The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated rejection

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MEETING REPORT

The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated rejection

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The XV. Banff conference for allograft pathology was held in conjunction with the annual meeting of the American Society for Histocompatibility and Immunogenetics in Pittsburgh, PA (USA) and focused on refining recent updates to the classification, advances from the Banff working groups, and standardization of molecular diagnostics. This report on kidney transplant pathology details clarifications and refinements to the criteria for chronic active (CA) T cell–mediated rejection (TCMR), borderline, and antibody-mediated rejection (ABMR). The main focus of kidney sessions was on how to address biopsies meeting criteria for CA TCMR plus borderline or acute TCMR. Recent studies on the clinical impact of borderline infiltrates were also presented to clarify whether the threshold for interstitial inflammation in diagnosis of borderline should be i0 or i1. Sessions on ABMR focused on biopsies showing microvascular inflammation in the absence of C4d staining or detectable donor-specific antibodies; the potential value of molecular diagnostics in such cases and recommendations for use of the latter in the setting of solid organ transplantation are presented in the accompanying meeting report. Finally, several speakers discussed the capabilities of artificial intelligence and the potential for use of machine learning algorithms in diagnosis and personalized therapeutics in solid organ transplantation.

**KEYWORDS**
classification systems: Banff classification, clinical decision-making, clinical research/practice, kidney (allograft) function/dysfunction, kidney transplantation/nephrology, molecular biology; mRNA/mRNA expression, pathology/histopathology, rejection, translational research/science

## INTRODUCTION

The XV. Banff Conference for Allograft Pathology was held September 23-27, 2019, in Pittsburgh, PA (USA), in conjunction with the Annual Meeting of the American Society for Histocompatibility and Immunogenetics (ASHI). A total of 1253 delegates from 31 countries attended the conference, including pathologists, immunologists, physicians, surgeons, and immunogeneticists as well as representatives from industry. The focus of kidney sessions at the 2019 conference was to clarify diagnostic criteria for antibody-mediated rejection (ABMR) and chronic active (CA) T cell–mediated rejection (TCMR) to harmonize the pathologic diagnosis and consequent therapeutic strategies. In addition, consensus of the diagnosis of borderline (suspicious) for acute TCMR was reached. The current literature on biomarkers and molecular transplant diagnostics was also reviewed, and recommendations of the Banff Molecular Diagnostics Working Group regarding clinical validation and adoption of the latter into the Banff classification will be presented in a separate meeting report. Continuing a theme from the Banff 2015 meeting, results of studies using artificial intelligence (AI) and integrative epidemiological approaches were presented. Their applicability in prediction, prognostication, and clinical trials could change standards of
care for transplant recipients. The conference was preceded by a premeeting on "Regenerative Medicine and Digital Pathology" and a joint session between the ASHI and Banff key opinion leaders, which presented insights into future tissue and organ engineering and new technologies in solid organ transplantation. Precise detection and characterization of anti-HLA or non-HLA donor-specific antibodies (DSAs) was also revisited. This report summarizes the main outcomes of the Banff 2019 kidney sessions and their impact on the Banff classification.

2 | UPDATES FROM THE BANFF WORKING GROUPS

The current active and new Banff working groups (BWGs) and their aims, leaders, and progress are listed in Table 1. One new BWG has been formed, the Digital Pathology BWG. The aim of this working group is to define standards for digital pathology in the context of Banff lesion scores in order to standardize diagnostic scoring and reduce inter-observer variability. In addition, the peritubular capillary (ptc) BWG has been reactivated. Recent studies have shown diagnostic and prognostic relevance of reporting the extent of capillaritis (diffuse vs focal) in addition to the Banff ptc score, in diagnostic and prognostic relevance. BWG has been reactivated. Recent studies have shown diagnostic and prognostic relevance of reporting the extent of capillaritis (diffuse vs focal) in addition to the Banff ptc score, in different clinical scenarios including ABMR, mixed ABMR/TCMR, and interstitial (diffuse vs focal) in addition to the Banff ptc score, in different clinical scenarios including ABMR, mixed ABMR/TCMR, and low-grade microvascular inflammation (MVI). The aim of the BWG is to validate these findings in a multicenter study, and to evaluate optimal diagnostic thresholds.

At its meeting during Banff 2019, the electron microscopy (EM) BWG expanded on its previous recommendations and agreed to guidelines for tissue sampling and performing EM analysis for assessment of cg1a and peritubular capillary basement membrane multilayering (PTCML). These are summarized in Table 2. The group also recommended the use of specific terminology aligned where possible with ongoing work of the Renal Pathology Society working group developing consensus definitions for individual glomerular lesions by light microscopy and EM. As specified in Table 3, this includes the following, representing individual components of very early lesions of transplant glomerulopathy (cg1a); endothelial cell enlargement, subendothelial electron-lucent widening, and subendothelial neo-densa glomerular basement membrane. Reporting of other endothelial and basement membrane features in glomeruli and peritubular capillaries (PTCs) is left to the discretion of the pathologist as there are few data to support their use at present. Based on consensus opinion within the EM BWG, abbreviation for peritubular capillary basement membrane multilayering is recommended as PTCML.

At the 2019 conference, final data from the BWG on the classification of polyomavirus nephropathy (PVN) were presented. This BWG studied 192 patients with definitive PVN and identified two histologic markers predictive for graft function and graft survival: the Banff interstitial fibrosis (ci) score and a new score termed "the intrarenal polyomavirus load level" or pvl, the latter based on the fraction of tubules with evidence of PV replication by light microscopy OR immunohistochemical staining of epithelial cell nuclei for SV40 large T antigen (pvl1 ≤ 1%, pvl2 > 1%, and <10%, pvl3 ≥ 10%). The pvl and ci scores were used to define 3 PVN classes (Tables 4 and 5).

3 | CLARIFICATION AND UPDATES TO THE BANFF 2017 CLASSIFICATION REVISIONS

The Banff 2019 kidney sessions focused on reviewing the impact of the changes to the diagnostic criteria for both TCMR and ABMR that were made at the 2017 Banff conference. For TCMR, this involved mainly the implementation of CA TCMR: The extent to which this category is being used at different centers around the world, potential confusion regarding the wording of diagnoses within this category, how frequently patients with CA TCMR were being treated, and the efficacy of those treatments. The threshold for the interstitial inflammation score (i) in the diagnosis of borderline for acute TCMR, which has not been applied uniformly by different pathologists and been the subject of recent investigation was also discussed. For ABMR, discussions centered around potential simplification of the diagnostic criteria, including clarifying the description of activity and chronicity components within the category of CA ABMR—making the resultant report more intelligible and useful to treating clinicians.

Standardized reporting for TCMR and ABMR diagnoses were discussed, including the inclusion of individual Banff acute and chronic scores (i, t, g, cg, and so on) used in determining the subtype, activity, and chronicity and explanations of these scores. The clinical implications of MVI in the absence of (DSAs with and without C4d deposition were also presented). Final consensus recommendations were aided by questionnaires distributed to pathologists, nephrologists, and transplant surgeons attending the 2 kidney-specific sessions during and immediately after the meeting (Table 6).

3.1 | Chronic active TCMR criteria clarifications

To assess whether transplant centers worldwide were applying the 2017 Banff classification and diagnosing CA TCMR, we enlisted the assistance of The Transplantation Society (TTS) and the CyberNephrology online forum (Dr Kim Solez) in circulating a survey that was answered by 128 TTS members, including clinicians and pathologists, from six different continents before the meeting (Figure 1). Notably, pathologists at ~90% of surveyed centers diagnosed CA TCMR, and at >80% of these centers at least some patients with this diagnosis were treated with steroids or other immunosuppressive agents. However, those clinicians that do not routinely treat patients with CA TCMR (52/81, 64%) indicated a need for more definitive data on the efficacy of CA TCMR treatment, and a minority (22/81, 27%) felt that the risk of treatment outweighs the benefits. Two points that should be emphasized regarding CA TCMR are that inflammation in areas of the cortex with interstitial fibrosis and tubular atrophy (i-IFTA), while an essential component of CA TCMR, are not sufficient to make this diagnosis, which also requires
## Table 1: Updates of Banff Working Groups

| Working group                           | Leaders                  | Issues to address                                                                                           | Group progress/future plans                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TCMR                                   | V. Nickeleit, P. Randhawa | Integration of i-IFTA into classification; reevaluate thresholds for i and t and possible addition of other findings (e.g., edema) to TCMR diagnostic criteria | A multicenter clinicopathologic study aimed at addressing the listed issues is in progress. To date biopsies and accompanying clinical data from 154 patients with "pure" (no ABMR) acute TCMR/borderline, 18 with chronic active TCMR, 55 with no rejection, and 31 patients with stable graft function (not biopsied) have been accrued into the study cohort. Data analysis and slide review have commenced, but more cases, especially cases of chronic active TCMR and control cases with complete clinical data for statistical analysis of TCMR/borderline thresholds, are required. These cases need to have documented absence of DSA and sufficient follow-up in addition to detailed clinical information.                                                                                       |
| Sensitized                             | L. Cornell, R. Sapir-Pichhadze, E. Kraus, S. Bagnasco, C. Schinstock, D. Dadhania | Define criteria for highly sensitized patients (HS), determine consensus for what personnel and facilities are needed for centers to perform transplantation in HS recipients, standardize the definitions related to management of sensitized transplant recipients. 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 clinical care of HS patients. | Survey regarding clinical practice related to highly sensitized (HS) patients indicates that clinicians often fail to recognize chronic elements of ABMR (e.g., C4d > 0) and are more likely to consider a diagnosis of chronic active ABMR if C4d is negative, even if there is no TG, PTCML, or IFTA. The term "acute" is confusing in ABMR, and consequently it was removed from the Banff ABMR classification in 2017. Further improved communication between pathologists and clinicians regarding reporting of biopsy findings in HS. Follow-up preliminary survey results indicate that pathologists and clinicians have similar concerns about biopsy reporting of antibody-mediated injury. Banff classification is complex, changes frequently, and does not reflect the entire ABMR disease spectrum. Comprehensive literature review is in progress to outline patient risk spectrum with respect to antibody and to standardize definitions of incompatible transplants.                                                                                           |
| Molecular diagnostics                   | M. Mengel, R. Colvin     | Develop consensus discovery gene panel, which becomes available to the whole transplant community as standardized commercially available reagents. Design and conduct collaborative studies to validate clinical utility of molecular diagnostics in transplant biopsies. | Launch of a consensus based, commercially available (NanoString Inc), standardized Banff Human Organ Transplant (B-HOT) discovery gene panel, which can reproducibly be applied to FFPE samples across organs and in multicenter studies. Development of an open source data sharing platform to exchange results from studies using the B-HOT panel to allow multicenter and multiorgan validation of clinical utility of molecular diagnostics in transplant biopsies. Details given in a separate meeting report.                                                                                           |
| HIV*/HIV+ renal transplants             | S. Bagnasco              | Compare kidney transplants from HIV+ and HIV-negative donors to HIV+ recipients with regard to graft function and graft survival; incidence, type and pathologic features of allograft lesions including rejection, recurrent and de novo HIV-related/unrelated renal disease; injury associated with antiretroviral and immunosuppressive treatment. | Based on preliminary data from the pilot phase of the US HOPE prospective multicenter trial for HIV+ to HIV+ kidney transplantation, TCMR is predominant, rejection appears to be unrelated to donor HIV status and may possibly be related to the type of immunosuppression. Additional data will become available with ongoing trial enrollment in upcoming years. The results of protocol/indication biopsies (archived as digital images), combined with comprehensive clinical information will be analyzed to expand these preliminary observations.                                                                                           |
| Electron microscopy (EM)                | C. Roufosse, H. K Singh  | Recommendations for the sampling and processing of tissue for EM and reporting of EM findings in transplant biopsies. Harmonize terminology with a list of definitions for cg1a and PTCML. Reduce inter-observer variability in the use of uniform guidelines for the evaluation of TG and PTCML Multicenter study of the natural history, associations and the predictive value of glomerular and peritubular capillary ultrastructural features (endothelium; basement membrane; electron dense deposits). | Consensus document produced at Banff 2019 meeting. Results of initial survey of interobserver variability were poor (presented at Banff 2017); a new comprehensive teaching module will focus on the most problematic lesions gleaned from the 2017 survey; Goal is to improve the uniform use of currently published criteria and the inter-observer variability. Research proposal presented at Banff 2019: pilot test case data collection in 2020; final study design to be agreed upon before initiation of the full study in 2020-21. Goal is the multicenter validation of ultrastructural features through correlation with outcomes.                                                                                           |
| Working group | Leaders | Issues to address | Group progress/future plans |
|---------------|---------|-------------------|----------------------------|
| Thrombotic microangiopathy (TMA) | M. Afrouzian, H. Liapis | Establish uniform diagnostic criteria for TMA. Determine the frequency with which TMA occurs in renal allograft biopsy specimens. Determine if there are specific features of TMA in renal allografts that help resolve the differential diagnosis of the TMA when the cause is not readily apparent from clinical history, DSA, C4d, etc. | Using Delphi methodology, two phases were designed: Phase I (with pathologists) and Phase II (with clinicians). Phase I (6/9 rounds completed) involving 23 centers; 1. We collected 37 transplant biopsies, and after 6 Delphi rounds, narrowed down 331 criteria to 61; 2. We classified the criteria into 4 classes (Pathology, Clinical, Laboratory and Differential Diagnosis) and 12 categories reflecting positive and negative criteria for LM, IF, EM, clinical, laboratory and genetic criteria; 3. Participants validated the 37 cases in 2 validation rounds. Results showed that 75% of the participants reached consensus in over 75% of cases, using the 61 criteria. 4. We identified the reasons for over- and under-diagnosis of TMA. Results of rounds 7, 8 and 9 are pending. Phase II: Recruitment of participants for the clinical Delphi starting January 2020. Future efforts will focus on completing the 3 remaining Delphi rounds (Phase I), soliciting nephrologists’ input (Phase II), combining Phase I and II results, dissecting diagnostic issues that emerged during Phase I, such as ABMR mimicking TMA and completing the molecular studies to generate the final consensus guidelines. The WG also plans to collaborate with groups that are working on native kidney TMA to compare results and generate a consensus document. |
| Recurrent glomerular disease | N. Alachkar, S. Bagnasco | Establish pathologic guidelines for early recurrence of glomerular diseases, including FSGS, IgA nephropathy, membranous nephropathy, MPGN/ C3GN. What are frequencies, clinical manifestations, and pathologic characteristics of recurrent/de novo glomerular diseases, and can any of these predict recurrence and/or graft outcomes? Understand the pathologic changes of recurrent glomerular diseases occurring concurrently with rejection and other transplant-associated lesions. | Biopsy specimens and clinical data are now being collected from 10 international centers. Preliminary results confirm IgA nephropathy and FSGS as the most prevalent recurrent diseases. Combine all data to create a posttransplant GN registry. Future directions: • Correlate GN findings with Banff classification • Correlate pathology with biomarkers, DSA, etc • Determine if outcomes of posttransplant GN can be improved with early detection, prevention and therapy. Are there 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 are needed for optimal and early diagnosis of recurrent disease? Is the apparent association of recurrent glomerular disease with acute rejection related to biopsy bias (ie incidental discovery of recurrent disease in biopsies done to rule out rejection), under-immunosuppression, or both? |
| Surrogate endpoints | A. Loupy, M. Naesens | Define valid surrogate endpoints and invasive or noninvasive biomarkers for clinical trials and how histology and lesions related to tissue injury or scarring have to be integrated in such systems. Insure Banff active involvement and interactions with agencies such as FDA/ EMA and societies (AST, ESOT, TTS). | New WG in progress |
| Banff rules and dissemination | J. U. Becker, C. Roufosse | Elaboration of diagnostic algorithms for the Banff Diagnostic Classes 1-6. Determination of the needs of the transplant community for dissemination of Banff content. Predominantly web-based dissemination of Banff content. | Collation of all Banff content for kidney allograft pathology up to and including Banff 2017 (Transplantation 2018; 102:1795-1814). Future plans include survey of the transplant community regarding dissemination needs, podcast based on the 2018 review article in collaboration with TTS, development and implementation of web-based tools and dissemination of relevant Banff content including the content of this 2019 update. |
(1) at least a moderate degree of total cortical inflammation and (2) moderate tubulitis involving cortical tubules other than severely atrophic tubules (Table 4). I-IFTA itself is not a specific lesion and is seen in the context of tissue injury due to many causes other than TCMR, including BK virus nephropathy and ABMR. According to Banff 2017, the tubulitis allowed for the diagnosis of CA TCMR may be within or outside of scarred areas. However, for clarity and future investigation we suggest that tubulitis be independently scored (providing that severely atrophic tubules are not scored) both in areas of preserved cortex (Banff t score) and within (Banff t-IFTA score) areas of cortical IFTA, as defined in Table 5. This may enable investigators and clinicians to determine the impact on treatment response and graft survival of these different forms of tubulitis. An important concern expressed by some clinicians and pathologists is that the Banff 2017 diagnosis of CA TCMR does not discriminate between cases where all or nearly all inflammation is limited to I-IFTA vs those instances where coexistent i-IFTA and inflammation within non-scarred areas meets criteria for additional borderline acute TCMR or acute TCMR grade IA or IB diagnoses. Questionnaire responses from meeting attendees clearly replied that reporting of “mixed” CA TCMR with grade IA or IB acute TCMR could be improved by indicating separately when biopsies simultaneously met criteria for borderline for acute TCMR or acute TCMR grade IA or IB (Table 6). Likewise, participants agreed that when intimal arteritis was present in addition to CA TCMR, this should also be specifically reported. These suggestions pertain only to CA TCMR reporting and the actual histologic criteria for this diagnosis remain unchanged (Tables 4 and 5). Nankivell et al reported that both development of i-IFTA and clearance of inflammation from scarred areas were dependent of the efficacy of immunosuppressive therapy. These data support the 2017 Banff criteria for CA TCMR, but also favor indicating the level of active inflammation in non-scarred cortex.

### 3.2 Borderline (suspicious) for acute TCMR criteria clarifications

The Banff ’97 criteria for diagnosis of borderline for acute TCMR required inflammation in at least 10% of nonscarred cortex (Banff i1) in addition to tubulitis. However, subsequent iterations of the Banff classification accepted tubulitis with minimal inflammation (isolated t; i0 t > 0) as sufficient for a diagnosis of borderline, and a recent survey showed variability among pathologists with regard to which threshold was used for this diagnosis. More recently, longitudinal studies of Nankivell et al showed no effect of isolated t lesions on graft outcomes, concluding that the original Banff ’97 threshold for borderline lesions should be applied, and 82% (57/69) of pathologists and clinicians (nephrologists and transplant surgeons) responding to the questionnaire distributed at the 2019 Banff conference agreed (Table 6). Consensus was therefore achieved that the diagnostic threshold for borderline for acute TCMR should read as follows: “interstitial inflammation involving 10%-25% of non-sclerotic cortex (Banff i1) with at least mild tubulitis (t > 0).” The minimum lesion for a borderline diagnosis is thus i1t1. As with previous versions of the Banff classification, lesions characterized by mild tubulitis (Banff t1) with inflammation involving >25% of nonsclerotic cortex (Banff i2/3) and no intimal arteritis are also included in the borderline category (Table 4). However,
TABLE 2 Banff recommendations for electron microscopy in renal transplant biopsies

Recommendations for taking of a sample for EM
Take a sample in all cases if possible, fixed and embedded as a resin block. At a minimum, this should be done if there is any suspicion of glomerular disease. While EM can be performed on samples recovered from paraffin blocks or frozen tissue to examine for electron dense deposits and to some extent the degree of foot process effacement, this is not recommended for assessment of glomerular basement membrane (GBM) thickness. cg1a or PTCLM. In all cases, light microscopic (LM) examination of semi-thin stained sections should be performed.

Recommendations for performing ultrastructural analysis
Recommended in cases with: (a) Clinical, light microscopic and/or immunohistochemical suspicion of glomerular disease or of other diseases where EM may assist in diagnosis; (b) Patients at risk for antibody-mediated rejection (ABMR); patients who are sensitized, have documented DSA at any time posttransplant, and/or who have had a prior biopsy showing features of ABMR (C4d staining, glomerulitis and/or peritubular capillaritis).
EM can also be useful: (a) To detect early recurrence in patients with biopsy-proven glomerular disease as the cause of native kidney failure; (b) In for-cause biopsies ≥3 mo posttransplant, and in all biopsies ≥6 mo posttransplant, to determine if early changes of transplant glomerulopathy (cg1a) are present, prompting testing for DSA.
In all cases, undertake an assessment for glomerular disease as in a native renal biopsy. If performing EM in the setting of possible ABMR, assess for cg1a and PTCLM as recommended below.

Recommendations for preparing the block for ultrastructural examination
Select an area in the resin block(s) of viable (non-necrotic) cortex, preferentially with minimal tubular atrophy/interstitial fibrosis. Aim to include ≥2 full glomeruli (at least 1). Do not taper the block to a “cone” or “pyramid” by removing cortical tissue around the glomeruli and aim to have at least 10 peritubular capillaries (PTCs) for examination.

Guidelines for ultrastructural assessment and reporting of cg1a
Exclude globally or partly sclerosed glomeruli, and severely ischemic glomeruli.
Examine 1 complete glomerulus as a minimum; where possible examine 2 or more.
Examine the capillary loops at high magnification (≥5000x). cg1a is defined as: (a) No GBM double contours on LM; (b) ≥3 capillary loops (in a single glomerulus) each showing: subendothelial neo-densa glomerular basement membrane (circumferential or not, single or multiple layers) AND endothelial cell enlargement and/or subendothelial electron-lucent widening. The report should state how many glomeruli were examined, and how many loops show cg1a.

Guidelines for ultrastructural assessment and reporting of PTCLM
Assess for PTCLM in the cortical peritubular capillaries between the glomeruli.
Exclude scarred cortex and necrotic or hemorrhagic areas.
Examine at least 10 PTC at high magnification (≥5000x).
Count layers of basement membrane (BM) in the 3 worst affected PTCs, for each counting in the PTC segment with the most layers (worst affected area along the circumference).
The report should state the number of PTC examined; the number of BM layers in the most affected PTC; and whether the Banff 2013 threshold for chronic ABMR (ptcml1; 1 PTC with ≥7 layers +2 PTC with ≥5 layers) is met.

TABLE 3 Definitions of the individual components of early lesions of transplant glomerulopathy

- Endothelial cell enlargement is defined as glomerular endothelial enlargement with associated increase in cytoplasm, decrease in the capillary luminal area and loss of fenestrations. This should be used rather than less precise or incorrect terminology such as “endothelial swelling”, “reactive endothelial changes”, “endothelial activation”, “endothelial injury” or “endothelial cell degeneration”.
- Subendothelial electron-lucent widening is defined as expansion of space between the glomerular endothelium and lamina densa of the glomerular basement membrane (GBM) by electron-lucent material. This should be used instead of “lamina rara interna expansion” or “subendothelial rarefaction”.
- Subendothelial neo-densa glomerular basement membrane is defined as circumferential or discontinuous, single or multiple basement membrane layer(s) clearly distinct from the original GBM.

biopsies with tubulitis (t > 0) but without inflammation in at least 10% of nonsclerotic cortex (i0) are no longer included in this category, and neither are cases with inflammation in the absence of tubulitis (i > 0, t0). These are simply reported in the microscopic description of the biopsy.

3.3 ABMR criteria clarifications

Since the introduction of ABMR into the Banff classification in 2003, the criteria for diagnosis of ABMR have become more complex, with major modifications in 2013 and 2017, which have improved diagnostic sensitivity and predictive value for graft outcomes. A major residual issue within the classification is that it still subclassifies ABMR into active or chronic active and chronic inactive (ie, transplant glomerulopathy without MVI and with current or historic DSA; Table 4) subtypes as opposed to representing the diverse morphologic and molecular lesions at different post-transplant time points in antibody-mediated tissue injury. In particular, the category of CA ABMR encompasses lesions with severe activity and mild chronicity (eg, g3 ptc3 cg1 c0 C4d3), those with mild activity and severe chronicity (eg, g1 ptc1 cg3 c3 C4d4), and intermediate cases. Thus a simple diagnosis of CA ABMR gives treating clinicians limited information for appropriate treatment options. Although the addition of individual Banff lesion scores to the diagnostic line of the report is interpretable by experienced clinicians, it may confuse some clinicians who are unfamiliar with subtleties of the Banff system. This concern was highlighted by the recent work from the BWG on highly sensitized patients who found that the classification was interpreted in a highly variable way with implications for resultant therapeutic decision making. Potential improvements in the wording of the pathologic diagnoses in standard reports were discussed, which remained within the context of Banff 2017 to optimally convey the activity and chronicity levels of CA ABMR cases. For example, in lupus nephritis, the previous designations of active (A), active and chronic (A/C), and chronic (C) were replaced with a revised
TABLE 4  Updates of 2019 Banff classification for ABMR, borderline changes, TCMR, and polyomavirus nephropathy. All updates are in boldface type

| Category 1: Normal biopsy or nonspecific changes |
|------------------------------------------------|
| Active ABMR; all 3 criteria must be met for diagnosis |
| 1. Histologic evidence of acute tissue injury, including 1 or more of the following: |
| • Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1 |
| • Intimal or transmural arteritis (v ≥ 0) |
| • 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 1 or more of the following: |
| • Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections) |
| • At least moderate microvascular inflammation (g + ptc ≥ 2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥ 1 |
| • Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated |
| 3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens), C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met |

| Category 2: Antibody-mediated changes |
|--------------------------------------|
| Active ABMR; all 3 criteria must be met for diagnosis |
| 1. Histologic evidence of acute tissue injury, including 1 or more of the following: |
| • Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1 |
| • Intimal or transmural arteritis (v ≥ 0) |
| • 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 1 or more of the following: |
| • Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections) |
| • At least moderate microvascular inflammation (g + ptc ≥ 2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥ 1 |
| • Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated |
| 3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens), C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met |

| Category 3: Borderline (Suspicious) for active ABMR |
|---------------------------------------------------|
| Chronic active ABMR; all 3 criteria must be met for diagnosis |
| 1. Morphologic evidence of chronic tissue injury, including 1 or more of the following: |
| • Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA, or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a) |
| • Severe peritubular capillary basement membrane multilayering (ptcml1; requires EM) |
| • Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required |
| 2. Identical to criterion 2 for active ABMR, above |
| 3. Identical to criterion 3 for active ABMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met. Biopsies meeting criterion 1 but not criterion 2 with current or prior evidence of DSA (posttransplant) may be stated as showing chronic ABMR, however remote DSA should not be considered for diagnosis of chronic active or active ABMR |

| Category 4: TCMR |
|------------------|
| Acute TCMR |
| Grade I: Intestinal inflammation involving >25% of non-sclerotic cortical parenchyma (t2 or t3) involving 1 or more tubules, not including tubules that are severely atrophic |
| Grade II: Intestinal inflammation involving >25% of non-sclerotic cortical parenchyma (t2 or t3) involving 1 or more tubules, not including tubules that are severely atrophic |
| Grade III: Transmural arteritis and/or arterial fibrinoid necrosis involving medial smooth muscle with accompanying mononuclear cell intimal arteritis (v3), with or without interstitial inflammation and/or tubulitis |

| Chronic active TCMR |
|---------------------|
| Grade I: Intestinal inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND > 25% of total cortical parenchyma (ti2 or ti3) with moderate tubulitis (t2 or t-IFTA2) involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out |
| Grade II: Intestinal inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND > 25% of total cortical parenchyma (ti2 or ti3) with severe tubulitis (t3 or t-IFTA3) involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out |

| Category 5: Polyomavirus nephropathy |
|-------------------------------------|
| PVN Class 1 |
| pvl 1 and ci 0-1 |
| PVN Class 2 |
| pvl 1 and ci 2-3 OR pvl 2 and ci 0-3 OR pvl 3 and ci 0-1 |
| PVN Class 3 |
| pvl 3 and ci 2-3 |

(Continues)
TABLE 4 (Continued)

| Individual Banff lesion scores are defined in Table 5, and it is recommended that these be included in the biopsy report. | It should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. | The clinical significance of these findings may be quite different in grafts exposed to anti-blood group antibodies (ABO-incompatible allografts), where they do not appear to be injurious to the graft and may represent accommodation. However, with anti-HLA antibodies, such lesions may progress to chronic ABMR, and more outcome data are needed. | Severely atrophic tubules are defined as having each of 3 features: diameter <25% of unaffected or minimally affected tubules in the same biopsy, an undifferentiated-appearing, cuboidal or flattened epithelium, and pronounced wrinkling and/or thickening of the tubular basement membrane. | It was felt by the majority of Banff 2019 meeting attendees that reporting of chronic active TCMR should be accompanied by a second diagnosis of borderline acute TCMR or acute TCMR (with appropriate grade) when criteria for both diagnoses are met. | PVN scores are defined in Table 5 and in detail in ref. 4. An adequate sample for such scoring should include 2 biopsies cores and contain medulla. PVN can coexist with ABMR or with TCMR grades 2 or 3. |

3.4 | Microvascular inflammation in the absence of detectable DSAs

At the Banff 2017 conference, updates to the ABMR classification were made to help with decision-making in cases where a biopsy showed at least moderate MVI ((g + ptc) >2) but no detectable antibodies against the graft. However, there are considerable numbers of biopsies with (g + ptc) >2 in the absence of detectable anti-HLA DSAs or C4d, and with molecular ABMR testing not widely adopted at this point, the clinical implications of these findings remain unclear. Recent evidence has suggested that patients with MVI on biopsies performed early posttransplant in the absence of DSAs had significantly better graft survival than those with anti-HLA DSAs (mainly low-level, preexisting DSAs), regardless of the presence or absence of PTC C4d staining on the biopsy. DSA+ patients were more frequently retransplant recipients and had C4d+ biopsies. By contrast, studies of patients biopsied much later with more severe MVI and frequent transplant glomerulopathy (TG) showed no difference in graft survival in the presence or absence of anti-HLA DSAs, which in these studies were de novo DSAs. Thus, at this point, we are unable to draw significant conclusions regarding the significance of biopsies showing (g + ptc >2) in the absence of anti-HLA DSAs, other than to comment that the biological behavior of such changes may well differ depending on whether these are seen relatively early posttransplant at a time when many DSAs represent persistent or recurrent/memory DSAs vs those seen later when most DSAs detected are de novo DSAs. In addition, the differential diagnosis of MVI with negative NSA and negative C4d should include T cell-mediated endothelial injury (ptc), membranoproliferative glomerulonephritis (g), and thrombotic microangiopathy (g). Furthermore, it has been shown recently in large populations that non-HLA antibodies could be independently associated with risk of allograft loss. These findings emphasize the importance of testing for clinically relevant non-HLA antibodies in patients with biopsies showing MVI.

It is also hoped that implementation of molecular diagnostics could help classifying these cases in a more pathogenesis-driven way, either employing the Molecular Microscope Diagnostic System (MMDx) or the NanoString platform that can be used with formalin-fixed, paraffin-embedded tissue, providing greater insight into factors predictive of the biological behavior of MVI without detectable anti-HLA DSAs, as well as cases with C4d staining without MVI. Current recommendations of the Banff Molecular Diagnostics Working Group in these and other circumstances are detailed in a separate meeting report. Presently, however, available data do not warrant making changes to the ABMR classification specifically relevant to these cases, beyond those made in Banff 2017.

4 | ROLE OF ARTIFICIAL INTELLIGENCE, DATA INTEGRATION, AND MACHINE LEARNING IN THE BANFF CLASSIFICATION

During the 2019 Banff meeting, many projects using artificial intelligence (AI), machine learning (ML), as well as deep learning (DL) were presented, with a heavy focus on applying the Banff classification in an automated fashion, clustering of patients, and digital pathology. However, the field is still poorly understood by most clinicians and pathologists. Several speakers at the 2019 Banff meeting discussed the capabilities of AI and the potential for use of ML algorithms in diagnosis and personalized medication in organ transplantation (Table 7).

Computer-assisted digital pathology consists of analyzing whole slide digital images of biopsies by a machine, and remains a challenge
TABLE 5 Banff reporting standardization scheme: Individual Banff scores used in grading of acute and chronic active ABMR and TCMR. Inclusion in the biopsy report of table similar to the below or a simple listing of individual scores in a comment is advised.

| Acute Banff scores | Grading (0, 1, 2, 3) | Chronic Banff scores | Grading (0, 1, 2, 3) | Acute & chronic Banff scores | Grading (0, 1, 2, 3) |
|-------------------|---------------------|----------------------|---------------------|-------------------------------|---------------------|
| i                 | ci                  | ti                   |                     |                               |                     |
| t                 | ct                  | i-IFTA               |                     |                               |                     |
| v                 | cv                  | t-IFTA               |                     |                               |                     |
| g                 | cg                  | pvl                  |                     |                               |                     |
| ptc               | ptcml               |                       |                     |                               |                     |
| C4d               |                     |                       |                     |                               |                     |

Abbreviations: i, inflammation in non-scarred cortex, scored as 0 (absent/minimal, <10% of non-scarred cortex inflamed), 1 (mild, 10%-25%), 2 (moderate 26%-50%), 3 (severe, >50%). The subcapsular cortex should not be considered; t, tubulitis in cortical tubules within non-scarred cortex, scored as 0 (none), 1 (mild, 1-4 mononuclear leukocytes per tubular cross-section or 10 tubular epithelial cells in most severely involved tubule), 2 (moderate, 5-10 mononuclear leukocytes), 3 (severe, >10 mononuclear leukocytes). Although the tubulitis score (1-3) is based on the single most severely involved tubule, at least mild fibrosis must be present in ≥2 cortical foci for a t score >0 to be assigned. Severely atrophic tubules should NOT be scored; v, endarteritis (intimal arteritis), scored as 0 (none), 1 (mild, 1 or more leukocytes directly beneath the endothelium of 1 or more arteries; endothelial cells typically appear enlarged with associated subendothelial edema; <25% luminal occlusion), 2 (moderate, as grade 1, but with ≥25% luminal occlusion), 3 (severe, with arterial fibrinoid necrosis or transmural inflammation). Note that only arteries (minimum 2 smooth muscle layers) are scored; g, glomerulitis, scored as 0 (none), 1 (mild, with ≤1 leukocyte AND associated endothelial swelling occluding >50% of 1 of more capillary lumina in at least one but <25% of glomeruli), 2 (moderate, these changes involving 25%-75% of glomeruli), 3 (severe, involving >75% of glomeruli). Ischemic, collapsed glomeruli and glomeruli with >50% sclerosis should not be scored; ptc, peritubular capillaritis, scored as 0 (minimal, with <3 leukocytes in the most severely involved cortical PTC and/or leukocytes in <10% of cortical PTCs), 1 (mild, with ≥1 leukocyte in ≥10% of cortical PTCs AND 3-4 leukocytes in the most severely involved PTC), 2 (moderate, as grade 1 but with 5-10 leukocytes in most severely involved PTC), 3 (severe, as grades 1-2 but with >10 leukocytes in most severely involved cortical PTC). The extent of PTC inflammation should be documented as focal (10%-50% of cortical PTCs) or diffuse (>50%). Note that medullary capillaries are NOT scored; C4d, linear staining in PTCs or medullary vasa recta by immunofluorescence (IF) on frozen sections of fresh tissue or immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded tissue, scored as 0 (none), 1 (minimal, staining in >0 but <10% of PTCs), 2 (focal, 10%-50% of PTCs), 3 (diffuse, >50% of PTCs). By IF on frozen sections scores ≥2 are considered positive; by IHC on paraffin sections all scores >0 are considered positive; ci, interstitial fibrosis in cortex, scored as 0 (minimal, ≤5%), 1 (mild 6%-25%), 2 (moderate, 26%-50%), 3 (severe, >50%). The subcapsular cortex should not be scored; ct, tubular atrophy in cortex, scored as 0 (none), 1 (mild, 1-4% of cortical tubules, 2 (moderate, 5-10%), 3 (severe, >10%). The subcapsular cortex should not be scored; cv, arterial intimal fibrosis (fibrointimal thickening), scored as 0 (none), 1 (mild, present but with ≥25% narrowing of luminal area in the most involved artery), 2 (moderate, 26%-50% luminal narrowing), 3 (severe, >50% luminal narrowing); cg, chronic glomerulopathy (transplant glomerulopathy), scored as 0 (none, no GBM double contours by light microscopy [LM] or EM), 1a (early mild, no GBM double contours by LM but subendothelial neo-densa in ≥3 glomerular capillaries by EM with by endothelial cell enlargement and/or subendothelial electron-lucent widening, 1b (mild, GBM double contours by LM in 1%-25% of glomerular capillaries by LM in the most severely involved glomerulus), 2 (moderate, double contours by LM in 26%-50% of capillaries), 3 (severe, double contours by LM in >50% of capillaries). Ischemic, collapsed glomeruli and glomeruli with >50% sclerosis should not be scored; ptcm, peritubular capillary basement membrane multilayering (requires EM), scored as 1 (≥7 basement membrane layers in the most affected PTC AND ≤5 layers in two additional PTCs), 0 (not meeting these criteria), or NA if EM is not performed; ti, total cortical inflammation, including scarred and non-scarred cortex, scored as 0 (absent/minimal, <10%), 1 (mild, 10%-25%), 2 (moderate, 26%-50%), 3 (severe, >50%); i-IFTA, inflammation in scarred cortex, scored as 0 (absent/minimal, <10% of non-scarred cortex inflamed OR if the extent of cortical IFTA is <10%), 1 (mild, 10%-25% of scarred cortex inflamed), 2 (moderate 26%-50% of scarred cortex inflamed), 3 (severe, >50% of scarred cortex inflamed). The subcapsular cortex should not be considered; t-IFTA, tubulitis in tubules within scarred cortex, scored as 0 (none), 1 (mild, 1-4 mononuclear leukocytes per tubular cross-section or 10 tubular epithelial cells in most severely involved tubule), 2 (moderate, 5-10 mononuclear leukocytes), 3 (severe, >10 mononuclear leukocytes). Severely atrophic tubules should NOT be scored; pvl, intrarenal polyomavirus load level, defined by the overall fraction of tubules in the entire biopsy (cortex and medulla) with at least 1 epithelial cell showing a viral inclusion body by light microscopy OR nuclear staining for SV40 large T antigen by IHC. As IHC is more sensitive, proper pvl scoring requires IHC. Scored as 0 (none), 1 (mild, positive cells in ≤1% of tubules), 2 (moderate, >1% and <10%), 3 (severe, ≥10%). The pvl score in combination with the ci score is used to define the PVN class (Table 4).

even with most advanced image analyzing algorithms such as convolutional neural networks. At this point DL-based histopathologic assessment of kidney tissue shows the ability to distinguish glomeruli, proximal and distal tubules, and areas of fibrosis.26-30 The current approach is promising but still shows high variability and poor correlation with clinical outcomes. A BWG on Digital Pathology has been formed at the 2019 Banff meeting to standardize scanning and analytical practices through facilitating studies focusing on IFTA and inflammation scoring while using algorithms fitting the most current Banff classification to decrease inter-observer variability. Because personalized medicine has been a major focus in recent years, utilizing algorithms and archetype analysis has the potential to combine biopsy results with clinical and laboratory data and to provide a more complete pathologic and prognostic picture, especially in the era of expanding electronic medical records.31 Furthermore, A. Loupy presented the capability of natural language processing (NLP) to help such algorithms assist clinicians and reduce human errors. NLP could be used for an otherwise time-consuming meta-analysis or accelerated reading of large numbers of pathology reports. Finally, since the Banff rules are becoming increasing complex with numerous possible scenarios,
**TABLE 6**  Survey results on reporting of chronic active T cell–mediated rejection (CA TCMR), chronic active antibody-mediated rejection (CA ABMR), and Banff I threshold for borderline (BL) lesions

| Preferred diagnosis wording | CA TCMR | CA TCMR + active component meeting criteria for BL or acute TCMR | CA TCMR | Acute TCMR + moderate inflammation IFTA | Other |
|----------------------------|---------|---------------------------------------------------------------|---------|----------------------------------------|-------|
| i1 t2 t2 iIFTA3 ci2 ct2    | 46%     | 33%                                                           | 20%     | 0%                                     | 1%    |
| + noMVI                    |         |                                                               |         |                                        |       |
| i2 t2 t2 iIFTA3 ci2 ct2    | 61%     | 21%                                                           | 5%      | 12%                                    | 1%    |
| + noMVI                    |         |                                                               |         |                                        |       |
| i1 t2 t2 iIFTA3 ci2 ct2    | 70%     | 12.5%                                                         | 6.5%    | 10%                                    | 1%    |
| + v1 + noMVI               |         |                                                               |         |                                        |       |
| CA ABMR                    |         |                                                               |         |                                        |       |
| Current wording: CA ABMR   |         |                                                               |         |                                        |       |
| + specify g and ptc scores | 14%     | 26%                                                           | 27%     | 29%                                    | 4%    |
| Preferred threshold        |         |                                                               |         |                                        |       |
| Borderline (suspicious) for |         |                                                               |         |                                        |       |
| acute TCMR                 |         |                                                               |         |                                        |       |
| Inflammation in <10% of   |         |                                                               |         |                                        |       |
| nonsclerotic cortex (i0 t  > 0) | 15% | 82%                                                           | 3%      |                                        |       |
| Inflammation in 10%-24% of |         |                                                               |         |                                        |       |
| nonsclerotic cortex (i1 t > 0) |     |                                                               |         |                                        |       |
| Inflammation in 5%-24% of  |         |                                                               |         |                                        |       |
| nonsclerotic cortex (with t > 0) |     |                                                               |         |                                        |       |

Note: This table summarizes the answers obtained from a survey distributed to Banff attendees during or immediately after the meeting. These results rely on answers from 69 pathologists and clinicians regarding preferred wording in situation of CA TCMR, and CA ABMR and regarding preferred threshold for borderline for acute TCMR.

Abbreviations: BL, borderline for acute TCMR; CA ABMR, chronic active antibody-mediated rejection; IFTA, interstitial fibrosis and tubular atrophy; MVI, microvascular inflammation.
there is increasing demand for an automated coding of Banff rules. This would require integration of experienced pathologists to decode the Banff rules and computer/data scientists to create an algorithm to apply the Banff rules. Key to achieving quality results from ML-based diagnosis are the integration of multiple centers providing quality input data to construct a standardized and reproducible analytical process.

5 | CONCLUSIONS

The international consensus-building framework provided by the Banff process is ongoing. Much has been done in the field of diagnostic assessment of allograft pathology, but many issues remain to be studied further. Although our experience in continually updating...
the diagnostic criteria for renal allograft rejection and related lesions has improved diagnostic accuracy and clinicopathologic correlations,\(^\text{10}\) this experience has also helped clarify the limits of histology and immunohistology in renal allograft biopsy interpretation and emphasized the need for development of additional diagnostic modalities, including molecular diagnostics. Current recommendations regarding the further clinical validation and use of the latter are detailed in a separate meeting report; this and other themes will also be addressed at the XVI. Banff meeting, which will be held jointly with the Canadian Society of Transplantation in Banff, Canada, October 4-7 2021, celebrating the 30-year anniversary of the Banff classification at the original location of its inception.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article or its supplementary material.

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