Kidney Summary

Mark Haas
Cedars-Sinai Medical Center
Los Angeles, California, USA

Key Issues to Address re: the Classification

1. Incorporation of i-IFTA + tubulitis into the TCMR classification
    - Defining interstitial inflammatory component
    - Assessing and defining a threshold for tubulitis
    - What do we call it?
2. Can we diagnose ABMR without detectable DSA?
    - C4d as a surrogate marker
    - Molecular surrogate marker(s)
3. Should we remove the word “active” from acute/active ABMR?

What interstitial inflammatory component should be required?

1. Total inflammation in cortex (ti) ≥2
2. Fraction of sclerotic cortex with inflammation (i-IFTA) ≥2
3. Both (1) and (2)
4. i ≥1 and i-IFTA ≥1
5. ti ≥2 with i-IFTA ≥1 and at least 5% i

Note that regardless of which of the above is ultimately selected, it is specified that inflammation due to infection (viral or bacterial) or PTLD should be excluded.

How to incorporate tubulitis?

It was generally agreed that a threshold of t2 should be required for this diagnosis, and that at least some of this tubulitis should be in area(s) of i-IFTA. Within this context, should we:

1. Keep current thresholds for t1, t2, t3 and requirement that tubulitis be scored only in tubules with no more than mild/early atrophy
2. Keep current thresholds but allow scoring in all but severely atrophic tubules

What terminology to use?

1. Just call the lesion TCMR, regardless of the ratio of i to ti (molecular classifiers do not recognize "chronic, active" TCMR – just TCMR – but these were trained primarily on early biopsies!)
2. If criteria for inflammation and tubulitis on the previous 2 slides are met, call it:
    a) chronic, active TCMR
    b) chronic and acute TCMR
    c) smoldering TCMR
    d) chronic TCMR
    e) other

How to proceed?

1. Make a change in the Banff TCMR criteria now.
2. Ask that the Paris group (Clement Gosset) and DeKAF group (Roz Mannon) further analyze their data to determine the options for interstitial inflammation and tubulitis best correlated with graft outcomes and (if feasible) response to therapy for TCMR; incorporate changes into the 2017 Banff meeting report based on our discussions plus their findings.
3. Have the TCMR Working Group similarly analyze the data from their cases, present these findings at 2019 meeting and wait until 2019 meeting to change criteria.

Can C4d be considered a surrogate marker for DSA in diagnosis of ABMR?

Banff 2013 Classification of Antibody-Mediated Rejection (ABMR) in Renal Allografts

Acute/Active ABMR; all 3 features must be present for diagnosis[a]

1. Histologic evidence of acute tissue injury, *including one or more of the following*:
   - Microvascular inflammation (g > 0[b] and/or ptc > 0)
   - Intimal or transmural arteritis (v > 0)[c]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, *including at least one of the following*:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2)[d]
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, *if thoroughly validated*
3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

[a] These lesions may be clinically acute, smoldering, or subclinical. Biopsies showing two of the 3 features may be designated as "suspicious" for acute/active ABMR.

[b] Recurrent/de novo glomerulonephritis should be excluded

[c] These lesions may be indicated of ABMR, TCMR, or mixed ABMR/TCMR

[d] In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc ≥2 alone is not sufficient to define moderate microvascular inflammation and g must be ≥1.

Banff 2013 Classification of Antibody-Mediated Rejection (ABMR) in Renal Allografts

Acute/Active ABMR; all 3 features must be present for diagnosis[a]

1. Histologic evidence of acute tissue injury, *including one or more of the following*:
   - Microvascular inflammation (g > 0[b] and/or ptc > 0)
   - Intimal or transmural arteritis (v > 0)[c]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, *including at least one of the following*:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2)[d]
   - Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, *if thoroughly validated*
3. Serologic evidence of donor-specific antibodies (HLA or other antigens), OR linear C4d staining [C4d2 or C4d3?] in peritubular capillaries [as specified above?]

[a] These lesions may be clinically acute, smoldering, or subclinical. Biopsies showing two of the 3 features may be designated as "suspicious" for acute/active ABMR.

[b] Recurrent/de novo glomerulonephritis should be excluded

[c] These lesions may be indicated of ABMR, TCMR, or mixed ABMR/TCMR

[d] In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc ≥2 alone is not sufficient to define moderate microvascular inflammation and g must be ≥1.

Can ABMR Classifier (or other transcript set[s]) be used as a surrogate marker for DSA in patients with biopsy showing (g + ptc) ≥2 without C4d staining or detectable DSA or non-HLA antibodies?

Issues to consider

1. Completeness of the DSA testing
2. Specificity of molecular test and threshold
3. Terminology – do we want to call lesions with (g + ptc) ≥2, no detectable DSA or non-HLA antibodies, and positive ABMR classifier "ABMR", or something less definite?
4. At what point to add to the classification?
5. An important issue for the Molecular WG and Banff as a whole to consider!

Should we remove the word “acute” from acute/active ABMR?

As I understand it, the word acute was added at the request of the clinicians, not the pathologists

A footnote in Table 2 of Banff 2013 paper states that “these lesions may be clinically acute, smoldering, or subclinical”

Noting this, if the clinicians find the term “acute/active ABMR” confusing, the pathologists have no objection to changing this to simply “active ABMR” – although this would create a terminology different from that used for TCMR.

Working Group Summaries

Current WGs

Electron Microscopy

Highly Sensitized

Recurrent Glomerular Disease

Thrombotic Microangiopathy

T Cell-Mediated Rejection

Molecular Diagnostics

Proposed WG

Web-based Banff education/information

Electron Microscopy WG

Key Questions/Objectives

Evaluate current practices of EM use in renal allograft biopsies

Clarify lesion definitions and improve inter-observer agreement in evaluating cg1a and ptcbml

Evaluate the impact of cg1a and ptcbml on graft outcomes

Define possible lower levels of ptcbml and ptc endothelial cell changes that represent earlier and possibly reversible levels of injury (compared to level of ptcbml required to diagnose chronic, active ABMR in Banff 2013)

Highly Sensitized WG

Key Questions/Objectives

Evaluate current practices of centers performing renal transplants in sensitized recipients

Evaluate how clinicians interpret and apply Banff nomenclature, and recommend changes to wording of classification to optimize the use of Banff data in patient care

Improve communication between pathologists and clinicians regarding reporting of biopsy findings, including the presence of C4d-negative early ABMR

Recurrent GN WG

Key Questions/Objectives

Establish pathologic guidelines for early recurrence of glomerular diseases, including FSGS, IgA nephropathy, and MPGN/C3GN

Understand the pathologic changes of recurrent glomerular diseases occurring concurrently with rejection and other transplant-associated lesions

Within each recurrent glomerular disease (FSGS, IgAN, etc):

Are the clinical and/or pathologic features of the native disease that predict likelihood of recurrence?

Are there clinical and/or pathologic features of the recurrent disease in the allograft that predict graft loss?

Which pathologic analyses (IF, EM, others) needed for optimal, early diagnosis of recurrent disease?

Thrombotic Microangiopathy WG

Key Questions/Objectives

Establish uniform diagnostic criteria for TMA in concert with other groups

Determine the frequency with which TMA occurs in renal allograft biopsies

Compare and contrast features of TMA in known cases of CNI-related TMA from native kidneys of recipients of other solid organs, TMA in the setting of well-documented ABMR (DSA+, C4d+), and recurrent aHUS to assess differences in morphologic and other (e.g., laboratory) features that may be useful in the determining the most likely etiology in transplant TMA cases where this is not clear-cut.

New WG Proposal – Jan Becker

Key Objectives

Comprehensive, online collation of all currently valid content from prior Banff meeting reports – including most up-to-date definitions of individual lesions, tables, flow charts, illustrative photomicrographs, training sets, and references

Downloadable spreadsheets for research

Electronic assignment of Banff diagnostic categories based on entry of individual lesion data

THANK YOU

QUESTIONS?