

## **Recurrent Glomerular Disease after Kidney Transplantation**

**ASN Renal Week 2010**

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### **Objectives**

- **To review reported incidence of and graft loss due to recurrent GN post-transplant**
- **To highlight findings of recent protocol biopsy studies**
- **To discuss uncertainty regarding specific treatment of recurrent GN post-transplant**

## Case Presentation

**A 56-year-old female kidney transplant recipient presents for a routine follow-up visit.**

**She received a living-related kidney transplant from her sister for ESRD due to presumed chronic glomerulonephritis 3 years ago.**

**Her medications are prednisone, MMF, tacrolimus, simvastatin, amlodipine, and a calcium/vit D supplement.**

**Immunosuppressive levels have been within target ranges.**

## Case Presentation

**She has noticed some lower extremity edema over the past 3-4 months.**

**Her blood pressure, which was previously well-controlled, has been running 140-150/90s.**

**Creatinine has gradually increased:**

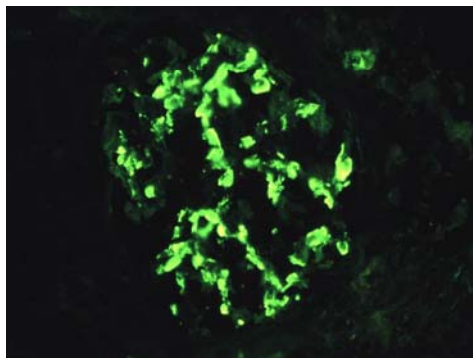
- **2008 1.3 – 1.5 mg/dl**
- **2009 1.5 – 1.6 mg/dl**
- **2010 1.7 mg/dl**

## Case Presentation

Testing for BK virus is negative.  
**What is the cause of her allograft dysfunction?**

Allograft ultrasound is unremarkable.

**What is her prognosis?** <sup>ite</sup> rejection on light microscopy. There is mild IF/TA (Banff ci1, ct1).



**Incidence  
of  
Recurrent  
GN After  
Kidney  
Transplant**

## Recurrent GN Post-Kidney Transplant

- Variable prevalence reported
  - 3% - 18.5%
- Impact on graft survival hard to determine since other factors coexist
- Likely underestimated

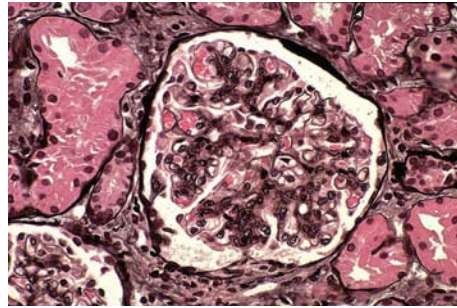
*Ivanyi B. Nature Clin Pract Neph 2008;4:446-457.*

## Rates of Recurrence and Graft Loss

Type of GN	Clinical Recurrence Rate (%)	Graft Loss at 10 years (%)
FSGS	20-40	20
Membranous GN	10-30	50
MPGN Type 1	20-33	High
MPGN Type 2	67-100	34-66
Anti-GBM	< 5	Can occur
ANCA-associated GN	0-20	8
IgA Nephropathy	7-30	3-16
Idiopathic D- HUS	33-82	90

*Ivanyi B. Nature Clin Pract Neph 2008;4:446-457.*

## Barriers to Diagnosis of Recurrent GN



## Original Diagnosis Uncertain

- **Pre-tx native kidney biopsy for diagnosis not routinely done for patients presenting with advanced disease**
- **Implantation biopsy not routinely performed**
  - **Will miss rare instances of donor GN**
  - **IgA, TBMN, mild SLE**

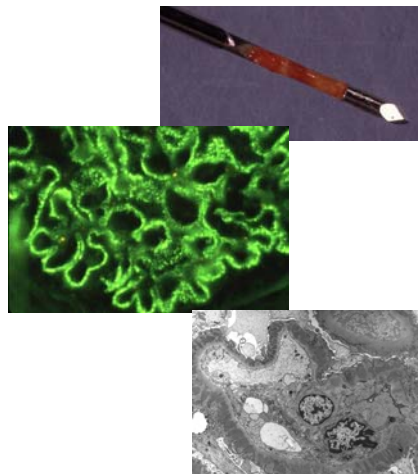
## Routine Work-up Not Fully Performed

- Allograft biopsy may not be done
- Recipients with proteinuria, hematuria, ↑Cr are evaluated differently than those without
- Urinalysis to detect proteinuria may not be performed routinely at time of biopsy

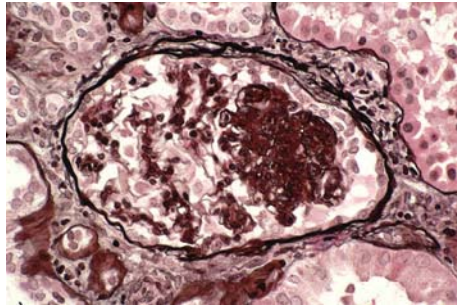
*Ivanyi B. Nature Clin Pract Neph 2008;4:446-457.*

## Limited Processing of Biopsy

- Biopsy diagnosis of recurrent disease requires more than LM and C4d
  - Need IF for IgG, IgA, IgM, kappa, lambda, C3, C1q
  - Need EM to localize deposits



*Ivanyi B. Nature Clin Pract Neph 2008;4:446-457.*



## Allograft Loss due to Recurrent GN

## Recurrent GN Causing Allograft Loss

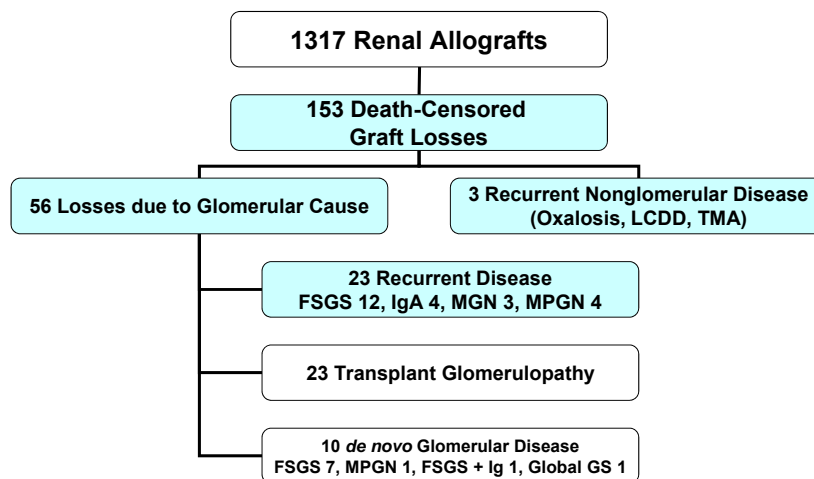
- **ANZDATA 1988-1997**
  - 1505 recipients with ESRD due to biopsy proven GN
  - 10-yr incidence of graft loss due to recurrence was 8.4%
  - Indication biopsies performed
  - FSGS=16, IgAN=15, MGN=5, MPGN type 1=5, HSP=4, pauci-immune crescentic GN=2, MPGN type 3=1

## Recurrent GN Causing Allograft Loss

- Mayo Clinic 1996-2006
- 1317 total recipients
  - Protocol biopsies performed
  - 2.1% graft losses overall due to recurrent GN
  - FSGS=12, IgA=4, MGN=3, MPGN=4
- Additional 10 cases presumed nonrecurrent disease

*El-Zoghby et al. Am J Transplant 2009;9:527-535.*

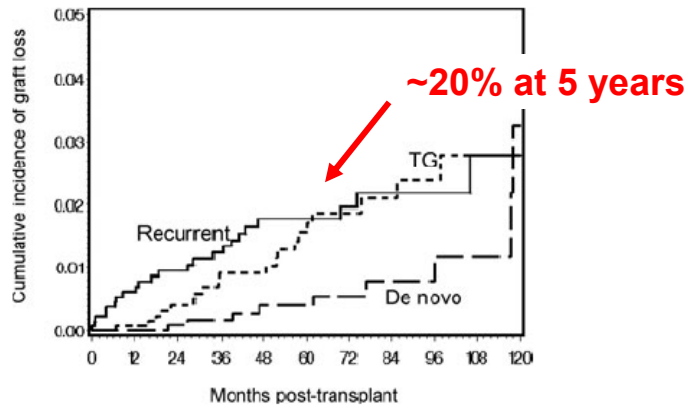
## Causes of Allograft Loss



*El-Zoghby et al. Am J Transplant 2009;9:527-535.*

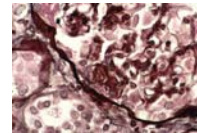


## Time Course of Allograft Loss due to Glomerular Causes



El-Zoghby et al. Am J Transplant 2009;9:527-535.

## Focal Segmental Glomerulosclerosis (FSGS)



- Can recur within weeks
  - 80% nephrotic
  - HTN, hematuria, acute allograft dysfunction common
  - Pathology:
    - Foot process effacement seen on EM within days of proteinuria recurrence
    - LM histology seen in 4-6 wks

Ivanyi B. Nature Clin Pract Neph 2008;4:446-457.

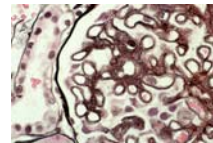
## Risk factors for FSGS Recurrence

- Younger age
- Caucasian, Asian
- Rapid progression of native ESRD < 3 yrs
- Related donor?
  - Recent reports of similar recurrence in living vs deceased donors
- Prior graft failure due to recurrence
  - If first loss occurred within 1<sup>st</sup> yr, >80% will recur in later allograft
- Mesangial hypercellularity on native bx
- Columbia classification not useful in predicting recurrence

Canaud G et al. *Nephrol Dial Transplant* 2009;1321-1328

Choy BY et al. *Am J Transplant* 2006;6:2536-2542.

## Membranous GN Recurrence by Protocol Biopsy



- Incidence of recurrent MGN 42%
  - 2 – 61 months, median 4 months
  - LM changes subtle or absent
  - All with granular GBM IgG but little or absent C3 on IF
  - Subepithelial deposits on EM in all

Dabade et al. *Am J Transplant* 2008;8:1318-1322

## Cumulative Incidence of Recurrent Membranous GN

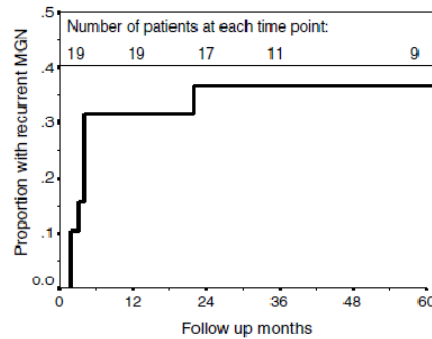
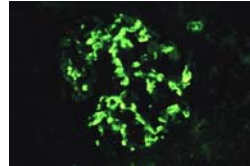


Figure 1: Cumulative incidence of recurrent MN after kidney transplantation. Number of patients at each time point is indicated in the figure.

Dabade et al. *Am J Transplant* 2008;8:1318-1322

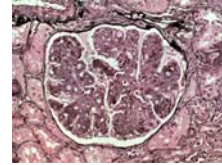
## IgA Nephropathy Recurrence



- **50-60% with protocol bx**
  - Detected months to decade post tx
  - Graft dysfunction or loss in 9.7% (1.3% - 16%)
  - Risk of recurrence in 2<sup>nd</sup> transplant 20-100%
  - Yet, other series report good graft function despite recurrence, up to 92 months

Ivanyi B. *Nature Clin Pract Neph* 2008;4:446-457.

## Recurrent MPGN



- High rates of recurrence yet allograft loss not as common
- Type 1 MPGN recurrence 20-50%
  - Allograft loss at 10 yrs 15%
- Type 2 MPGN 80-100%
  - Loss at 5 yrs 15-30%

*Choy BY et al. Am J Transplant 2006;6:2536-2542.*

## Recurrent MPGN Type 1

- 41% recurrence by protocol bx
- 29 pts
  - 67% of recurrences subclinical
  - Occurred 1 week to 14 months post-tx
  - 17% allograft loss, 7% on chronic plasmapheresis

*Lorenz et al. Kidney Int 2010;77:721-728.*

## Cumulative Incidence of Recurrence MPGN Type 1

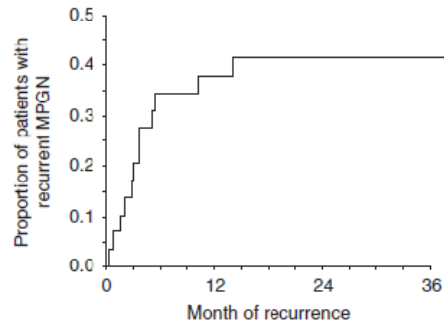


Figure 1 | Kaplan-Meier plot of the cumulative incidence of recurrent membranoproliferative glomerulonephritis (MPGN) after kidney transplantation.

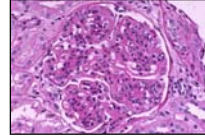
*Lorenz et al. Kidney Int 2010;77:721-728.*

## Risk Factors for MPGN Type 1 Recurrence

- Living donor
- Hypocomplementemia
- Presence of serum monoclonal protein

*Lorenz et al. Kidney Int 2010;77:721-728.*

## Recurrent Lupus Nephritis



- **Wide variation in reported incidence**
  - **2.44%:** UNOS database period prevalence 1987-2006 (6850 patients)
  - **54%:** Cross sectional surveillance biopsy in 41 patients
  - **30%:** 50 patients with indication biopsies done in 31 patients
  - **11%:** 177 patients with indication biopsies

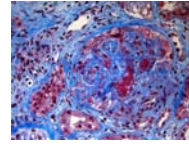
*Contreras et al. J Am Soc Neph 2010;21:1200-1207*  
*Norby GE et al. Ann Rheum Dis 2010;69:1484-1487*  
*Goral et al. Transplantation 2003;75:651-656.*  
*Burgo et al. Arthritis Rheum 2009;60(9):2757-2766.*

## Recurrent Lupus Nephritis

- **Most recurrences described as WHO Class II, III or V**
  - **Several cases of recurrence with WHO Class IV reported**
- **Risk factors: female, Black, age < 33**
- **Graft loss due to recurrence rare**
  - **~7% attributed to recurrence in UNOS database**
  - **Higher in smaller studies with indication biopsies**

*Weng, Nature Clin Pract Neph 2005;1(2):62-63.*

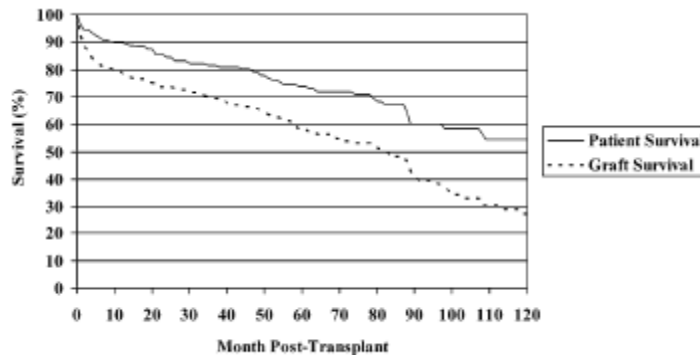
## Recurrent Scleroderma Renal Crisis



- UNOS data for 260 patients transplanted for scleroderma 1987-2004:
  - Overall graft loss 28.8%
  - Graft loss due to recurrence 6.7%
- Usually occurs within 1-2 years
- May be heralded by progressive skin thickening and anemia

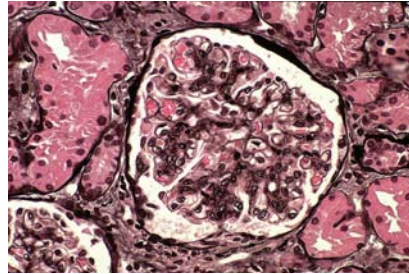
Pham et al. Am J Transplant 2005;5:2565-2569.

## Patient and Graft Survival after Kidney Transplantation for Scleroderma



Pham et al. Am J Transplant 2005;5:2565-2569.

## Treatment of Recurrent GN



## General Measures

- **Strict BP control**
- **RAAS blockade**
  - **Based on studies of native kidney disease**
- **Randomized, controlled trials not available**



## Treatment of Recurrent FSGS

- **Begins pre-transplant**
  - **Reduce proteinuria as much as possible (<1g/day)**
  - **Bilateral native nephrectomy if needed**
  - **Enables detection of post-tx proteinuria can be detected**
  - **Consider plasmapheresis pre-tx**

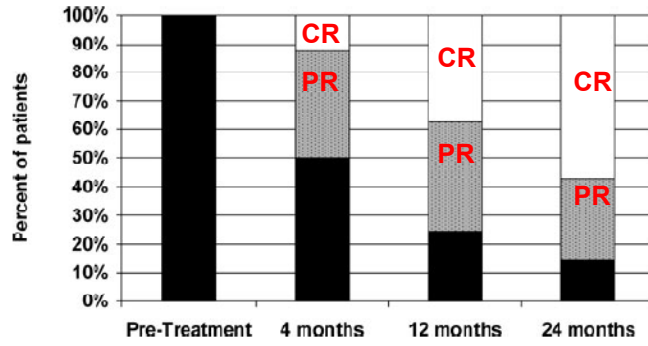
*Ivanyi B. Nature Clin Pract Neph 2008;4:446-457.*

## Treatment of Recurrent FSGS

- **Post-transplant**
  - **Pre-emptive peri-operative plasmapheresis for ~2 weeks in high risk patients**
  - **Frequent monitoring of proteinuria**
  - **Diagnostic allograft biopsy**
  - **Chronic plasmapheresis after relapse**
  - **CNI-based immunosuppression over sirolimus?**

*Choy BY et al. Am J Transplant 2006;6:2536-2542.*

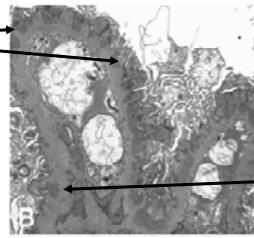
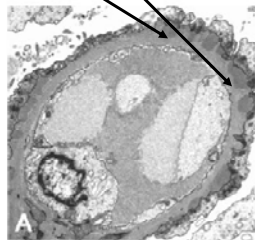
## Treatment of Recurrent Membranous GN with Rituximab\*



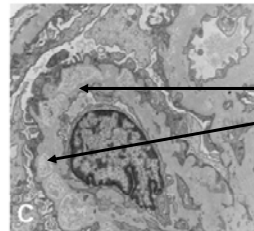
\*Off-label use

El Zoghby et al. Am J Transplant 2009,9:2800-2807.

Before Treatment:  
Subepithelial Deposits



1 Year Post  
Treatment:  
Intramembranous  
Deposits



2 Years Post  
Treatment:  
Intramembranous  
Electron Lucent  
Areas

El Zoghby et al. Am J Transplant 2009,9:2800-2807.

## Back to the Case Presentation...

- **Suspect recurrent GN as cause of renal allograft dysfunction and proteinuria in patients at risk**
- **Prognosis depends on type of GN recurrence**
- **Accurate pathologic diagnosis is necessary**

Thank you



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1. Ivanyi B. A primer on recurrent and de novo glomerulonephritis in renal allografts. *Nature Clin Pract Neph* 2008;4(8):446-457.
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4. Canaud G, Dion D, Zuber J, Gubler MC, Sberro R, Thervet E, Snanoudj R, Charbit M, Salomon R, Martinez F, Legendre C, Noel LH, Niaudet P. Recurrence of nephrotic syndrome after transplantation in a mixed population of children and adults: course of glomerular lesions and value of the Columbia classification of histologic variants of FSGS. *Nephrol Dial Transplant* 2009:1321-1328.

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