Chronic Active TCMR: i, iatr, i-IFTA, and the clinical implications

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Professor of Surgery, Division of Transplantation
Director of Research, Comprehensive Transplant Institute
I have no financial relationships to disclose within the past 12 months relevant to my presentation and My presentation does include discussion of off-label or investigational use therapies
The Etiology of Chronic Graft Injury ("CGI"): The Bench and Bedside Knowledge

- IF/TA—interstitial fibrosis and tubular atrophy
  - May also be associated with glomerular or arterial lesions
- Association with TGFβ and other growth factors
- Association with CNI toxicity (chronic)
- Association with antibody mediated injury (allo, auto)
- Inflammation in unscared kidney “i” + IFTA
- “Chronic inflammation” in areas of atrophy “iatr”

Final common pathway for many injuries
Causes of Graft Loss Over Time

T cell Mediated Rejection

60/312 for cause biopsies developed allograft failure
## Cellular Rejection: Evolution of Criteria

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute TCM Rejection</strong></td>
<td>Grade I: i2–i3 and/or t2</td>
<td>Type IA: i2,i3, &amp;t2</td>
<td>Type IB: t3</td>
<td>ditto</td>
<td>Type IA i2 or i3 +t2</td>
<td>Type IB i2 or i3 +t3</td>
</tr>
<tr>
<td>Grade II: t3 and/or intimal arteritis: v1, v2</td>
<td>Type IIA: mild-mod arteritis v1</td>
<td>Type IIB: severe intimal v2</td>
<td>ditto</td>
<td>Type IIA: v1</td>
<td>Type IIB severe intimal arteritis comprising &gt;25% of luminal area v2</td>
<td>ditto</td>
</tr>
<tr>
<td>Grade III: transmural arteritis v3</td>
<td>Type II: transmural arteritis V3</td>
<td>ditto</td>
<td>Type III: transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells accompanying lymphocytic inflammation v3</td>
<td>ditto</td>
<td>ditto</td>
<td></td>
</tr>
<tr>
<td><strong>“Chronic rejection”</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
Grading Chronic TCMR
Banff 2005

Chronic TCMR was defined by sclerosing transplant arteriopathy. This lesion is characterized by intimal widening due to the de novo accumulation of collagens I and III, lack of elastosis, and varying degrees of intimal inflammation with mononuclear inflammatory cells.

Arterial intimal thickening (cv)
% narrowing lumen of most severely affected vessel

<table>
<thead>
<tr>
<th>Grade</th>
<th>0%</th>
<th>&lt;25%</th>
<th>26-50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

Am Jnl Transplant 2007; 7: 518
“The findings on core biopsy indicate that significant arteriosclerosis is often present in kidneys from normotensive donors with normal renal function, particularly those older than 40 years.”

Cluster Analysis of Lesions in Nonselected Kidney Transplant Biopsies: cv as a correlate of parenchymal scarring

Sis et al. Am Jnl Transplant 2010;10(2): 421

"cv lesion may be produced by various stresses, and acts as a nonspecific feature of time-dependent scarring rather than a feature of antibody-mediated injury"
Progression of cv is associated with transplantation and accelerated in presence of DSA [Hill et al. JAMA 2011; 22(5): 975].

Builds a case for cv as a chronic AMR feature
Tissue Regeneration versus Fibrosis: The Process of Wound Healing

Initiation Phase
- Ag dependent
- Ag independent

Matrix Phase

Fibrogenesis Phase

Inflammatory response

Proliferative response

Jnl Clin Investigation 2007; 117: 524
Graft Survival is Lower in Patients With SCR Associated with IFTA (i+IFTA)


- Surveillance biopsies with i in non-scarred areas and IFTA [IFTA + i] are associated with shorter graft survival.

Banff 2007 Criteria: Scoring of Total Inflammation (ti) in the Allograft

- Total index of interstitial inflammation which uses the same semi-quantitative criteria used for determining the i score, for all cortical tissue present, including the sub-capsular cortex, perivascular cortex and areas of IF/TA.
- Cortical nodular infiltrates will be included in the i or ti score depending on their localization

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ti 0</td>
<td>No or trivial interstitial inflammation (&lt;10% of parenchyma)</td>
</tr>
<tr>
<td>ti1</td>
<td>10–25% of parenchyma inflamed</td>
</tr>
<tr>
<td>ti2</td>
<td>26–50% of parenchyma inflamed</td>
</tr>
<tr>
<td>ti3</td>
<td>&gt;50% of parenchyma inflamed</td>
</tr>
</tbody>
</table>
Total i Score: Better Predictor of Outcome (and gene expression)

- 129 biopsies
- 2004-2006
- Total i=
  - infiltrates in areas of nonscarred tubulointerstitium,
  - in areas of interstitial fibrosis and tubular atrophy (IFTA),
  - nodular infiltrates
  - perivascular infiltrates,
  - subcapsular infiltrates

IFTA + i and DSA

- 598 kidney transplant recipients of low immune risk (CTX neg, PRA<20%, DSA neg)
  - Basiliximab, CNI based therapy
  - 6w and 12m biopsies with DSA measurements (LabScreen)/ MFI<1000 = negative
    - normal histology (i+t≤1 and ci+ct≤1)
    - inflammation (i+t≥2 and ci+ct≤1)
    - IFTA (i+t≤1 and ci+ct≥2)
    - IFTA+i (i+t≥2 and ci+ct≥2)
- Findings of IFTA+i @ 6w are independent risk for dnDSA (8.9% of pop at 1y)

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR of dnDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLADR MM</td>
<td>1.95 (1.09-3.49)</td>
</tr>
<tr>
<td>“i” score at 6w biopsy</td>
<td>5.49 (1.67-10.03)</td>
</tr>
<tr>
<td>IFTA+i at 6w</td>
<td>4.09 (1.67-10.05)</td>
</tr>
</tbody>
</table>

_Garcia-Carro et al. Transplantation 2016; PMID 27163535_
Deterioration of Kidney Allograft Function (DeKAF) Study (NIH U01 AI58013)

7 transplant centers
Hennepin County Med Center (Kasiske)
Mayo Clinic (Cosio)
University of Alabama (Gaston/Mannon)
University of Alberta (Halloran/Gorishankar)
University of Iowa (Hunsicker)
University of Manitoba (Rush)
University of Minnesota (Matas)

Central pathology
Mayo Clinic (Grande)

Central anti-HLA antibody
UCLA (Cecka)

Central urine metabolomics
University of Manitoba (Rush)

Multicenter database and Biostatistics Core
University of Minnesota (Connett, Leduc, Fieberg)
**Deterioration of Kidney Allograft Function (DeKAF) Study**

• Prospective cohort (N=3751)
  - Kidney or kidney-pancreas transplant with no other organs simultaneously transplanted
  - Enrolled within 10 days post-transplant
  - Clinical and biopsy data entered into the database

• Cross sectional cohort (N=440)
  - Enrolled as of 02/01/2006
  - sCR < 2.0 mg/dL prior to 01/01/06
  - Deterioration of function (>25% baseline) or new proteinuria, i.e. Biopsy for cause
  - Pathology, urine mass spec, serum for DSA
  - *Mean Creatinine* - 1/2006 - 1.4 ± 0.3 mg/dl
## Characteristics of Cohorts

*Am J Transplant 2010; 10:324-337*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CSC (N=422)</th>
<th>Prospective (N=2270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>211 (50%)</td>
<td>864 (38%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>333 (79%)</td>
<td>1740 (77%)</td>
</tr>
<tr>
<td>AA</td>
<td>56 (13%)</td>
<td>376 (17%)</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>48 ± 18</td>
<td>48 ± 14</td>
</tr>
<tr>
<td>Diabetes</td>
<td>169 (41%)</td>
<td>813 (37%)</td>
</tr>
<tr>
<td>Years Post Transplant to Biopsy</td>
<td>7.4 ± 6.1 (median 5.7y)</td>
<td>1.0 ± 0.6 (median 0.8y)</td>
</tr>
<tr>
<td>Living Donor</td>
<td>262 (62%)</td>
<td>1239 (59%)</td>
</tr>
<tr>
<td>% graft Survival (post enrollment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6m</td>
<td>89.5%</td>
<td>98%</td>
</tr>
<tr>
<td>12m</td>
<td>79%</td>
<td>96%</td>
</tr>
<tr>
<td>18m</td>
<td>74%</td>
<td>95%</td>
</tr>
</tbody>
</table>
**Cross Sectional Cohort Local Biopsy Diagnoses**

* adds up to >100% as 2 diagnoses/biopsy

<table>
<thead>
<tr>
<th>Primary/Secondary DX</th>
<th>N=425 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft nephropathy</td>
<td>196 (48)</td>
</tr>
<tr>
<td>CNI toxicity</td>
<td>116 (29)</td>
</tr>
<tr>
<td>Other (e.g., pyelo)</td>
<td>91 (22)</td>
</tr>
<tr>
<td>Transplant glomerulopathy</td>
<td>82 (20)</td>
</tr>
<tr>
<td>Acute cellular rejection</td>
<td>76 (19)</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>53 (13)</td>
</tr>
<tr>
<td>Art. nephrosclerosis</td>
<td>33 (8)</td>
</tr>
<tr>
<td>Borderline change</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Acute antibody mediated rejection</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Glomerulonephritis (de novo)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>ATN</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Polyomavirus (BK)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>NPD</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>
Impact of CAN (IF/TA): Graft Survival in CSC After Renal Biopsy

DeKAF Cross Sectional Cohort: Graft Survival after Biopsy
CNI Toxicity versus none

Time to Graft Failure – All CS Index Biopsies

Percent without Event

Months from Biopsy

Primary or Secondary CNI Toxicity
No CNI Toxicity

Logrank = 4.12  p = 0.0424

CNI +:  53  51  47  46  39  19  17  13  13
CNI -: 108  97  83  72  64  51  42  28  22

Depiction of Clusters - “Cluster Clock” With additional histo scores

Legend
Each spoke represents a Banff score
Length of spokes = % with finding
............... = Banff 1
--------- = Banff 2
----- = Banff 3

All BANFF shown
Clustering based on Banff scores (i, t, g, v, ct, ci, cv, cg, mm, ah) plus tatr, iatr, ptc
Hierarchical Cluster Analysis of CS Biopsies Using Selected Banff Scores

Legend

Length of spokes = % with finding
.... = Banff 1
----- = Banff 2
— = Banff 3

Clusters
1—no inflam, min ci and min mm
2—i, t
3 +4—mm, ah, cv
5 +6—inflam, and 2, 3, 4

Score Distributions for DeKAF Clusters
N=253. 13 Observations in 3 Clusters not shown
Demographics of Clusters

No major differences in:

• donor or recipient age
• race/ethnicity
• primary kidney disease
• living/deceased donor
• prior transplants
• transplant era
• initial immunosuppressive protocol
Actuarial Graft Survival Based on Clustering

Am J Transplant 2010; 10:315-323
Characteristics of the 6 Computer-Generated Clusters

Table 6: Local pathologists’ primary or secondary diagnoses for biopsies in the 6 clusters

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN (%)</td>
<td>53%</td>
<td>40%</td>
<td>54%</td>
<td>50%</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td>Tx glomerulopathy (%)</td>
<td>8%</td>
<td>5%</td>
<td>38%</td>
<td>21%</td>
<td>48%</td>
<td>36%</td>
</tr>
<tr>
<td>CNI toxicity (%)</td>
<td>45%</td>
<td>8%</td>
<td>21%</td>
<td>7%</td>
<td>41%</td>
<td>21%</td>
</tr>
<tr>
<td>Acute cellular rejection (%)</td>
<td>5%</td>
<td>73%</td>
<td>17%</td>
<td>29%</td>
<td>3%</td>
<td>36%</td>
</tr>
<tr>
<td>Ab-mediated rejection (%)</td>
<td>3%</td>
<td>13%</td>
<td>17%</td>
<td>17%</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1. 25 biopsies were not clustered; of these, 52% had local pathologists diagnosis of CAN.

CAN, chronic allograft nephropathy; Tx, transplant; CNI, calcineurin inhibitor toxicity; Ab, antibody.
Findings in For Cause Biopsies in Late Allograft Dysfunction

IATR

TATR

“iatr”—inflammation in areas of tubular atrophy
0 = inflammation in less than 10% of atrophic regions
1 = inflammation in 10-25% of atrophic regions;
2 = inflammation in 26-50% of atrophic regions;
3 = inflammation in >50% of atrophic regions.

Impact on Presence of IATR on Graft Failure after Biopsy

Grade of IATR Impacts Time to Graft Loss

<table>
<thead>
<tr>
<th>iatr</th>
<th>Hazard Ratio [95% Confidence Interval]; P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>REF*</td>
</tr>
<tr>
<td>1</td>
<td>2.27 [0.891, 5.77]; 0.0860</td>
</tr>
<tr>
<td>2</td>
<td>2.98 [1.07, 8.34]; 0.0371</td>
</tr>
<tr>
<td>3</td>
<td>4.75 [1.58, 14.27]; p=0.0055</td>
</tr>
</tbody>
</table>

IATR Has Independent Effect on Time to Death Censored Graft Failure

![Graph showing percent survival over months from biopsy with different categories: None, IATR only: I=0 IATR >=1, Some I: I >=1 regardless of IATR. Logrank statistic is 10.07, p=0.0065.]

None: 102 101 91 87 83 65 54 44 39 17 16 6 3
IATR only: I=0 IATR >=1
Some I: I >=1 regardless of IATR

Months from Biopsy
## Proportional Hazards Regression Models of Time to Death-Censored Graft Failure:
**IATR and Other Factors**

<table>
<thead>
<tr>
<th>Group</th>
<th>Model 1 Adjusted for creatinine</th>
<th>Model 2 Adjusted for i and creatinine</th>
<th>Model 3 Adjusted for ci and creatinine</th>
<th>Model 4 Adjusted for ct and creatinine</th>
<th>Model 5 Adjusted for ci and ct and creatinine</th>
<th>Model 6 Adjusted for i, ci, ct, C4d+, DSA+ and creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>iatr=0</td>
<td>REF*</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>iatr=1</td>
<td>1.91 [0.95,3.90]; 0.075</td>
<td>2.47 [1.17,5.20]; 0.018</td>
<td>1.59 [0.77,3.30]; 0.212</td>
<td>1.68 [0.81,3.48]; 0.161</td>
<td>1.60 [0.77,3.32]; 0.207</td>
<td>3.36 [1.05,10.68]; 0.0403</td>
</tr>
<tr>
<td>iatr=2</td>
<td>2.52 [1.26,5.02]; 0.009</td>
<td>4.38 [1.95,9.82]; &lt;0.001</td>
<td>2.12 [1.02,4.38]; 0.043</td>
<td>2.00 [0.96,4.16]; 0.065</td>
<td>2.07 [0.99,4.35]; 0.053</td>
<td>5.11 [1.44,18.07]; 0.0114</td>
</tr>
<tr>
<td>iatr=3</td>
<td>6.35 [2.91,13.85]; &lt;0.001</td>
<td>12.0 [4.4,32.61]; &lt;0.001</td>
<td>3.36 [1.39,8.13]; 0.007</td>
<td>3.44 [1.42,8.33]; 0.006</td>
<td>3.23 [1.29,8.06]; 0.012</td>
<td>8.07 [1.71,38.07]; 0.0083</td>
</tr>
</tbody>
</table>

**Overall p-value for iatr**

- REF refers to the reference category.
- The p-values are given in italics and indicate statistical significance.
- The models adjust for various factors, including creatinine (creatinine), iATR, ci, and ct.
Summary

• Late allograft failure attributed to T cell rejection is less commonly described in the literature.

• Arteriosclerotic lesions may classify Banff Chronic TCMR but are in part donor derived, worsen during the post-transplant period, and accelerated in the setting of donor specific antibodies.

• Late cellular rejection can be seen in allograft biopsies and contributes to graft loss.

• In biopsies for late allograft dysfunction, inflammation in areas of atrophy is an independent risk factor for death-censored graft loss, even in the setting of antibody mediated injury features.
Conclusions

The classification of Chronic TCMR needs updating and will need inclusion of both T and B cell activation reflecting contributions of both cellular (innate and adaptive) and humoral arms of the immune response.
Selection of Final Number of Clusters

Selection of the final number of clusters requires specification of objective criteria and clinical input.

Heuristic measures are available depending on the specific clustering algorithm (pseudo-F, pseudo-R^2, cubic clustering criterion).

When the 'true' number of clusters is unknown, one heuristic is to select a number close to $\text{Sqrt}(N/2)$. 
2 Clustering Analyses

February / 09

November / 08
Selected Banff - i, g, ct, cv, mm, ah, and tatr - used in clustering:

i - mononuclear cell interstitial infiltrate  
mm - mesangial matrix

$g$ - glomerulitis  
hyaline

c-t - tubular atrophy  
thickening

cv - vascular fibrous intimal thickening

tatr - tubulitis in areas of atrophy

ah - arteriolar

All Banff (plus iatr, tatr, ptc) depicted:

t - tubulitis  
v - intimal arteritis

Ci - interstitial fibrosis

cg - glomerulopathy

iatr - infl in areas of atrophy

ptc - peritubular capillary infiltrates
Selected Banff – I, g, ct, cv, mm, ah, and tatr

Cluster
1 – no infl; min ci; min mm
2 – I,T
6 – infl & severe ci,ct

DeKAF clusters (n=265); 25 observations not depicted
Introduction

Majority of recipients with slow deterioration of function are labeled as having “chronic rejection”, “chronic allograft nephropathy” (CAN), or "interstitial fibrosis with tubular atrophy" (IF/TA).

These diagnostic terms do not define specific entities from the etiologic, physiologic, pathologic, or prognostic point of view.

The above factors make development of treatment algorithms for care of recipients with persistent and/or progressive graft dysfunction difficult, if not impossible.
Inflammation in Areas of Atrophy: Strong Negative Predictor of Outcome

DeKAF Study:
289 recipients in cohort
59 with graft loss
89 with iatr=0, and iatr>1

"iatr"—inflammation in areas of tubular atrophy
0 = inflammation in less than 10% of atrophic regions
1 = inflammation in 10-25% of atrophic regions;
2 = inflammation in 26-50% of atrophic regions;
3 = inflammation in >50% of atrophic regions.
Fibrosis and Fibrogenesis Transcripts in BK PVN Biopsies

![Graph showing transcript expression levels in normal kidney and BK PVN biopsies.](image)

**Structural**
- COLIA1
- FN1
- VIM
- FGF2
- IGF1
- CTGF
- VEGF

**Growth Factors**
- COLIVA5
- PDGFβ
- TGF-β

**EMT Regulators**
- E-CAD
- S100A4
- α-SMA
- MMP2
- MMP9
- PAI-1
- BMP7

- *: SF versus AR
- #: SF versus PVN
- †: AR versus PVN

**Notes**
- Mannon et al. AJT 2005; 5:2883-2893
Alloantibody and Autoantibody
Associations with CGI

- Endothelial injury mediated by antibody, complement, monocytes, leukocytes
- Outcomes impacted by presence of DSA.
- Effective treatment options?
Chronic graft injury is a considerable long term problem for solid organ transplant recipients. The etiologies are multi-factorial and include both antigen dependent and independent events, some of which are beyond clinical control. Regardless of insult, the response to inflammation is fibrosis. Primary injury may occur in the endothelium, microvasculature, or epithelium. In the kidney, epithelial injury occurs and may be associated with EMT. CNI toxicity contributes to allograft fibrosis, but is not the only factor. Identifying novel mediators and targets may provide for specific opportunities for therapy.
## Local Pathologists Primary or Secondary Diagnosis for Each Cluster

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>#1 (n=94)</th>
<th>#2 (n=40)</th>
<th>#3 (n=49)</th>
<th>#4 (n=14)</th>
<th>#5 (n=29)</th>
<th>#6 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN (%)</td>
<td>53</td>
<td>40</td>
<td>54</td>
<td>50</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>Transplant glomerulopathy (%)</td>
<td>8</td>
<td>5</td>
<td>38</td>
<td>21</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>CNI toxicity (%)</td>
<td>45</td>
<td>8</td>
<td>21</td>
<td>7</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Acute cellular rejection (%)</td>
<td>5</td>
<td>73</td>
<td>17</td>
<td>29</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>Ab-mediated rejection (%)</td>
<td>3</td>
<td>13</td>
<td>17</td>
<td>7</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>
# Characteristics at Biopsy for Each Cluster

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>#1 (n=94)</th>
<th>#2 (n=40)</th>
<th>#3 (n=49)</th>
<th>#4 (n=14)</th>
<th>#5 (n=29)</th>
<th>#6 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4d positive (%)</td>
<td>29</td>
<td>50</td>
<td>49</td>
<td>50</td>
<td>36</td>
<td>58</td>
</tr>
<tr>
<td>Donor specific Ab⁺ (%)</td>
<td>18</td>
<td>40</td>
<td>53</td>
<td>43</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Proteinuria &gt;60 mg/g CR (%)</td>
<td>19</td>
<td>35</td>
<td>51</td>
<td>50</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Time from tx to biopsy (mos) (± SD)</td>
<td>85 (65)</td>
<td>53 (52)</td>
<td>71 (53)</td>
<td>58 (32)</td>
<td>134 (104)</td>
<td>126 (78)</td>
</tr>
</tbody>
</table>
Other Analyses – Cross-sectional Cohort

1) Level of C4d+ staining of peritubular capillaries correlates with long-term graft survival
   Optimal” cutoff has not been determined; ≥ 10% strong predictor of graft loss

2) Time to graft failure is significantly associated with C4d+ status but not AR (in late post-transplant biopsies)
Depiction of Clusters - “Cluster Clock”

Legend

Each spoke represents a Banff score
Length of spokes = % with finding
.... = Banff 1
----- = Banff 2
____  = Banff 3

Clustering based on
6 Banff scores (i, g, ct, cv, mm, ah) plus tatr

Cluster 1: N = 94
**Depiction of Clusters – “Cluster Clock”**

**Legend**

Each spoke represents a Banff score.

Length of spokes = % with finding.

.... = Banff 1
----- = Banff 2
____ = Banff 3

Clustering based on 6 Banff scores (i, g, ct, cv, mm, ah) plus tatr.

Cluster 6
Histopathologic Clusters Differentiate Subgroups Within the Nonspecific Diagnoses of CAN or CR: Preliminary Data from the DeKAF Study

25 observations not depicted

Cluster 1: N=94
Cluster 2: N=40
Cluster 3: N=49
Cluster 4: N=14
Cluster 5: N=29
Cluster 6: N=14

Am Jnl Transplant 2010; 10: 315
Histopathologic Clusters Differentiate Subgroups Within the Nonspecific Diagnoses of CAN or CR: Preliminary Data from the DeKAF Study

Am Jnl Transplant 2010; 10: 315-323
C4d⁺ progressed more rapidly to graft failure than DSA⁺

Patients with C4d or DSA or both had worse outcomes ($p<0.0001$)

Inflammation in Areas of Atrophy: Strong Negative Predictor of Outcome

DeKAF Study: 289 recipients in cohort
59 with graft loss
89 with iatr=0, and iatr>1

0 = inflammation in less than 10% of atrophic regions
1 = inflammation in 10-25% of atrophic regions;
2 = inflammation in 26-50% of atrophic regions;
3 = inflammation in >50% of atrophic regions.

Mannon RB. *Am Jnl Transplant* 2010; 10: 2066-2073
Similar data relating inflammation with fibrosis and poor outcome:
Cosio AJT 2005; 5:1464

“Chronic TCMR was defined by sclerosing transplant arteriopathy. This lesion is characterized by intimal widening due to the de novo accumulation of collagens I and III, lack of elastosis, and varying degrees of intimal inflammation with mononuclear inflammatory cells.

In sclerosing transplant arteriopathy, the intima usually contains varying numbers of myofibroblasts, occasional foam cells, and, in active disease stages, scattered, often clustered mononuclear inflammatory cells that may be most prominent along the inner elastic lamina. Endothelial cells are often enlarged with reactive nuclei sometimes overlying an ill-defined ring of smooth muscle cells: that is, so-called neomedia formation.”
Cohort Local Biopsy Diagnoses
* adds up to >100% as 2 diagnoses/biopsy

<table>
<thead>
<tr>
<th>Primary/Secondary DX</th>
<th>CSC (N=425) N (%)</th>
<th>Prospective (N=227) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute antibody mediated rejection</td>
<td>29 (7)</td>
<td>18 (8)</td>
</tr>
<tr>
<td><strong>Acute cellular rejection</strong></td>
<td><strong>76 (19)</strong></td>
<td><strong>77 (34)</strong></td>
</tr>
<tr>
<td>ATN</td>
<td>18 (4)</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Allograft nephropathy</td>
<td>196 (48)</td>
<td>61 (27)</td>
</tr>
<tr>
<td>Art. nephrosclerosis</td>
<td>33 (8)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Borderline change</td>
<td>28 (7)</td>
<td>18 (8)</td>
</tr>
<tr>
<td><strong>CNI toxicity</strong></td>
<td><strong>116 (29)</strong></td>
<td><strong>25 (11)</strong></td>
</tr>
<tr>
<td>Glomerulonephritis (de novo)</td>
<td>23 (6)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>NPD</td>
<td>9 (2)</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Polyomavirus (BK)</td>
<td>11 (1)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>53 (13)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Transplant glomerulopathy</td>
<td>82 (20)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>4 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other (e.g., pyelo)</td>
<td>91 (22)</td>
<td>48 (21)</td>
</tr>
</tbody>
</table>
Tissue Regeneration versus Fibrosis: The Process of Wound Healing

Initiation Phase
- Ag dependent
- Ag independent

Matrix Phase

Fibrogenesis Phase
- Inflammation and migration
- Angiogenesis and myofibroblast proliferation and activation

Inflammatory response
- Proliferative response

Jnl Clin Investigation 2007; 117: 524
Graft Survival is Lower in Patients With SCR Associated with IFTA (i+IFTA)

6 month protocol bx

Similar data relating inflammation with fibrosis and poor outcome:
Cosio AJT 2005; 5:1464

Tubulointerstitial inflammation in early surveillance biopsies is associated with progression of IF and decreased allograft survival [Nankivell et al. Transplantation 2004; 78:242; Choi et al. AJT 2005;5: 1354].

Surveillance biopsies with i in non-scarred areas and IFTA [IFTA + i] are associated with shorter graft survival.
IFTA + i and DSA

- 598 kidney transplant recipients of low immune risk (CTX neg, PRA<20%, DSA neg)
  - Basiliximab, CNI based therapy
  - 6w and 12m biopsies with DSA measurements (LabScreen)/ MFI<1000 = negative
    - normal histology (i+t≤1 and ci+ct≤1)
    - inflammation (i+t≥2 and ci+ct≤1)
    - IFTA (i+t≤1 and ci+ct≥2)
    - IFTA+i (i+t≥2 and ci+ct≥2)

- Findings of IFTA+i @ 6w are independent risk for dnDSA (8.9% of pop at 1y)

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR of dnDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLADR MM</td>
<td>1.95 (1.09-3.49)</td>
</tr>
<tr>
<td>“i” score at 6w biopsy</td>
<td>5.49 (1.67-10.03)</td>
</tr>
<tr>
<td>IFTA+i at 6w</td>
<td>4.09 (1.67-10.05)</td>
</tr>
</tbody>
</table>

Garcia-Carro et al. Transplantation 2016; PMID 27163535