CLINICAL HISTORY

9 year old Caucasian girl with severe growth retardation and dwarfism.

• Age 3: presented with ESRD and proteinuria:
  • Native renal biopsy with advanced chronic tubulointerstitial scarring, 50% global glomerulosclerosis.
  • IF and EM examinations: no characteristic and diagnostic glomerular abnormalities.
  • Native kidney 4.5cm in length

• Age 5: underwent renal transplantation from deceased donor source:
  • 13 year old “healthy” boy with self-inflicted gun shot wound; donor kidney 11 cm in length
  • Intra abdominal graft placement with anastomosis to aorta

Zero Hour Implantation Biopsy

• Light Microscopy: Focal Acute Tubular Injury

• Immunofluorescence
  • Negative
  • Complement degradation product C4d not detected along peritubular capillaries and glomerular basement membranes

Post transplantation

Immunosuppression:

• Cellcept, Tacrolimus & steroids (patient compliant)

Renal function:

• Stable (S-Cr 0.2-0.3 mg/dl)

Post transplantation

Proteinuria

• Year 1: UPC ratio of 1.7
• Year 3: nephrotic range (8.1 grams/24 hours)

Minimal Microscopic hematuria

No Donor Specific Antibodies detected on repeat testing

All standard laboratory tests within normal limits

• S-Cr 0.2-0.3 mg/dl
3 years post transplantation an allograft biopsy was performed.

Allograft Biopsy 3 years post transplantation

19 Glomeruli
None with sclerosis

Allograft Biopsy – Immunofluorescence

<table>
<thead>
<tr>
<th>GBM</th>
<th>Mesangium</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>minimal linear accentuation</td>
</tr>
<tr>
<td>IgM</td>
<td>focal and segmental granular 1+2+</td>
</tr>
<tr>
<td>IgA</td>
<td>0</td>
</tr>
<tr>
<td>C3</td>
<td>focal and segmental granular 1+</td>
</tr>
<tr>
<td>C1q</td>
<td>0</td>
</tr>
<tr>
<td>Kappa</td>
<td>focal and segmental trace</td>
</tr>
<tr>
<td>Lambda</td>
<td>focal and segmental trace</td>
</tr>
</tbody>
</table>

Post-transplant biopsy - Immunofluorescence

<table>
<thead>
<tr>
<th>GBM</th>
<th>Mesangium</th>
<th>Peritubular capillaries</th>
<th>Tubules</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4d</td>
<td>Global and diffuse pseudolinear 3+</td>
<td>trace 0</td>
<td>0</td>
</tr>
</tbody>
</table>
Electron Microscopy

Differential Diagnosis

- Changes of hereditary nephropathy
- Chronic rejection (antibodies) with transplant glomerulopathy
- Other
Is this Hereditary Nephropathy?

Zero Hour Implantation Biopsy
Electron Microscopy on reprocessed frozen material from IF

CLINICAL HISTORY

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Differential Diagnosis

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• Chronic rejection (antibodies ?) with transplant glomerulopathy

• Other

Transplant Glomerulopathy due to (antibody mediated) rejection
Allograft Biopsy – 3 years post transplantation

Transplant Glomerulopathy

Pronounced subendothelial GBM remodeling with new densa formation

Current Case


<table>
<thead>
<tr>
<th>TG [TRANSPLANT GLOMERULOPATHY]</th>
<th>PERITUBULAR CAPILLARY MULTILAMINATION - SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGL caused by presumptive antibody mediated rejection, C4d+, no cellular rejection</td>
<td>100%</td>
</tr>
<tr>
<td>TGL caused by presumptive cellular rejection, C4d-</td>
<td>50%</td>
</tr>
<tr>
<td>TGL caused by presumptive mixed cellular and antibody mediated rejection, C4d+</td>
<td>73%</td>
</tr>
</tbody>
</table>

[Modified from Table 4]
Absence of marked circumferential Peritubular capillary basement membrane multilamination is powerful to exclude chronic AMR from the diagnostic possibilities

Negative Predictive Value = 92%

Diagnostic significance of peritubular capillary basement membrane multilaminations in kidney allografts: old concepts revisited.
Liapis G, Singh HK, Derebail VK, Gasim AM, Kozlowski T, Nickens V.
Transplantation. 2012 Sep 27;94(6):620-9

Differential Diagnosis
- Changes of hereditary nephropathy
- Chronic rejection (antibodies ?) with transplant glomerulopathy
- Other

Descriptions of “too small for body size mismatched grafts”

Diffuse glomerular basement membrane lamellation in renal allografts from pediatric donors to adult recipients.
Nadasdy T, Abdi R, Pitha J, Stacey D, Racusen L.

Abstract
The transplantation of kidneys from pediatric cadaveric donors into adult recipients is performed in many centers. However, some studies indicate that the outcome of such renal transplants may be inferior compared with that of adult donors, particularly if the donor is an infant. Morphologic studies of failed pediatric donor kidneys in adult recipients describe various degrees of segmental or global glomerular sclerosis. The authors have performed ultrastructural examinations on such transplants and have identified six cases with diffuse irregular lamellation of the glomerular basement membrane (GBM), a change that may develop as early as 10 weeks after transplantation. The age of all donors was < or =6 years; three were infants. The incidence of the lesion was 9% at our institution in renal transplant patients who received a graft from donors <10 years old. Diffuse GBM lamellation has not been found in renal transplants from adult donors. Light microscopy showed various degrees of diffuse mesangial expansion, usually with segmental glomerular sclerosis. The patients had severe proteinuria. While recurrent focal segmental glomerular sclerosis (FSGS) has to be excluded, such diffuse GBM lamellation is generally not seen in recurrent FSGS cases. The pathogenesis of the lesion is most likely related to hyperperfusion injury of small pediatric donor kidneys grafted into adult recipients.
Current Case

Opposite clinical scenario

• Too big for body size donor kidney
  • Grafted at age 5 from deceased donor source (13 year old “healthy” boy with self-inflicted gun shot wound; donor kidney 11 cm in length)
  • Intra abdominal graft placement with anastomosis to aorta.

Current Case

Complex adaptive mechanisms:

• Alterations in blood flow and intracapillary pressures → stress to the glomerular capillary wall results in remodeling and change to filtration barrier → proteinuria.

Isolated Glomerular Global and Diffuse Pseudolinear Staining for C4d

Current Case

• No staining along peritubular capillaries
• No DSAs detected on multiple measurements
• No other significant glomerular immunoglobulin or complement factor deposits detected except for minor IgM and C3 focal and segmental granular deposits different from the C4d staining
  • no immune deposits by EM
Glomerular C4d Deposits can Mark Structural Capillary Wall Remodeling in Thrombotic Microangiopathy and Transplant Glomerulopathy: C4d beyond Active Antibody Mediated Injury.

Gasim AH, Chua JS, Wolterbeek R, Schmitz J, Weimer E, Singh HK, Nickeleit V.

Abstract

Peritubular capillary C4d (ptc-C4d) usually marks active antibody mediated rejection, while pseudolinear glomerular capillary C4d (GBM-C4d) is of undetermined diagnostic significance, especially when seen in isolation without concurrent ptc-C4d. We correlated GBM-C4d with structural GBM abnormalities and active antibody mediated rejection in 319 renal transplant and 35 control native kidney biopsies. In kidney transplants ptc-C4d was associated with GBM-C4d in 97% by immunofluorescence microscopy (IF) and 61% by immunohistochemistry (IHC; p<0.001). Transplant glomerulopathy correlated with GBM-C4d (p<0.001) and presented with isolated GBM-C4d lacking ptc-C4d in 69% by IF and 40% by IHC. Strong isolated GBM-C4d was found post year-1 in repeat biopsies with transplant glomerulopathy. GBM-C4d staining intensity correlated with Banff cg scores (rs=0.45, p<0.001). Stepwise exclusion and multivariate logistic regression corrected for active antibody mediated rejection showed significant correlations between GBM duplication and GBM-C4d (p=0.001). Native control biopsies with thrombotic microangiopathies demonstrated GBM-C4d in 92% (IF, p=0.001), and 35% (IHC). In conclusion pseudolinear GBM-C4d staining can reflect two phenomena: 1) structural GBM changes with duplication in native and transplant kidneys, or 2) active antibody mediated rejection typically accompanied by ptc-C4d. While ptc-C4d is a dynamic 'etiologic' marker for active antibody-mediated rejection, isolated strong GBM-C4d can highlight architectural glomerular remodeling.

Current Case: Follow-up Data

- Repeat renal biopsy performed 4 years post transplantation in the setting of unchanged clinical and laboratory data, normal renal function, undetected DSAs and nephrotic range proteinuria [4.2g/24 hours].
  - Biopsy findings identical to current biopsy shown.
  - No rejection or increase in chronic allograft injury.
- Last follow-up 58 months post transplantation:
  - Stable graft function: SCr 0.3 – 0.4 mg/dl
  - Persistent proteinuria: Urine protein to creatinine ratio: 9.2
  - Minimal hematuria
- Therapy: no changes to immunosuppression drug regimen
- Blood pressures well controlled

Summary

- Size mismatch glomerulopathy: First report of “too large for body size” mismatched graft.
- Clinical presentation:
  - Nephrotic range proteinuria
  - Minimal microscopic hematuria
  - Renal function and standard laboratory tests normal
- Ultrastructural findings resemble hereditary nephropathy
- Distinct from transplant glomerulopathy [due to antibody induced injury]
- Outcome favorable over short and medium length followup (58 months)