RECURRENT AND DE NOVO RENAL DISEASES IN THE ALLOGRAFT
HISTOPATHOLOGIC DISORDERS AFFECTING THE ALLOGRAFT OTHER THAN REJECTION

RECURRENT DISEASE
- Glomerular
- Non-gglomerular

DE NOVO DISEASE
- Glomerular

TRANSPLANT GLOMERULOPATHY
- Chronic Rejection
TRANSPLANT GLOMERULOPATHY

**Pathogenesis:** consequence of chronic rejection; inverse relation with donor and 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 IgM 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%
**TRANSPLANT GLOMERULOPATHY**

**Pathogenesis:** consequence of chronic rejection; inverse relation with donor and recipient compatibility; repetitive episodes of endothelial injury

**Histology:** endothelial and mesangial cell swelling; GBM reduplication; myointimal proliferation progressing to fibrosis leading to obliterative arteriopathy; IF- capillary wall IgM 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%
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%
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

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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<tbody>
<tr>
<td>FSGS</td>
<td>HSP</td>
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<tr>
<td>Membranous</td>
<td>HUS</td>
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<tr>
<td>Nephropathy</td>
<td>SLE</td>
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<tr>
<td>MPGN I</td>
<td>DM</td>
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<tr>
<td>MPGN II</td>
<td>Amyloidosis</td>
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<tr>
<td>IgA Nephropathy</td>
<td>Wegener’s</td>
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<tr>
<td>Anti-GBM</td>
<td>Cryoglobulinemia</td>
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<tr>
<td></td>
<td>(EMC)</td>
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<tr>
<td></td>
<td>Monoclonal</td>
</tr>
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<td></td>
<td>Gammopathy</td>
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</table>

## 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
RECURRENT MEMBRANOUS NEPHROPATHY

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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 (?)
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 (?)
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 (?)
RECURRENT IgA NEPHROPATHY

Recurrence rate - ~50% (range 20-75%)
Histology – prominent mesangial IgA staining
Clinical – hematuria, proteinuria; recurrence more common in LRA (83%)/HLA B35, DR4; IgA rheumatoid factors may be elevated; graft loss is minimal (<10%)
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 IgA) ~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 – microangiopathic 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
Recurrence rate – 100%

Histology – GBM thickening (2 years); 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

<table>
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<tr>
<th></th>
<th>45 amyloid</th>
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<tbody>
<tr>
<td>3 yr pt survival</td>
<td>51%</td>
<td>79%</td>
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<tr>
<td>3 yr graft survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- including death</td>
<td>38%</td>
<td>45%</td>
</tr>
<tr>
<td>- excluding death</td>
<td>53%</td>
<td>49%</td>
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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 in the 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, arthralgias) 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
1. Multiple myeloma – may recur as plasmacitic infiltration, tubular cast formation; fibrillar crescentic GN (graft loss)

2. Macroglobulinememic nephropathy – one case report of recurrence of IgM and lambda light chain staining and diffuse mesangio-capillary changes (stable function)

3. Light chain deposition disease with or without serum monoclonal proteins have recurred with or without effect 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 – Success 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)
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>
<thead>
<tr>
<th>Patient No.</th>
<th>Age¹/Sex</th>
<th>Disorder²</th>
<th>Hematocrit Pre-Tx³</th>
<th>Hematocrit Last⁴</th>
<th>Sickle Crisis</th>
<th>Loss of Allograft</th>
<th>Allograft Survival</th>
<th>Comments</th>
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<tbody>
<tr>
<td>1</td>
<td>29/M</td>
<td>SS</td>
<td>24</td>
<td>35</td>
<td>Yes</td>
<td>Sickling</td>
<td>2 mo.</td>
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<td>2</td>
<td>13/M</td>
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<td>4</td>
<td>18/M</td>
<td>SS</td>
<td>14</td>
<td>33</td>
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<td>? Sepsis</td>
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<tr>
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<td>36/M</td>
<td>SS</td>
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<td>23</td>
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<td>Sickling</td>
<td>3 d</td>
<td>Alive – Transplant Nephrectomy</td>
</tr>
<tr>
<td>6</td>
<td>34/F</td>
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<td>34</td>
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<td>7</td>
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<td>3 d</td>
<td>Died</td>
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<tr>
<td>8</td>
<td>40/M</td>
<td>SB</td>
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<td>20</td>
<td>Yes</td>
<td>Rejection</td>
<td>2 mo.</td>
<td>Alive – Transplant Nephrectomy</td>
</tr>
</tbody>
</table>

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 IgG 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