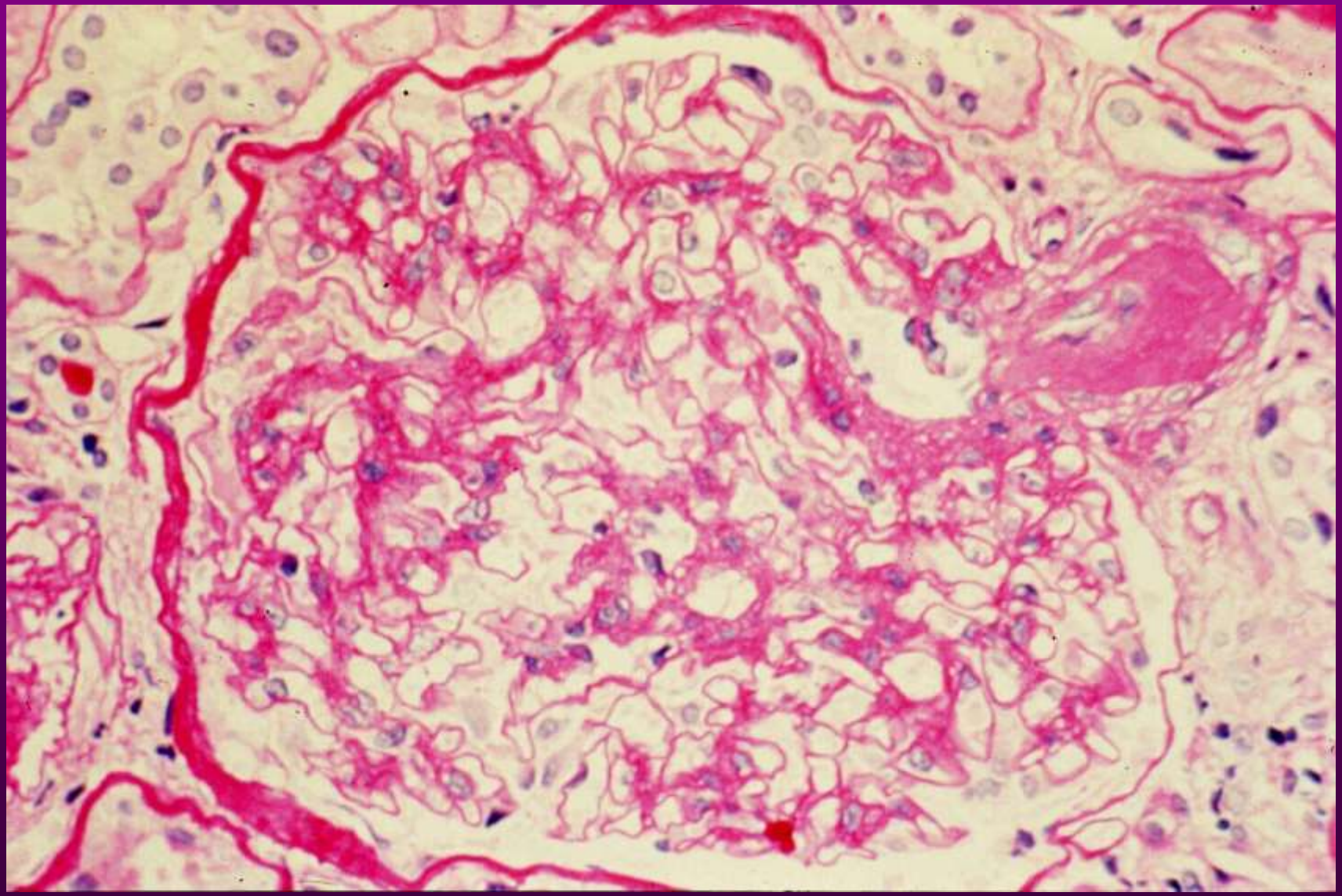


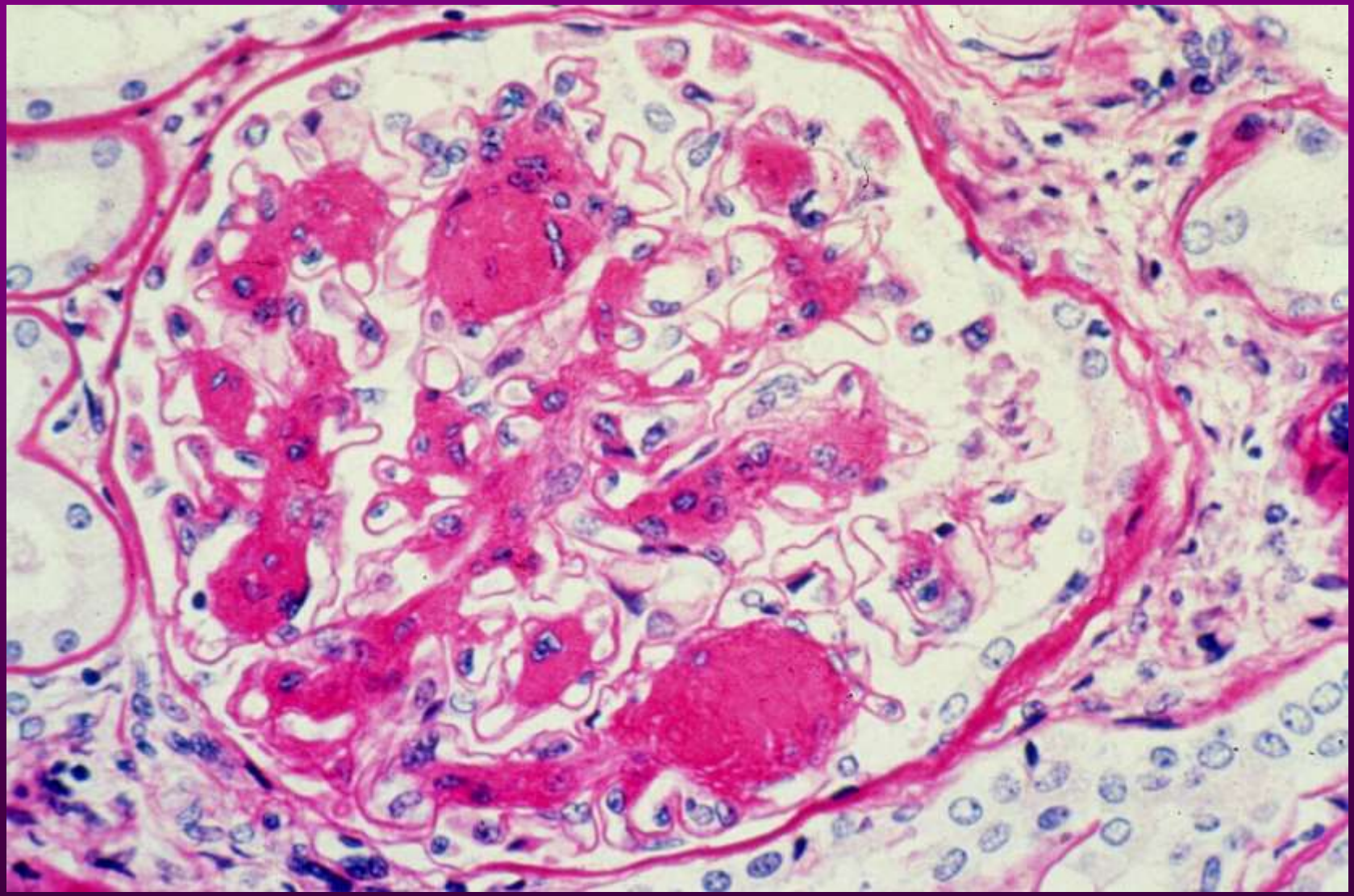
RECURRENT DIABETIC NEPHROPATHY

Recurrence rate – 100%

Histology – GBM thickening (2years); hyalinization of afferent and efferent arterioles (4 years); related to glycemic control (lesions not observed in renal/pancreas transplants)

Clinical – proteinuria; decline in renal function much faster than diabetic nephropathy in native kidneys





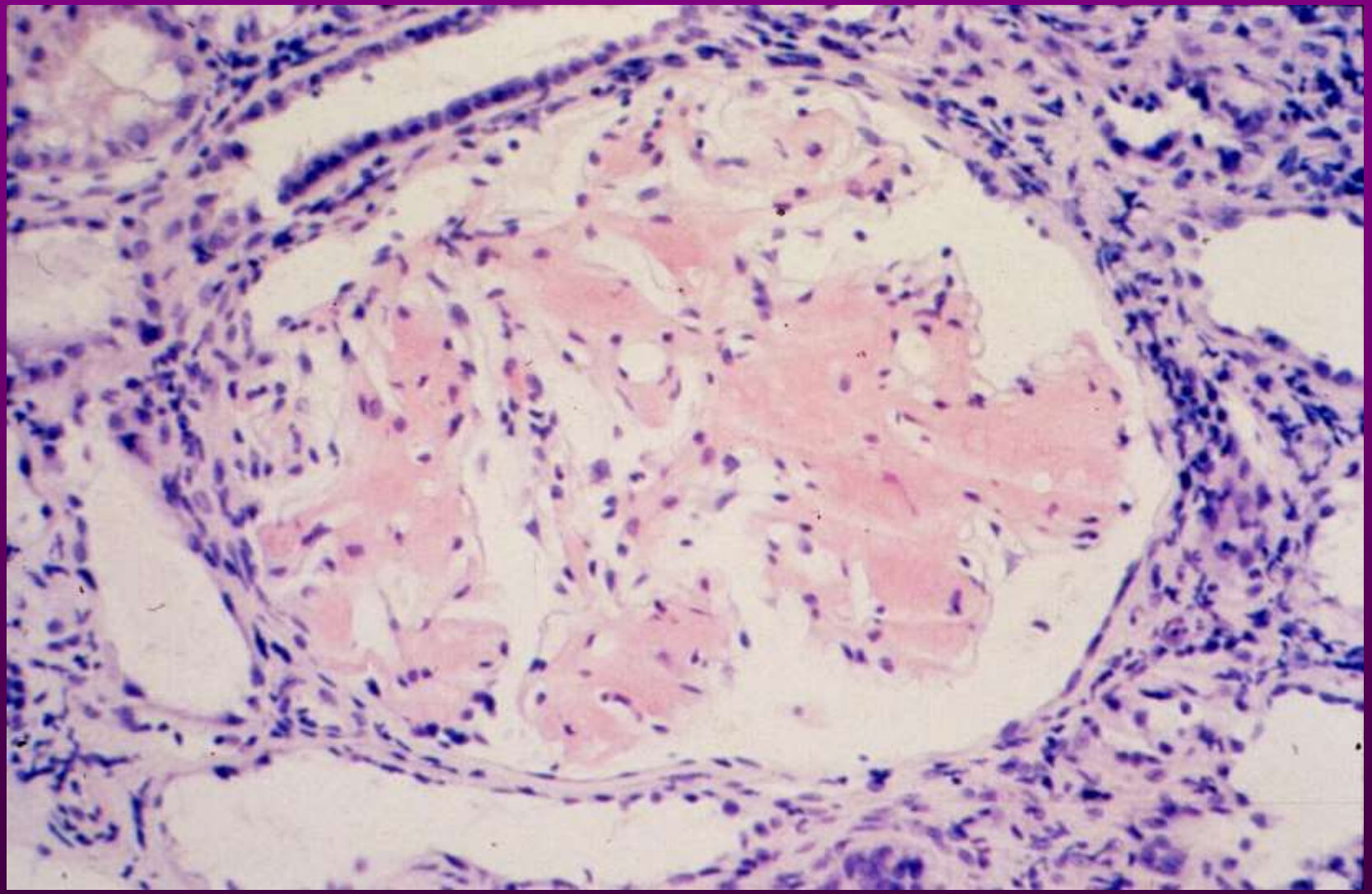
AMYLOIDOSIS

	45 amyioid	45 control tx
3 yr pt survival	51%	79%
3 yr graft survival		
- including death	38%	45%
- excluding death	53%	49%

Pasternak et al

Recurrence rate - ~20% (10%, 33%)

Graft loss rate – rare to 30%



WEGENER'S GRANULOMATOSIS

Few case reports

Recurrence successfully treated by the use of cyclophosphamide and increase int eh steroid dose

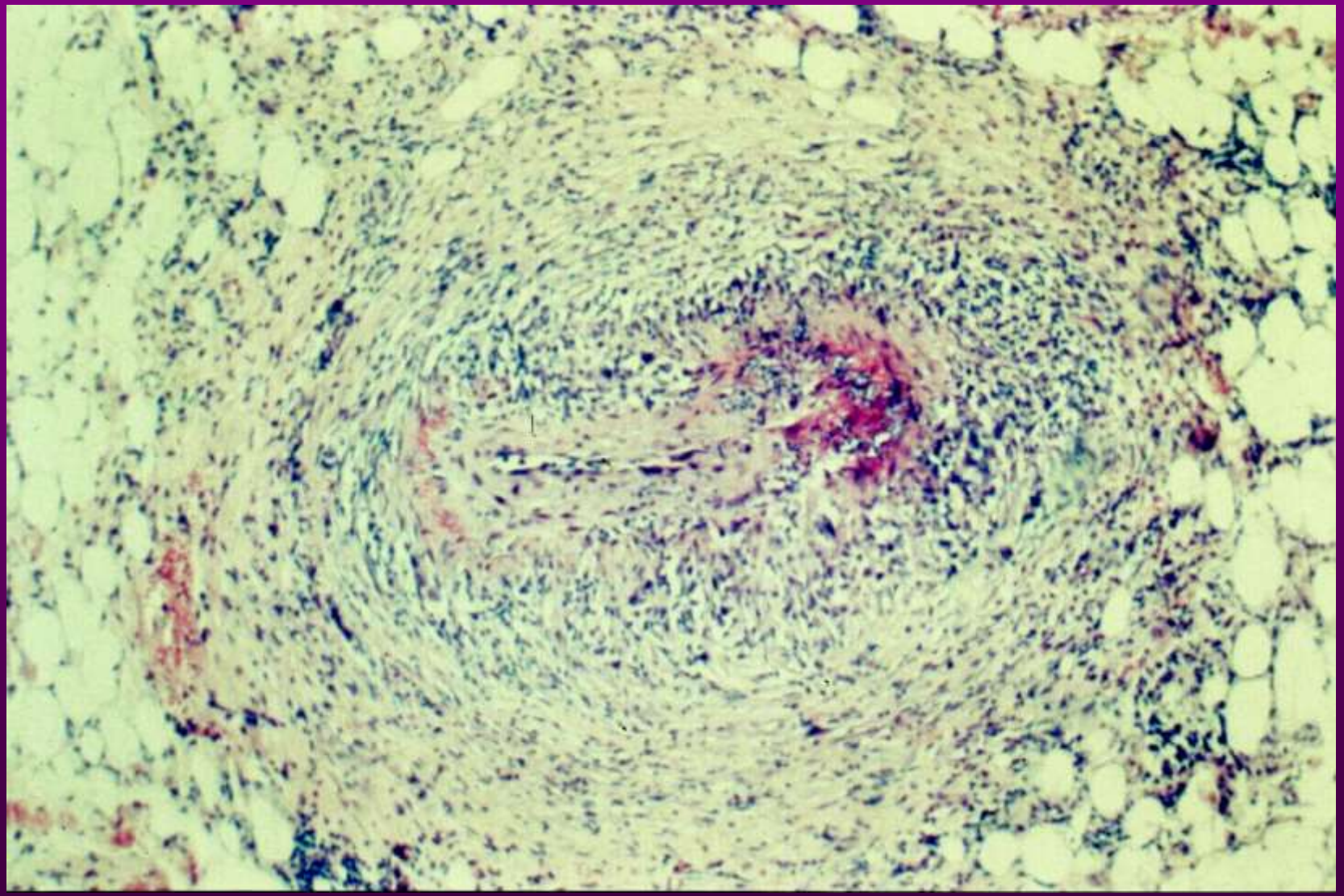
WEGENER'S GRANULOMATOSIS

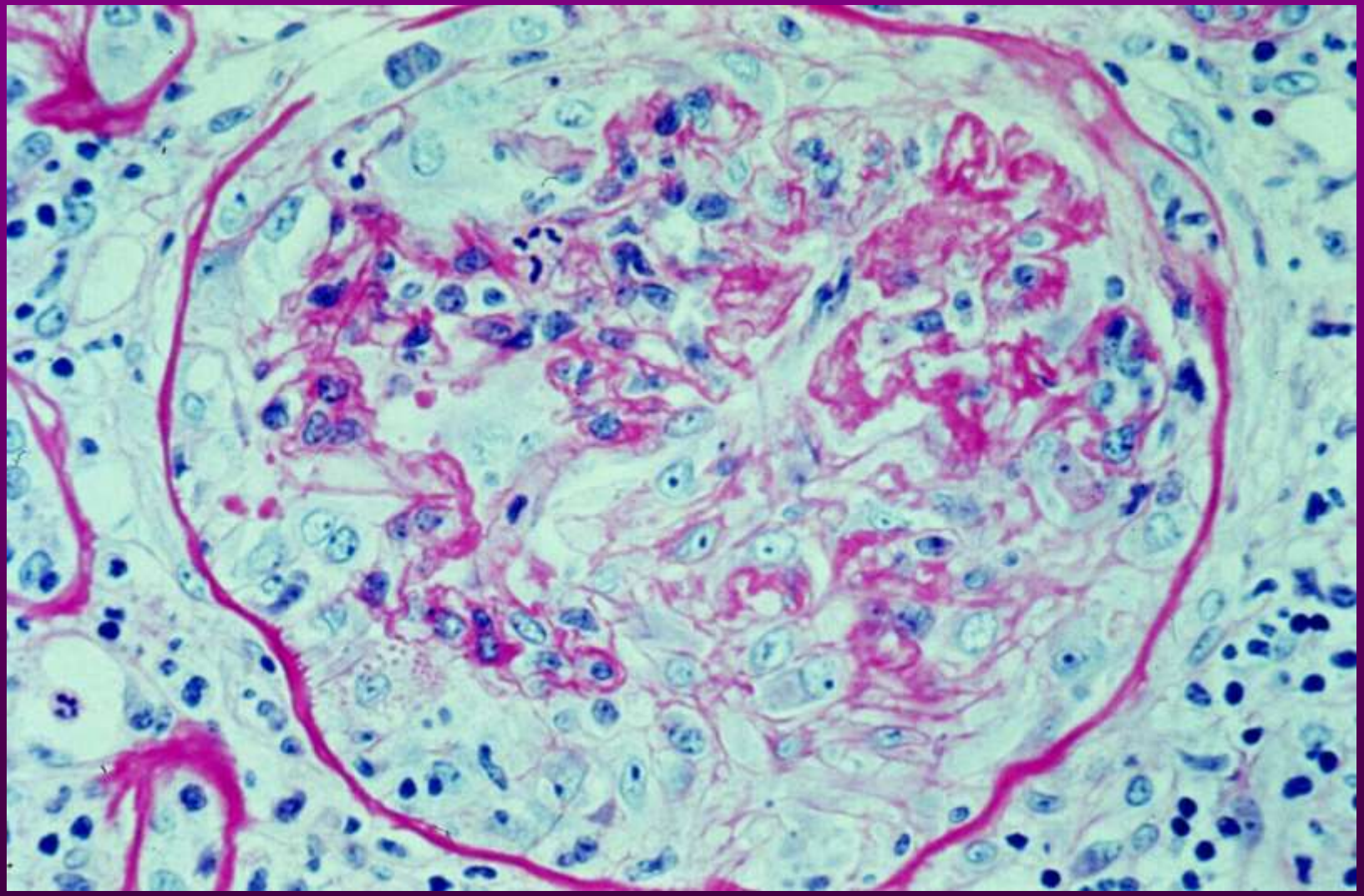
I case report:

ESRD secondary to Wegener's; S/P CRA- one rejection treated with pulse steroids.

One year post-tx CXR with nodular infiltrate; serum creatinine 200 to 750 μmol/L graft biopsy with focal and segmental GN with crescents (40%); ANCA 1:60

Treatment: methylprednisolone 500mg qd x 5 days (plum only); CsA added to Aza/pred x 3 weeks- → no change; Switch aza to cyclophosphamide (1.5 mg/kg/d) → reversed plum and renal impairment; continued on CsAcyclophos/pred; ANCA negative





ESSENTIAL MIXED CRYOGLOBULINEMIA

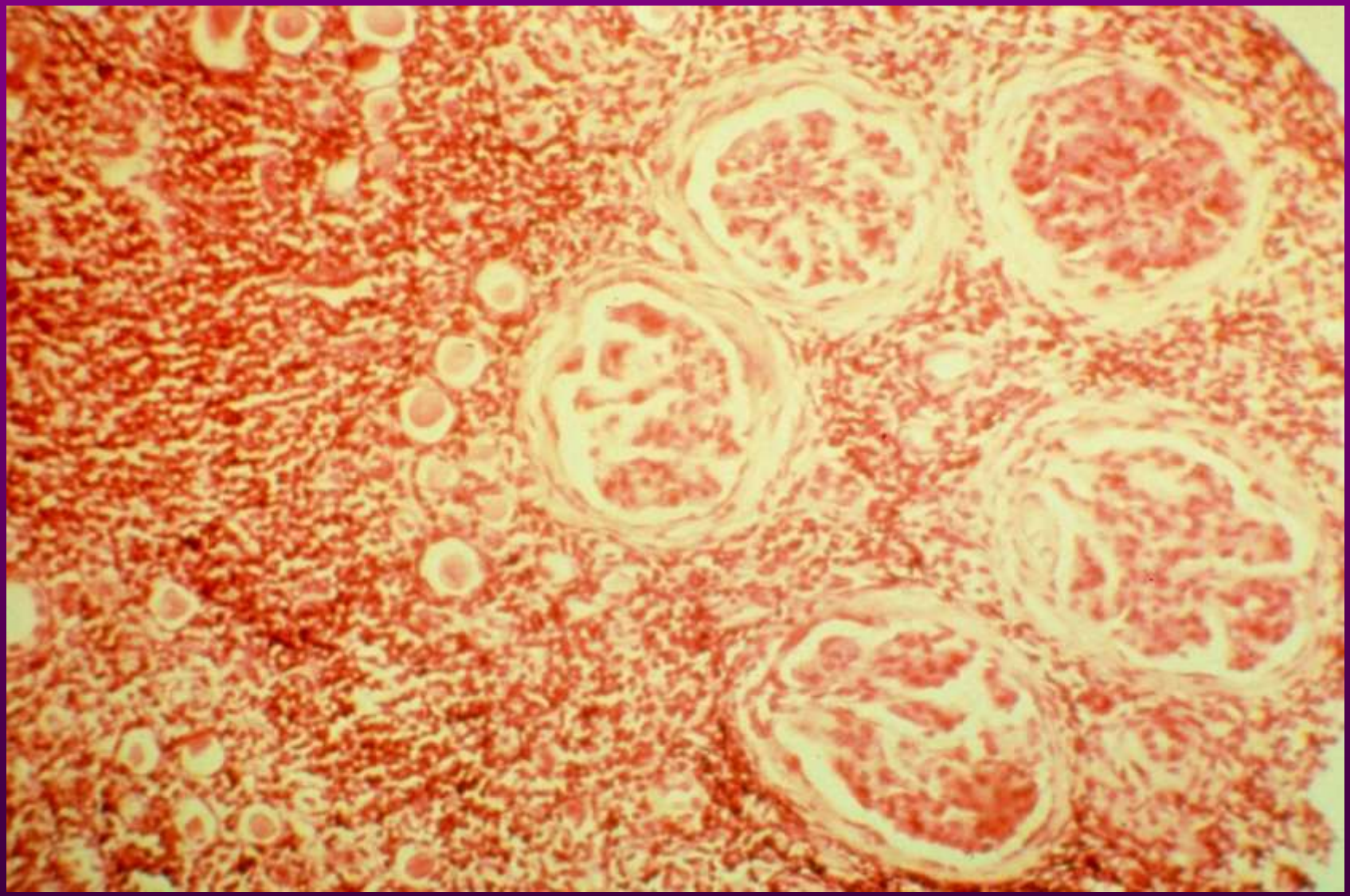
Recurrence rate - ~50%

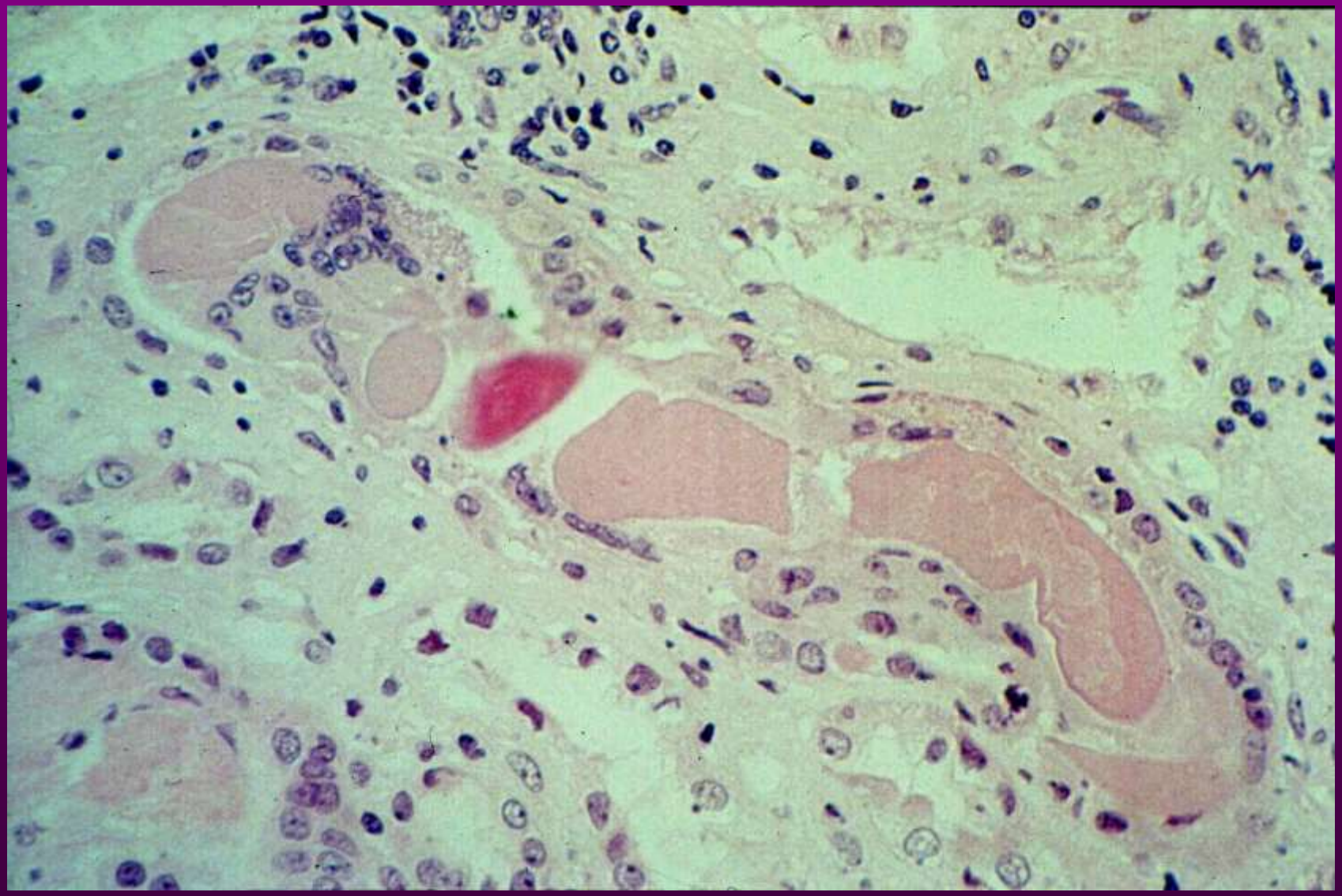
Clinical – renal (proteinuria, hematuria) and extrarenal (purpura, arthraigias) manifestations; cryoglobulins, rheumatoid factor and decreased C3 and C4 levels in the serum

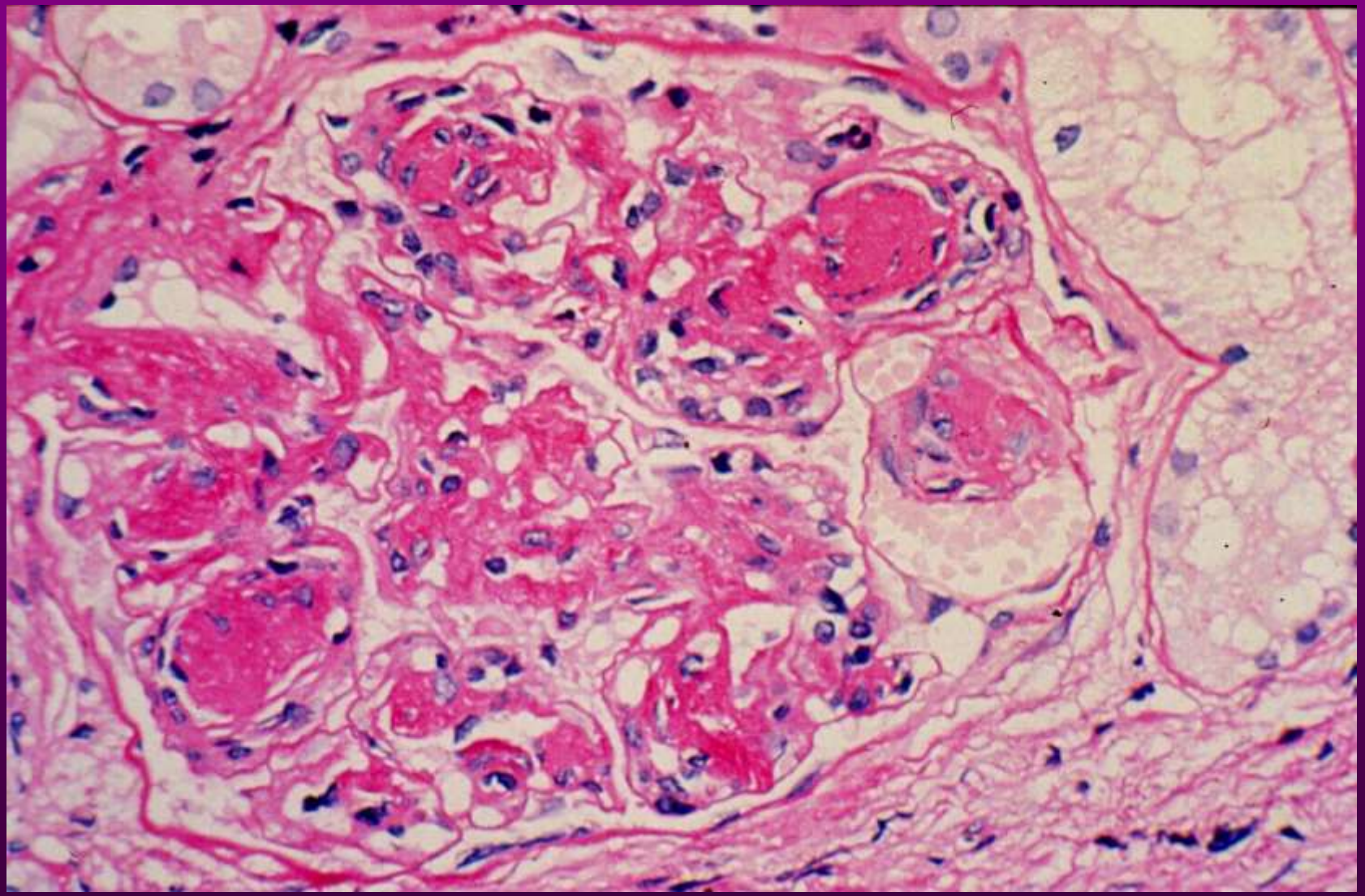
Recurrence may occur despite clinical and serologic quiescence; may lead to graft loss

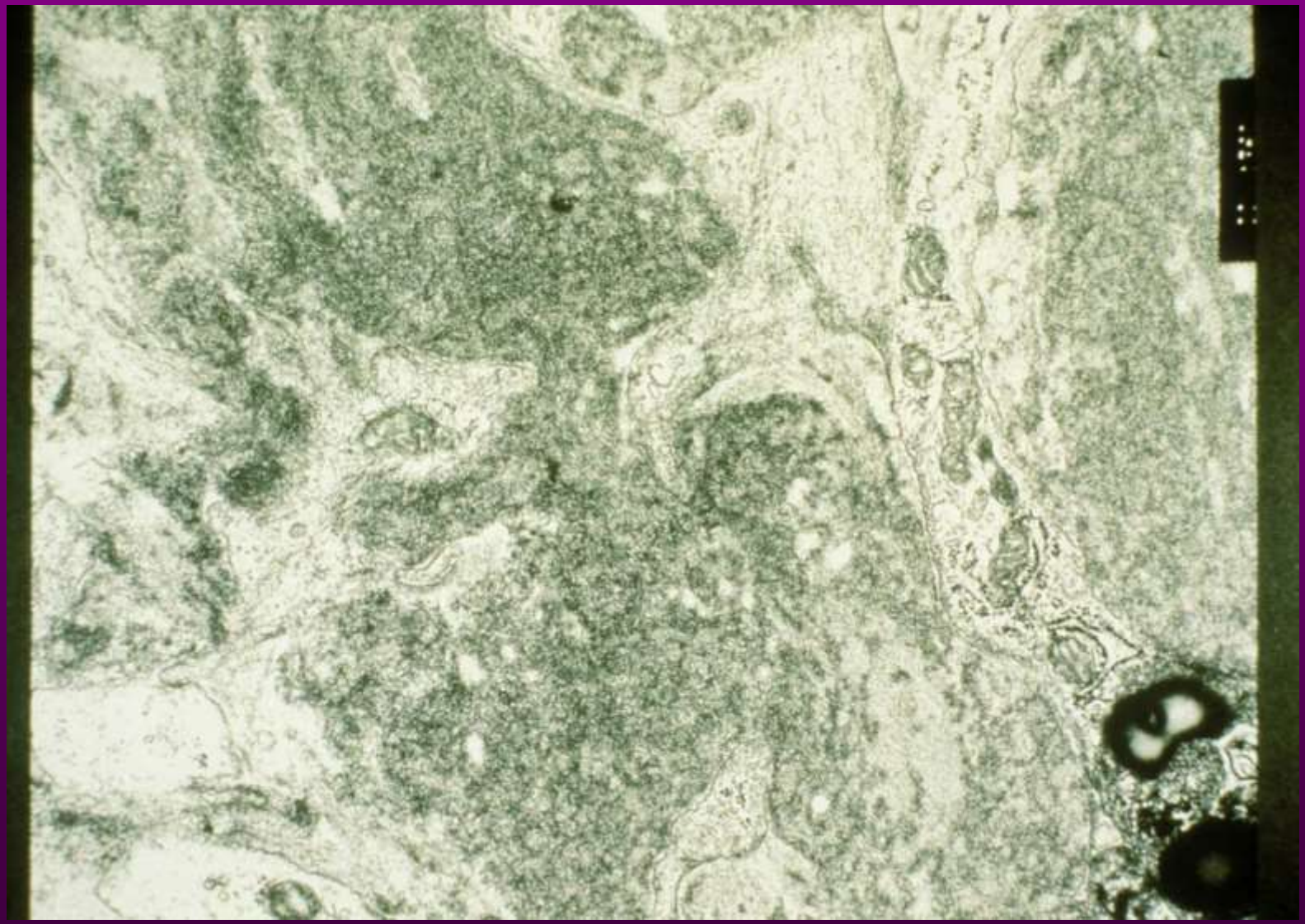
MONOCLONAL GAMMOPATHY

1. Multiple myeloma – may recur as plasmactic infiltration, tublar cast formation; fibrillar crescentic GN (graft loss)
2. Macroglobulinemic nephropathy – one case report of recurrence of lgM and lambda light chain staining and diffuse mesangiocapillary changes (stable function)
3. Light chain deposition disease with or without serum nonoclonal proteins have recurred with or without effet on the allograft
4. Fibrillary GN – 5.5 yrs post-tx with 17 gm proteinuria









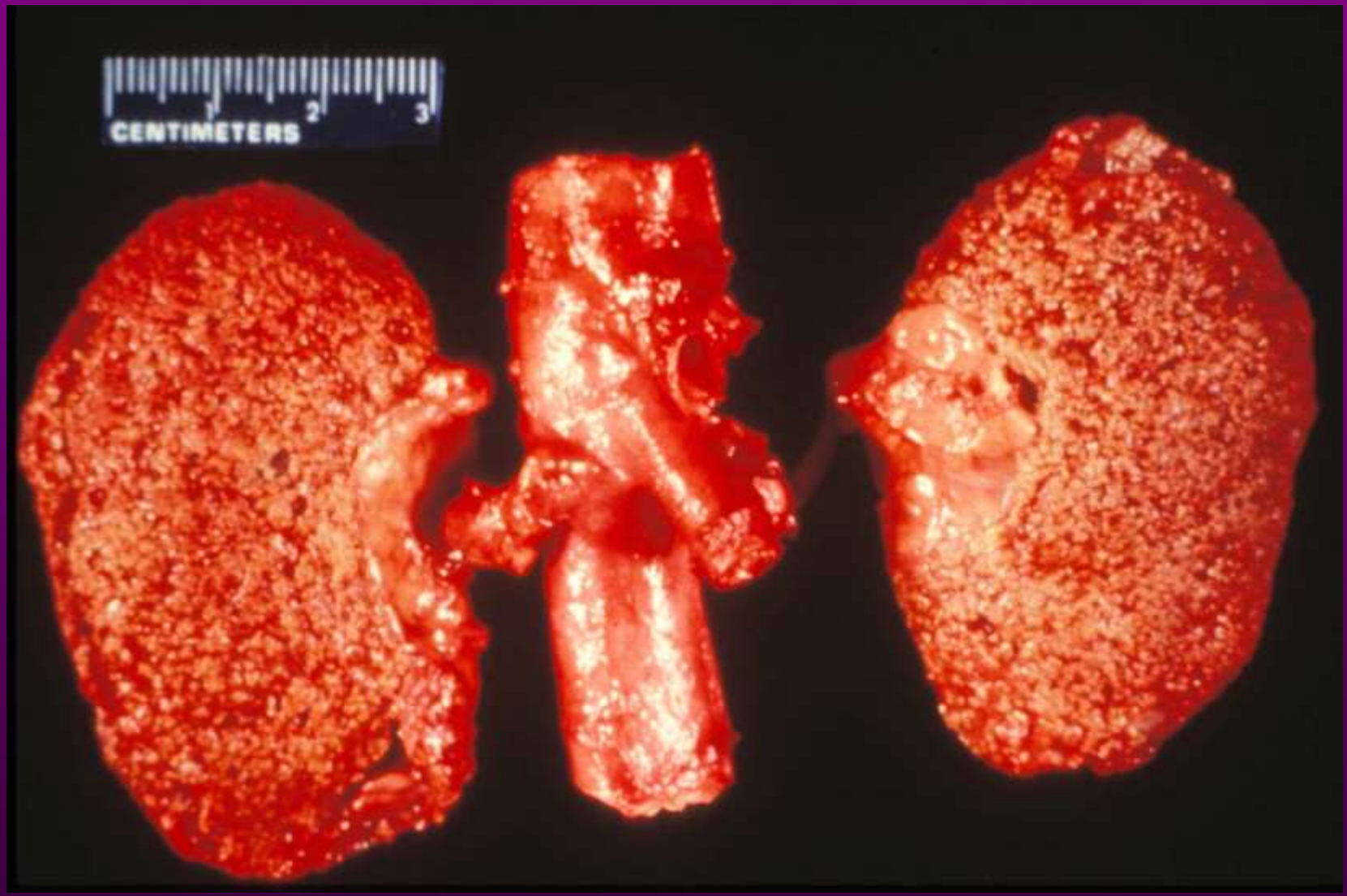
OXALOSIS

Inborn error in glyoxalate metabolism – oxalate accumulation

Recurrence rate – 90%

Clinical – Sucdess more likely if:

1. Early tx – GFR ~20 ml/min1.73 meter squared
2. Aggressive pre-op dialysis to deplete oxalate pool
3. Maintenance of high rates of urine flow; avoid allograft non-function and rejection
4. Simultaneous renal-liver transplant (enzyme replacement)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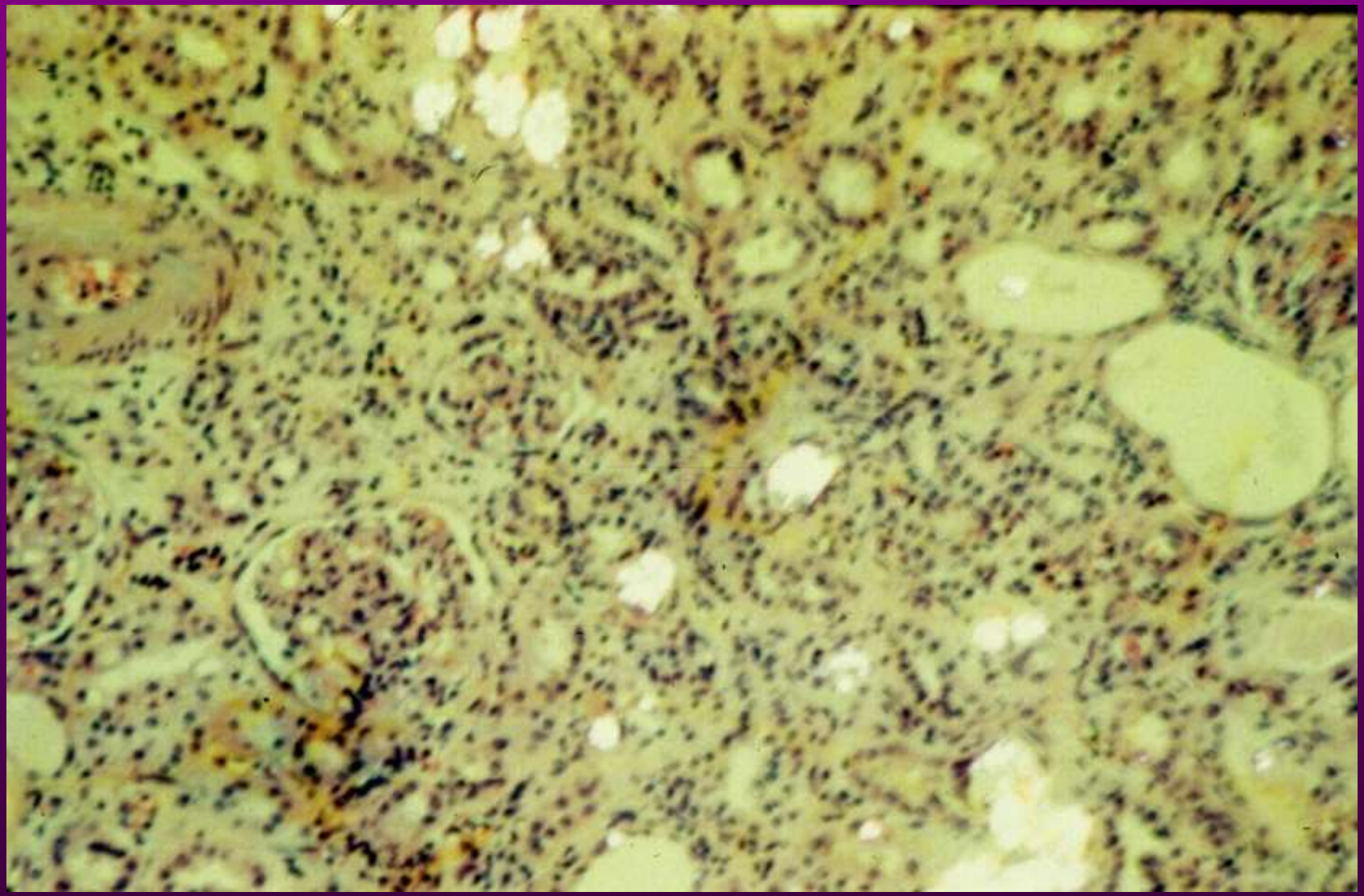


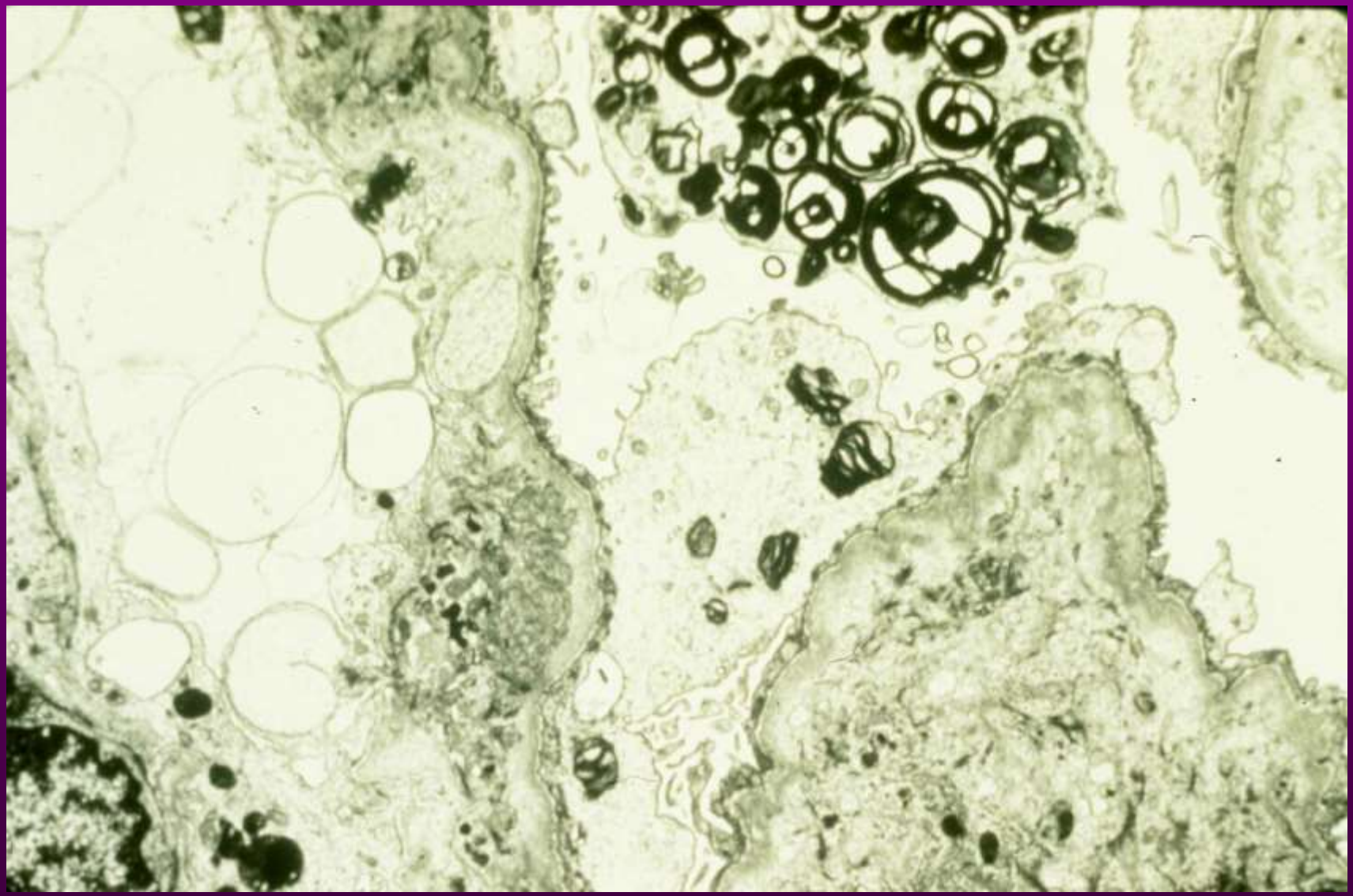
FABRY'S DISEASE

Inborn error of glycosphingolipid metabolism ??

Transplanted kidney – source of missing enzyme

Experience – disappointing; high patient mortality

Dialysis – preferred renal replacement therapy

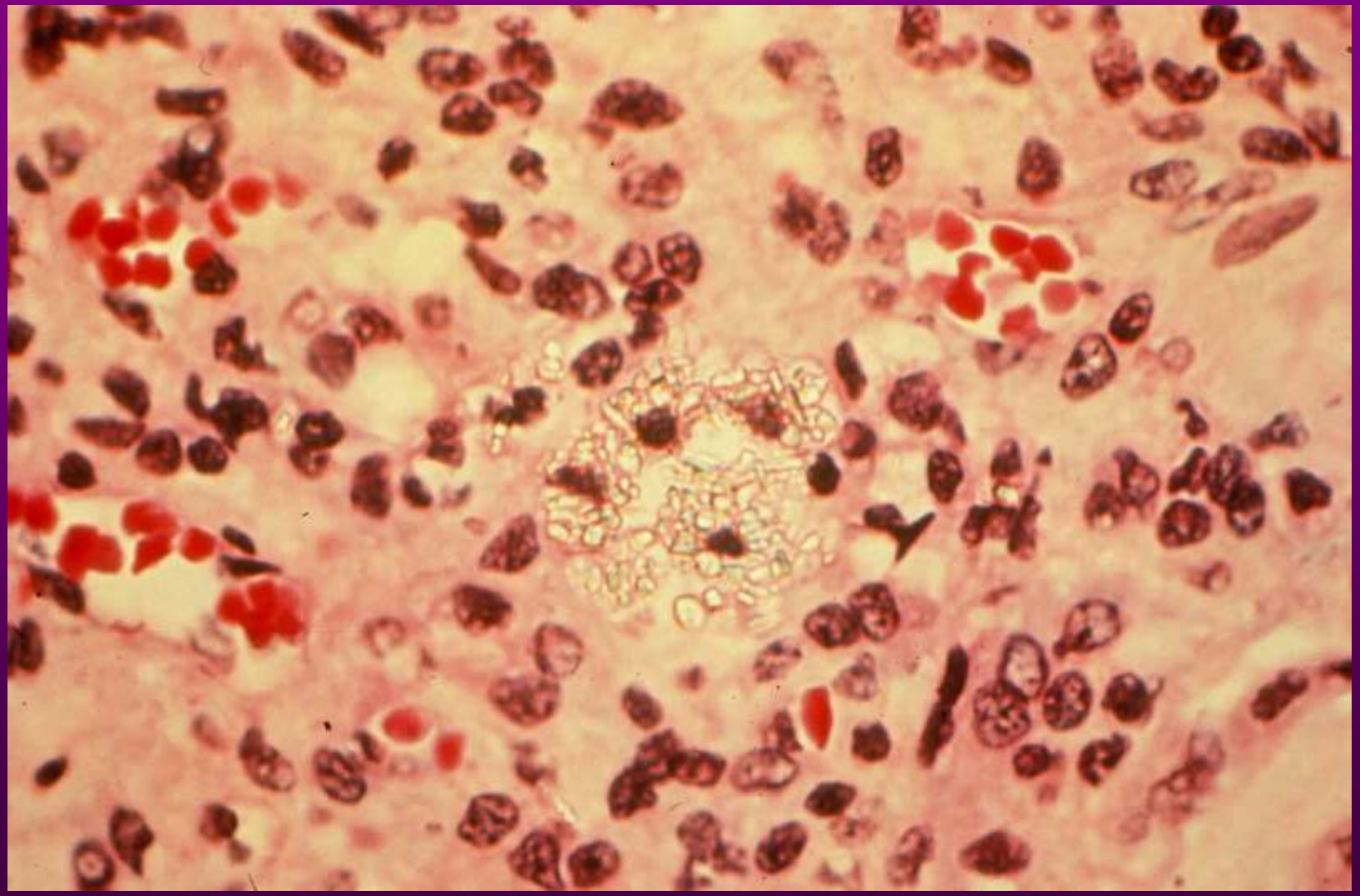


CYSTINOSIS

Inborn error in sulfur metabolism – cystine accumulation

Recurrence rate - ~10%

Clinical – minimal impairment in graft function; continued systemic manifestations; preferred mode of treatment of ESRD in children



SICKLE CELL NEPHROPATHY

University of Alabama experience – disappointing with most graft loss to sickling and rejection

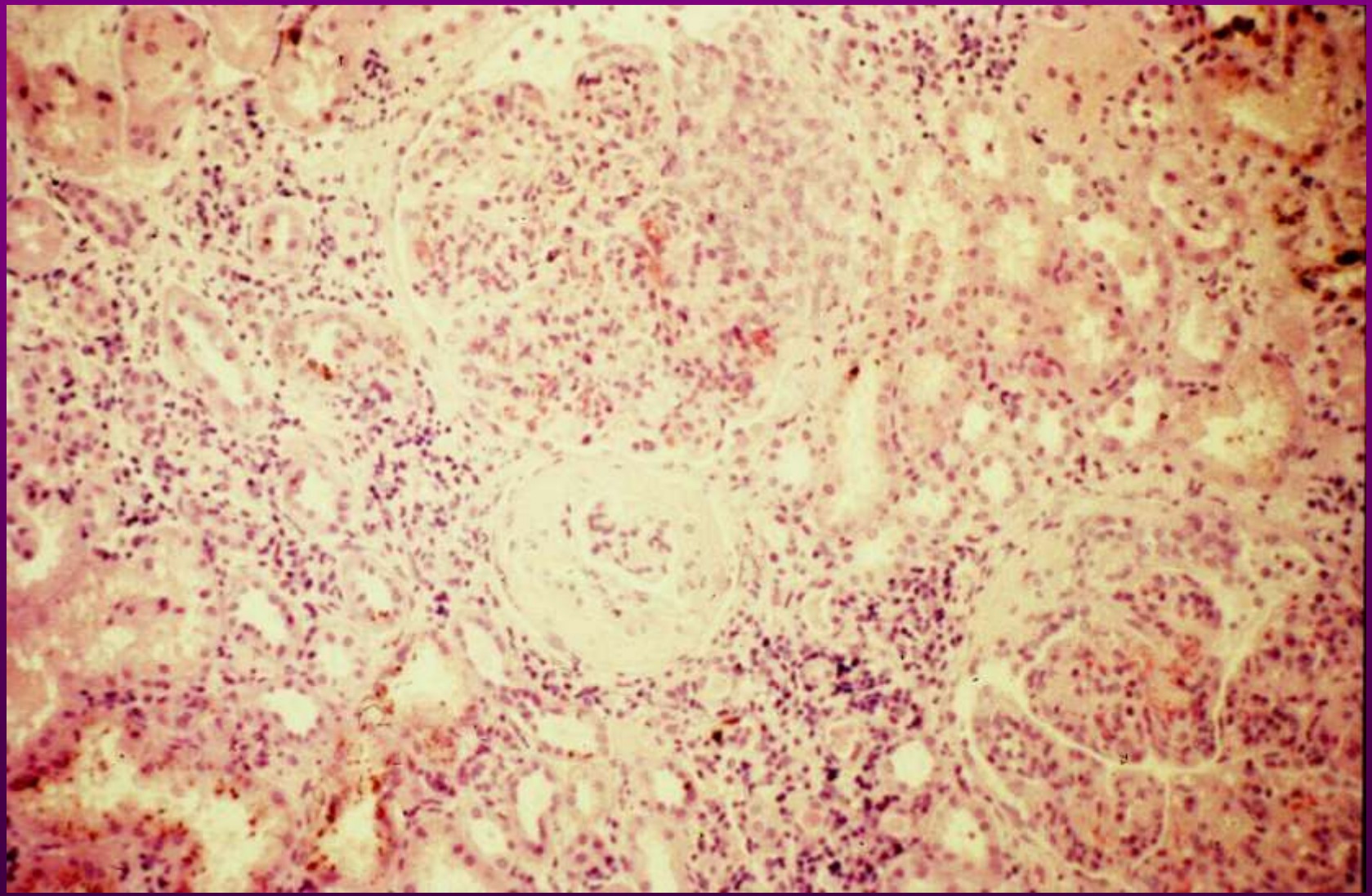
Cumulative data (other centers) – 80% 1 year graft survival

Recurrence of SC nephropathy – rare; one case report of prominent hemosiderosis with chronic ischemic damage, interstitial fibrosis, tubular atrophy

Table 1. Patients with sickle cell disorders undergoing cadaveric renal transplantation

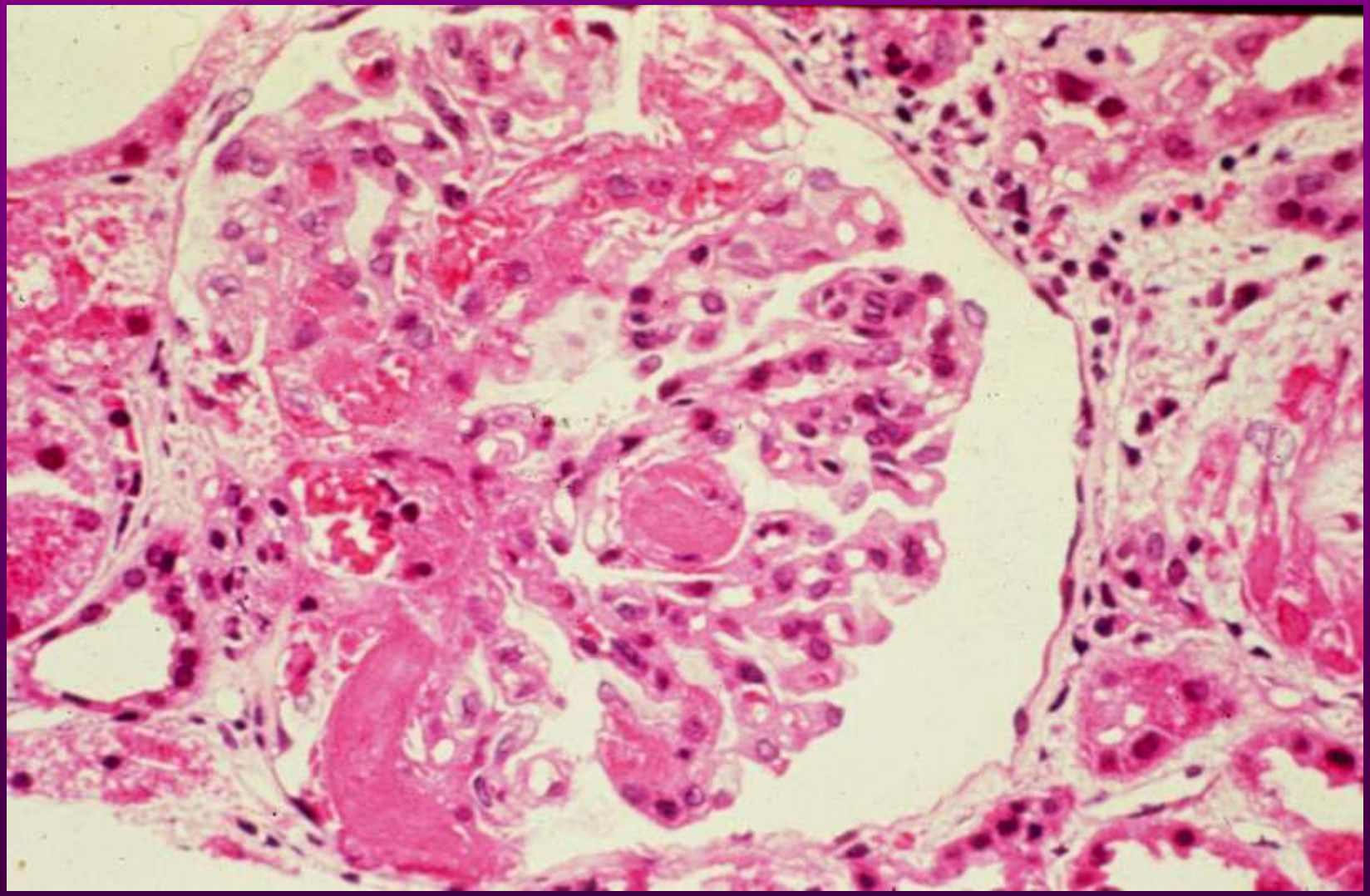
Patient No.	Age[1]/Sex	Disorder[2]	Hematocrit Pre-Tx[3]	Hematocrit Last[4]	Sickle Crisis	Loss of Allograft	Allograft Survival	Comments
1	29/M	SS	24	35	Yes	Sickling	2 mo.	Died
2	13/M	SS	16	15	No	No	49 mo.	Chronic rejection
3	23/M	SS	23	23	Yes	Sickling	5 mo.	Alive – Transplant Nephrectomy
4	18/M	SS	14	33	Yes	? Sepsis	15 mo.	Died
5	36/M	SS	23	23	No	Sickling	3 d	Alive – Transplant Nephrectomy
6	34/F	SS	21	34	No	Rejection	1 mo.	Alive – Transplant Nephrectomy
7	45/M	SC	26	44	Yes	Sickling	3 d	Died
8	40/M	SB	23	20	Yes	Rejection	2 mo.	Alive – Transplant Nephrectomy

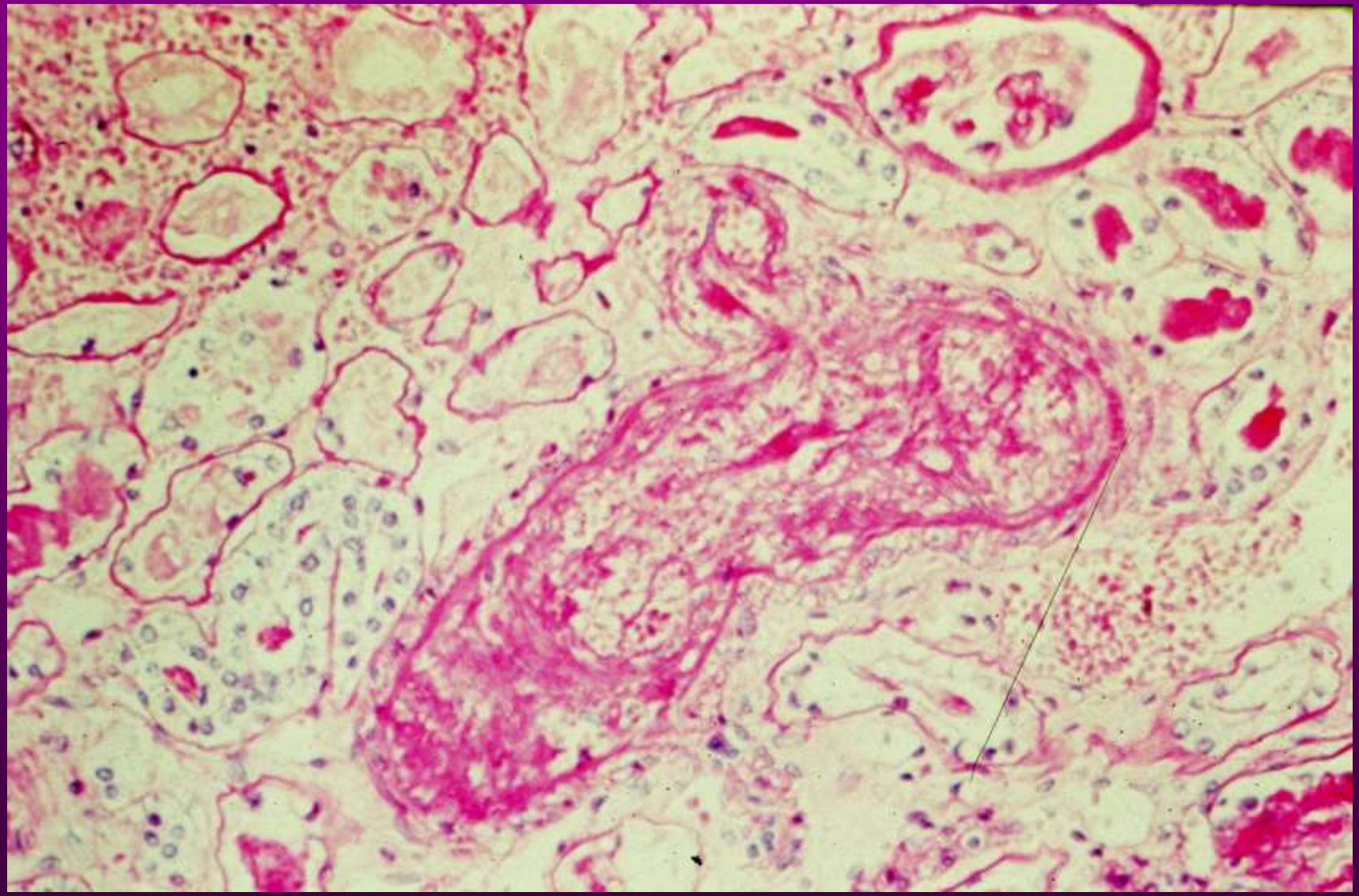
[1] Age on date of transplantation.
[2] SS denotes sickle cell anemia, SC HbS-HbC disease, SB HbS – Beta thalassemia disease.
[3] Immediately before transplantation.
[4] At loss of allograft or last follow-up.

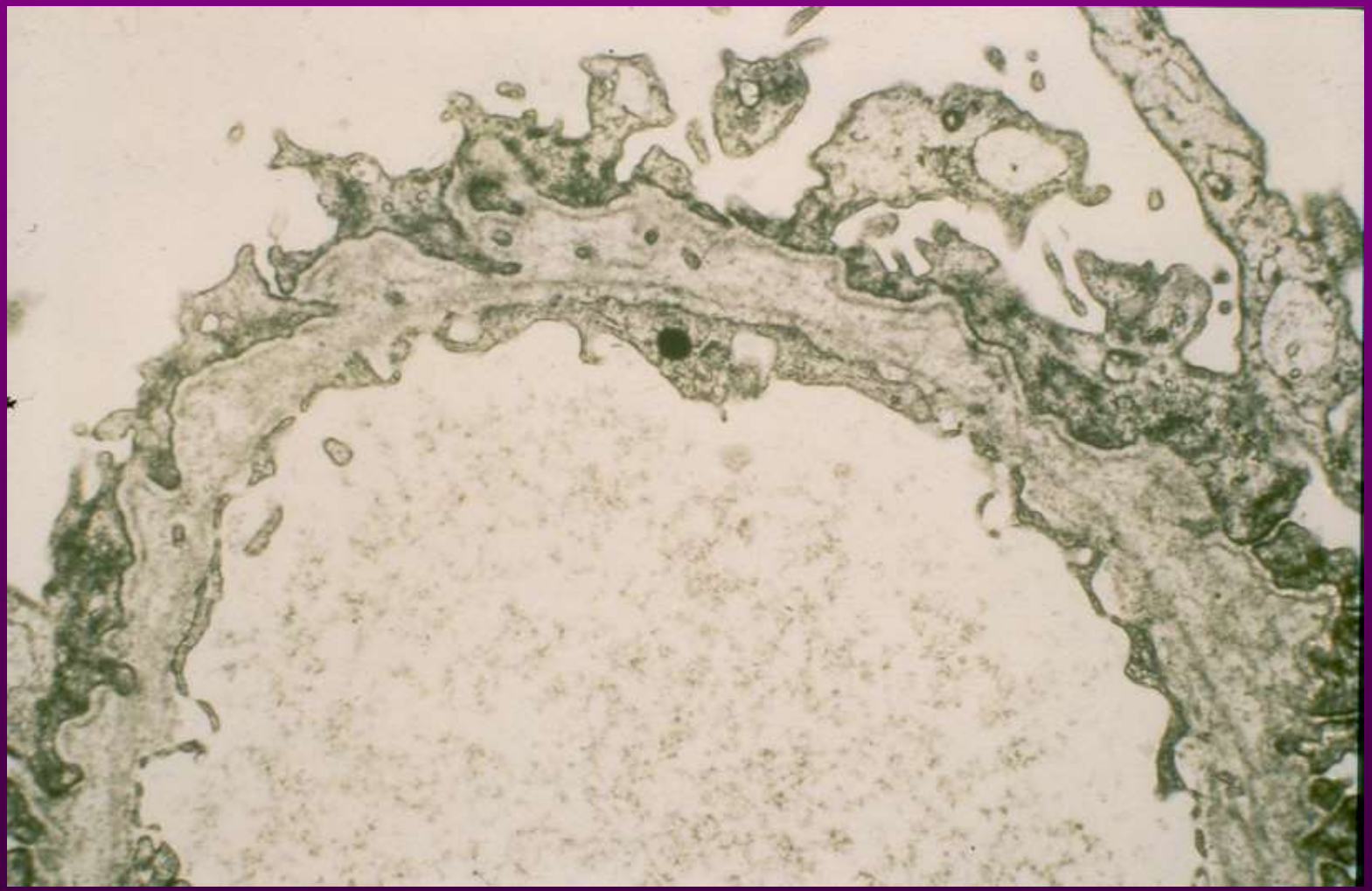


PROGRESSIVE SYSTEMIC SCLEROSIS

1. Patients who do well with dialysis or transplantation have had bilateral native nephrectomies (to control HTN)
2. Patients with recurrence (2 reports in literature) had a malignant course with onset of PSS to transplantation <1 year; anti-nuclear antibodies eluted from graft
3. Recommendation – delay transplantation until clinically stable and without visceral PSS activity







ALPORT'S SYNDROME

Recurrence – rare, only one reported case

Clinical – patients are at small risk to develop anti-GBM nephritis due to exposure to "normal" GBM antigens present in the allograft (lack a domain of type IV collagen)

May have serum anti-GBM Abs, abnormal U/A, linear lgG staining, GN; crescentic GN associated with graft loss

CONCLUSION

- THE TRANSPLANTED KIDNEY IS NOT IMMUNE FROM DE NOVO OR RECURRENT RENAL DISEASE
- THE MAGNITUDE OF THE PROBLEM IS STILL UNDER STUDY
- A REGISTRY IS NOW IN PLACE TO AIDE IN OUR UNDERSTANDING