i-IFTA in kidney transplantation

Marion Rabant
Pathology department
Hôpital Necker-Enfants malades, Paris
INSERM U1153, Université de Paris
1997-2017: inflammation in fibrosis is not diagnostic

Table 1. Banff 97 diagnostic categories for renal allograft biopsies

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal</td>
<td>see Definitions</td>
</tr>
<tr>
<td>2. Antibody-mediated rejection</td>
<td>Rejection demonstrated to be due, at least in part, to anti-donor antibody</td>
</tr>
<tr>
<td>A. Immediate (hyperacute)</td>
<td></td>
</tr>
<tr>
<td>B. Delayed (accelerated acute)</td>
<td></td>
</tr>
<tr>
<td>3. Borderline changes: “Suspicious” for acute rejection</td>
<td>This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross section) and at least 11</td>
</tr>
<tr>
<td>4. Acute/active rejection</td>
<td>Histopathological findings</td>
</tr>
<tr>
<td>IA (Grade t2)</td>
<td>Cases with significant interstitial infiltration (&gt;25% of parenchyma affected) and foci of moderate tubulitis (&gt;4 mononuclear cells/tubular cross section or group of 10 tubular cells)</td>
</tr>
<tr>
<td>IB (Grade t3)</td>
<td>Cases with significant interstitial infiltration (&gt;25% of parenchyma affected) and foci of severe tubulitis (&gt;10 mononuclear cells/tubular cross section or group of 10 tubular cells)</td>
</tr>
<tr>
<td>IIA = v1</td>
<td>Cases with mild to moderate intimal arteritis (v1)</td>
</tr>
<tr>
<td>IIB = v2</td>
<td>Cases with severe intimal arteritis comprising &gt;25% of the luminal area (v2)</td>
</tr>
<tr>
<td>III = v3</td>
<td>Cases with “transmural” arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (v3 with accompanying lymphocytic inflammation)</td>
</tr>
<tr>
<td>5. Chronic/sclerosing allograft nephropathy</td>
<td>Histopathological findings</td>
</tr>
<tr>
<td>Grade I (mild)</td>
<td>Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection</td>
</tr>
<tr>
<td>Grade II (moderate)</td>
<td>Moderate interstitial fibrosis and tubular atrophy (a) or (b)</td>
</tr>
<tr>
<td>Grade III (severe)</td>
<td>Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)</td>
</tr>
<tr>
<td>6. Other</td>
<td>Changes not considered to be due to rejection, see Table 14.</td>
</tr>
</tbody>
</table>

The Banff 97 working classification of renal allograft pathology


[Racusen, Kidney, 1999]
Banff 2005: Chronic T-cell mediated rejection

Acute antibody-mediated rejection

Type (grade)

I. ATN-like – C4d+, minimal inflammation

II. Capillary-margination and/or thromboses, C4d+

III. Arterial – v3, C4d+

Chronic active antibody-mediated rejection¹

Glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis and/or fibrous intimal thickening in arteries, C4d+

This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3 with i0 or i1) and a threshold for rejection diagnosis is not met (may coincide with categories 2, 5 and 6)

4. T-cell-mediated rejection¹ (may coincide with categories 2, 5 and 6)

Acute T-cell-mediated rejection

Type (grade)

IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)

IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)

IIA. Cases with mild to moderate intimal arteritis (v1)

IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)

III. Cases with ‘transmural’ arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Chronic active T-cell-mediated rejection¹

Chronic active TCMR = chronic allograft arteriopathy

‘Chronic allograft arteriopathy’ (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

Solez et al; American Journal of Transplantation 2007; 7: 518–526
Fibrosis + inflammation in non scarred areas

IF/TA

Fibrosis with Inflammation at One Year Predicts Transplant Functional Decline

Walter D. Park,* Matthew D. Griffin,† Lynn D. Cornell,‡ Fernando G. Cosio,§ and Mark D. Stegall*


➢ Decreased renal function
➢ Increased interstitial T cells and macrophages/dendritic cells
➢ Increased expression of transcripts related to acute rejection.

n=151 living donors
Low immunological risk
One- year protocol biopsy
Total inflammation score

- The impact of i-IFTA on graft outcome was first suggested by the finding of Mengel et al that total cortical inflammation « ti score » was more predictive of graft outcome than « i » score.
- Stronger correlations with microarray-based gene sets representing major biological processes during allograft rejection using ti score.

Total inflammation: ti score

Implemented in the Banff 2007 classification
« to be tested in the next years »

Total interstitial inflammation score:
• ti0: no or less than 10% of inflammation in the total (fibrotic or not fibrotic) cortical area, including the sub-capsular cortex, perivascular cortex and areas of IF/TA
• ti1: 10-25%
• ti2: 26-50%
• ti3: more than 50%

Solez K, Am J of Transplant 2008; 8: 753–760
Inflammation in scarred area: i-IFTA score

Inflammation in Areas of Tubular Atrophy in Kidney Allograft Biopsies: A Potent Predictor of Allograft Failure

DeKaF Study

n=337 biopsies
291 with IF/TA
108 iatr

Mannon RB, Am J Transplant 2010;10:2066-2073
Inflammation in scarred area: i-IFTA score

\( i-IFTA >25\% \) associated with graft failure even after adjusting for:

- Interstitial fibrosis (HR=2.31, [1.10-4.83]; p=0.026)
- Tubular atrophy (HR=2.42, [1.16-5.08]; p=0.191)
- Serum creatinine
- Time to biopsy
- \( i \) score

Mannon RB, Am J Transplant 2010;10:2066-2073
Inflammation in scarred area: i-IFTA score

The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology

A. Loupy
American Journal of Transplantation 2017; 17: 28-41

i-IF/TA 0 < 10% of inflammation in scarred cortical parenchyma

i-IF/TA 1 : 10-25% of inflammation in scarred cortical parenchyma

i-IF/TA 2 : 26-50% of inflammation in scarred cortical parenchyma

i-IF/TA 3 >50% of inflammation scarred cortical parenchyma

Chronic T-cell mediated rejection

The Banff 2015 meeting report noted for the first time that chronic active TCMR may be manifest in the tubulointerstitial as well as in the vascular compartment.

T cell–mediated rejection is a major determinant of inflammation in scarred areas in kidney allografts

Inflammation in scarred area: i-IFTA score

The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: The Banff i-IFTA lesion
1477 Kidney allograft recipients with a protocol biopsy at one year 2004 – 2010 Paris

Inflammation in scarred area: i-IFTA score

Prognosis? → Allograft Survival

Significance? → 37 determinants

IF/TA>0 N=893 (60%)

Day 0

Recipient:
- Age, Dialysis, Cardiovascular

Donor
- Age, Type, Cardiovascular

Transplant
- DGF/CIT, HLA Mismatch, Induction

Diagnosis on for cause biopsies
- Rejection process
  - TCMR, ABMR, DSA
- Infections
  - BKVAN, CMV, Pyelonephritis
- Recurrent disease
- Immunosuppressive regimen
  - Steroids, CNI, mTOR, IMPPHi

Time post transplantation

Overall population N=1477

Study Population N=893

IF/TA 0
N=584

IF/TA 1
N=383 (43%)

- Minimal i-IF/TA (0-1)
  N=320 (84%)
- Severe i-IF/TA (2-3)
  N=63 (16%)

IF/TA 2
N=299 (33%)

- Minimal i-IF/TA (0-1)
  N=226 (76%)
- Severe i-IF/TA (2-3)
  N=73 (24%)

IF/TA 3
N=211 (24%)

- Minimal i-IF/TA (0-1)
  N=153 (73%)
- Severe i-IF/TA (2-3)
  N=58 (27%)

Severe i-IF/TA is associated with tubulo-interstitial inflammation.

i-IF/TA is mostly correlated to t-IFTA, and to i, t and ti.

Inflammation in scarred area: i-IFTA score

893 one year protocol biopsies with IF/TA

Log-rank P<0.0001

893 one year protocol biopsies with IF/TA

Minimal i-IF/TA N=699 (78%)

Severe i-IF/TA N=194 (22%)

Severe i-IF/TA (score 2-3)
Decreased long term allograft survival

Inflammation in scarred area: i-IFTA score

Relative variable importance

iIF/TA

i

ti

t

0.0 0.2 0.4 0.6 0.8 1.0

i-IF/TA is superior to i, ti and t scores to predict allograft failure in patients with allograft fibrosis at one year.

Inflammation in scarred area: i-IFTA score

Determinants of presence of i-IF/TA at one year after transplantation: multivariate model

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Number of events</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-year T cell-mediated rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>798</td>
<td>306</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>142</td>
<td>85</td>
<td>2.73</td>
<td>[1.87-3.97]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First-year BK virus-associated nephropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>914</td>
<td>373</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>18</td>
<td>3.25</td>
<td>[1.38-7.67]</td>
<td>0.007</td>
</tr>
<tr>
<td>Six-month steroid therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>103</td>
<td>50</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>837</td>
<td>341</td>
<td>0.64</td>
<td>[0.42-0.98]</td>
<td>0.039</td>
</tr>
<tr>
<td>Six-month calcineurin inhibitor therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>51</td>
<td>29</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>889</td>
<td>362</td>
<td>0.47</td>
<td>[0.26-0.84]</td>
<td>0.011</td>
</tr>
<tr>
<td>Six-month IMPDH1 therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>50</td>
<td>29</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>890</td>
<td>362</td>
<td>0.46</td>
<td>[0.25-0.84]</td>
<td>0.011</td>
</tr>
<tr>
<td>HLA B mismatch (per 1-unit increment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>940</td>
<td>391</td>
<td>1.29</td>
<td>[1.06-1.59]</td>
<td>0.012</td>
</tr>
<tr>
<td>Yes</td>
<td>940</td>
<td>391</td>
<td>1.23</td>
<td>[1.01-1.50]</td>
<td>0.044</td>
</tr>
</tbody>
</table>

T cell-mediated rejection is a major determinant of inflammation in scarred areas in kidney allografts.

Inflammation in scarred area: i-IFTA score

2481 biopsies from 362 kidney pancreas recipients (429 indication and 2052 protocol biopsies)

6.9 biopsies/patient

1220 biopsies with IFTA, among which 62% with i-IFTA. 82% with mild i-IFTA 1 (574/702)

**Multivariable model 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early T cell rejection</td>
<td>1.464</td>
<td>1.062-2.017</td>
<td>.020</td>
</tr>
<tr>
<td>Early vascular rejection</td>
<td>1.660</td>
<td>1.129-2.442</td>
<td>.010</td>
</tr>
<tr>
<td>Tacrolimus era (vs cyclosporine)</td>
<td>0.219</td>
<td>0.157-0.306</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Inflammation in scarred area: i-IFTA score

Graft survival by 1 year i-IFTA

Renal function by 1 year i-IFTA

Significance of i-IF/TA

- Previous TCMR
- Under immunosuppression
- BK virus nephropathy
- Recurrent glomerulonephritis
- Pyelonephritis
- Obstruction
- ABMR
- PTLD
Significance of i-IF/TA

NEW CRITERIA FOR chronic active TCMR Banff 2017

- **Chronic active TCMR Grade IA:**
  Interstitial inflammation involving >25% of the total cortex \((ti \ 2/3)\)
  and >25% of the sclerotic cortical parenchyma \((i-IFTA \ 2/3)\)
  with moderate tubulitis \((t2)\) involving 1 or more tubules, **not including** severely atrophic tubules; other known causes of i-IFTA should be ruled out (BK, ABMR, GN, obstruction)

- **Chronic active TCMR Grade IB:**
  \(ti \ 2/3 \ and \ i-IFTA \ 2/3 \ with\) severe tubulitis \((t3)\) involving 1 or more tubules,

- **Chronic active TCMR Grade II:**
  Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)

- **No Borderline or suspicious category for chronic active TCMR**

- **A biopsy fulfilling the diagnostic criteria for chronic active TCMR should not be given a second diagnosis of Borderline or acute TCMR.**

A severely atrophic tubule is defined as one with each of the following three features:

- A diameter <25% of that of unaffected or minimally affected tubules on the biopsy
- An undifferentiated-appearing, cuboidal or flattened epithelium
- Pronounced wrinkling and/or thickening of the tubular basement membrane
What is the molecular signature of i-IF/TA?

Original Article

Molecular phenotype of kidney transplant indication biopsies with inflammation in scarred areas

Philip F. Halloran¹,² | Arthur Matas³ | Bertram L. Kasiske⁴ |
Katelynn S. Madill-Thomsen² | Martina Mackova¹ | Konrad S. Famulski¹

234 biopsies from 189 patients
• 53 biopsies with IF/TA 0
• 181 biopsies with IF/TA>0 (77%)
  - 73 biopsies with no i- IF/TA
  - 108 biopsies with i-IFTA>0
  - 37 biopsies with i-IFTA>25%

Am J Transplant. 2019 May;19(5):1356-1370
We believe that histologic i-IFTA in indication biopsies primarily represents the inflammatory component of the response to recent or ongoing parenchymal injury ("response to wounding").
• Inflammation in fibrosis >25% (i-IFTA 2 or 3) is associated with a poorer graft survival

• Inflammation in fibrosis is associated with previous episodes of TCMR and under-immunosuppression

• However, inflammation in fibrosis is not specific

• Molecular signature seems to be not consistent with TCMR in indication biopsies.

New molecular studies are needed
Thank you
Prognosis of inflammation and TCMR

n=302 rejets
TCMR/V- (n=139)
TCMR/V+ (n=26)
ABMR/V- (n=73)
ABMR/V+ (n=64)

Lefaucheur, Loupy et al, Lancet, 2013 Jan
PROGNOSTIC VALUE OF i-IF/TA IN TCMR

136 pure TCMR within the first year post-transplant

IF/TA progression over time (564 Bx)

Allograft Survival

IF/TA scoring

Steroid pulses +/- rATG

Day 0

TCMR N=136

1 Year

Time post transplantation
PROGRESSION OF IF/TA AFTER TCMR

Accelerated IF/TA over time after TCMR for patients with severe i-IF/TA at one year.
The persistence of inflammation in fibrosis after treatment is associated with a decreased allograft survival.