Clinical Significance of Revised Banff Criteria in the Diagnosis of Antibody-Mediated Rejection

Hyang Sook Jeong[a], Deok Gie Kim[b], Seung-Tae Lee[c], Kyu Ha Huh[b], Yu Seun Kim[b], Hyeon Joo Jeong[a], and Beom Jin Lim[a,*]

[a]Department of Pathology, Yonsei University College of Medicine, Seoul, Korea; [b]Department of Surgery, Yonsei University College of Medicine, Seoul, Korea; and [c]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Background. The diagnostic criteria of antibody-mediated rejection (ABMR) has been significantly changed since Banff 2013. The most important revision was adopting microvascular inflammation (MVI) as immunopathologic evidence for ABMR even in C4d-negative cases. In this study, we retrospectively reviewed previous allograft biopsy results and evaluated the impact of this change.

Methods. We reviewed results of 536 renal allograft biopsies at Severance Hospital during 2011 to 2013, which were diagnosed according to the Banff 2009 criteria. All biopsy results were reassessed according to the Banff 2017 criteria.

Results. According to the Banff 2009 criteria, antibody-mediated changes were observed in 48 cases out of the 536 allograft biopsies (9.0%). According to the Banff 2017 criteria, 28 additional cases (5.2%) were reclassified as antibody-mediated changes. Twenty-six of these cases were C4d-negative ABMR. The most frequent diagnostic finding in these cases was MVI comprising glomerulitis and peritubular capillaritis. Donor-specific antibodies were investigated in 14 of these cases, which revealed positive results in 12 cases.

Conclusion. The incidence rate of ABMR has increased after the recent revision of the Banff criteria. The MVI in C4d-negative ABMR cases is the major cause for this increase.

PATHOLOGISTS have tried to distinguish the histologic features of antibody-mediated rejection (ABMR). From the earliest attempt to incorporate the diagnostic criteria of ABMR into the Banff schema [1], linear peritubular capillary staining of C4d has been emphasized to be the most important evidence for antibody-mediated injury. The Banff 2013 classification made a major revision in the diagnosis procedure of ABMR by including C4d-negative ABMR criteria [2]. According to the most recent Banff classification, C4d positivity still remains important; however, C4d-negative ABMR can be diagnosed if patients have significant glomerulitis and peritubular capillaritis [3]. In this study, we retrospectively evaluated the clinical significance of the new diagnostic criteria of ABMR by reclassifying past cases.

METHODS

From 2011 to 2013, a total of 536 medical records of allograft biopsy after renal transplant were retrieved through an electronic medical chart maintained by the Department of Pathology and Department of Transplant Surgery at Severance Hospital, Yonsei University Health System. Renal allograft biopsy samples were processed using light, immunofluorescent, and electron microscopy at the time of biopsy, as described elsewhere [4]. All the biopsy results that were initially classified according to the Banff 2009 criteria [5] were reassessed according to the Banff 2017 criteria [3]. The number of cases categorized into antibody-mediated changes were counted, and the initial (Banff 2009) and reassessed (Banff 2017) diagnoses were compared. Patient data, especially the status of serum

H.S. Jeong and D.G. Kim contributed equally to this article.

Current affiliation of H.S. Jeong: Department of Pathology, St Vincent Hospital, The Catholic University of Korea, College of Medicine, Seoul, Korea.

*Address correspondence to Beom Jin Lim, Department of Pathology, Yonsei University College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea. Tel: +82-2-2019-3540; Fax: +82-2-3463-2103. E-mail: bjlim@yuhs.ac

0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.03.012

Table 1. Cases Originally Diagnosed as Antibody-Mediated Changes by the Banff 2009 Criteria

Age at transplant, mean (SD), y	42.6 (12.0)
Male sex, No. (%)	24 (50)
Original disease	
No pretransplant biopsy, No. (%)	34 (-70.8)
Hypertension	7 (14.6)
Diabetic nephropathy	3 (6.3)
IgA nephropathy	4 (8.3)
Systemic lupus erythematosus	1 (2.1)
Polycystic kidney disease	1 (2.1)
Predialysis duration, mean (SD), mo	32.6 (51.2)
Deceased donor, No. (%)	7 (14.6)
Living donor relation: 1st/2nd/unrelated, No. (%)	17 (35.4)/2 (4.2)/22 (45.8)
Retransplant recipients	3 (6.3)
Pretransplant PRA I > 5%	10 (20.8)
Pretransplant PRA II > 5%	10 (20.8)
HLA mismatch, No. (%), 1/2/3	10/45 (22.2)/9/45 (20.0)/22/45 (48.9)
Cross-match positive transplant	6 (12.5)
ABO-incompatible transplant	5 (10.4)

n = 48 for all data except HLA mismatch where n = 45.
Abbreviation: PRA, panel-reactive antibody.

donor-specific antibodies (DSAs), were collected whenever possible. Donor-specific antibody was examined using Luminex bead-based single-antigen assay (LABScreen SAB Class I and Class II; One Lambda, Canoga Park, Calif, United States). The presence of each type of anti-human leukocyte antigen (HLA) DSA (anti-HLA-A, -B, -DR, and -DQ) was determined and recorded as positive when the mean fluorescence intensity was >1000. This study was approved by the Institutional Review Board of Severance Hospital.

RESULTS

The Banff 2009 criteria classified antibody-mediated changes into the following: 1. C4d deposition without morphologic evidence of active rejection, 2. acute ABMR, and 3. chronic active ABMR. According to these criteria, 32 cases had histologic features of acute ABMR (6.0% of 536 total allograft biopsy results), and 16 cases (3.0%) had those of chronic active ABMR. The Banff 2017 classification, which is the most recent version of the revised criteria of ABMR, classifies antibody-mediated changes into 1. active ABMR, 2. chronic active ABMR, and 3. C4d staining without an evidence of rejection. After applying these criteria, the diagnosis of the 48 abovementioned cases remained unchanged (demographic data of these cases are summarized in Table 1); however, 28 cases (5.2%) had to be reclassified as having histologic features of antibody-mediated changes. Among the latter set of cases, 21 exhibited features of active ABMR, and 12 of these cases additionally exhibited acute T-cell-mediated rejection (TCMR) while 1 exhibited chronic TCMR. The remaining 7 cases exhibited features of chronic active ABMR, of which 1 exhibited a combined feature of acute TCMR. The initial diagnoses and their reassessments according to the Banff 2009 and 2017 criteria, respectively, are summarized in Table 2. Therefore, the total number of cases that exhibited histologic features of antibody-mediated changes increased from 48 (9.0%) to 76 (14.2%) after the revision of diagnostic criteria.

Most of the newly diagnosed ABMR cases were C4d-negative ABMR (26 of 28 cases, 92.9%). These cases satisfied the diagnostic criteria of the Banff 2017 classification by showing more than moderate microvascular inflammation (MVI) comprising glomerulitis and peritubular capillaritis (Table 3). All 7 cases having features of chronic active ABMR showed a duplication of glomerular basement membranes.

Donor-specific antibody was checked for 14 newly diagnosed cases, which was found to be positive in 12 (85.7%) cases. In 9 patients, DSA was checked at the time of renal biopsy (within 1 month) and all these patients showed positive results.

DISCUSSION

C4d positivity in peritubular capillaries has been considered the criterion standard to distinguish antibody-mediated injury in allograft kidneys. The Banff 2009 criteria listed the histologic features of ABMR such as acute tubular injury, capillaritis, glomerulitis, and transmural arteritis; however, C4d positivity was considered as a prerequisite for these features [5]. Subsequently, data showed that MVI is more closely associated with DSA and has a superior predictability for patient outcome than C4d positivity [6,7]. Based on these data, the Banff 2013 extensively revised the diagnostic criteria of ABMR, and the Banff 2017 further made some modifications. Currently, 3 categories of evidence are required to make an ABMR diagnosis. The first one is histologic evidence, encompassing MVI, intimal or transmural arteritis, acute thrombotic microangiopathy, and acute tubular injury for active ABMR and transplant glomerulopathy, peritubular basement membrane multilayering, and arterial intimal fibrosis for chronic active ABMR. The second category is the evidence of current and/or recent interaction of antibodies

Table 2. Cases Newly Diagnosed as Antibody-Mediated Changes by Applying the Banff 2017 Criteria

Initial Diagnosis (Banff 2009)	Revised Diagnosis (Banff 2017)	Cases, No. (%)
No rejection or suspicious for rejection	Active ABMR	8 (1.5)
Acute TCMR	Active ABMR + Acute TCMR	12 (2.2)
Chronic TCMR	Active ABMR + Chronic TCMR	1 (0.2)
TG with negative C4d	Chronic active ABMR	6 (1.1)
TG with negative C4d + Acute TCMR	Chronic active ABMR + Acute TCMR	1 (0.2)

Abbreviations: ABMR, antibody-mediated rejection; TCMR, T-cell-mediated rejection; TG, transplant glomerulopathy.

Table 3. Banff 2017 Diagnostic Criteria of Antibody-Mediated Rejection Found in the Newly Diagnosed Cases

	g > 0 and/or ptc > 0	v > 0	Acute TMA	Acute Tubular Injury	C4d Positivity	Moderate MVI [g + ptc] ≥ 2	cg > 0	PTCBMML	Arterial Intimal Fibrosis
Cases, No. (%)	27 (96.4)	0	0	5 (17.9)	2 (7.1)	26 (92.9)	7 (25.0)	5 (17.9)	0

Abbreviations: cg, glomerular double contour score; g, glomerulitis score; MVI, microvascular inflammation; TMA, thrombotic microangiopathy; ptc, peritubular capillaritis score; PTCBMML, peritubular capillary basement membrane multilayering; v, intimal arteritis score.

with endothelium, including linear C4d staining of the peritubular capillary, more than moderate degree of MVI, and ABMR-associated gene transcript expression. These features are applicable for both active and chronic active ABMR. The third category is serologic evidence, in other words, the presence of DSA [3]. All 3 categories are required to make a final diagnosis of ABMR, but our study focuses on the first and second categories.

Our study revealed that the frequency of occurrence of the histologic features of ABMR (according to the first and second categories) increased from 9.0% to 14.2% after the application of new diagnostic criteria. This result suggests that 5.2% of the ABMR cases could have been underdiagnosed and treated improperly previously. Although DSA was not checked for in all these cases, most of the patients for whom DSA was checked demonstrated positive results, which thereby supported the above conclusion.

In our cases, the most frequent histologic features that suggested the possibility of ABMR was more than moderate degree of MVI. There is an overlap between the histologic features of TCMR and ABMR [8]. Intimal arteritis was once considered to be a feature of TCMR, but according to the current Banff criteria, it can now be considered as a feature of both TCMR and ABMR [3,5]. Considering that the patients' outcome is more seriously affected by ABMR than TCMR [9], it is very important to distinguish and properly grade glomerulitis and peritubular capillaritis for optimal patient management.

A limitation of our study is the lack of DSA data among some patients and the lack of thorough clinical information to confirm that the newly diagnosed cases had previously been undertreated. However, our observation clearly revealed that the revised Banff criteria has a clinical significance that should further be followed by a clinicopathologic study.

REFERENCES

[1] Racusen LC, Colvin RB, Solez K, et al. Antibody-mediated rejection criteria - an addition to the Banff 97 classification of renal allograft rejection. Am J Transplant 2003;3:708–14.

[2] Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant 2014;14:272–83.

[3] Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. Am J Transplant 2018;18:293–307.

[4] Lim BJ, Hong SW, Jeong HJ. IgG nephropathy - confusion and overlap with C1q nephropathy. Clin Nephrol 2009;72:360–5.

[5] Sis B, Mengel M, Haas M, et al. Banff '09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. Am J Transplant 2010;10:464–71.

[6] de Kort H, Willicombe M, Brookes P, et al. Microcirculation inflammation associates with outcome in renal transplant patients with de novo donor-specific antibodies. Am J Transplant 2013;13:485–92.

[7] Verghese P, Dunn T, Najafian B, et al. The impact of C4d and microvascular inflammation before we knew them. Clin Transplant 2013;27:388–96.

[8] Hara S. Cell mediated rejection revisited: past, current, and future directions. Nephrology (Carlton) 2018;23(Suppl. 2):45–51.

[9] Levine MH, Abt PL. Treatment options and strategies for antibody mediated rejection after renal transplantation. Semin Immunol 2012;24:136–42.