Renal Transplant Pathology Series-III (C)

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Banff classification of renal allograft pathology has evolved considerably over the past 30 years and has truly become a multidisciplinary schema. With this evolution, it has also increased in complexity and level of difficulty. It is no longer possible for a sole histopathologist without input from other clinical colleagues and pathologists, such as immunologists, to accurately diagnose and classify renal transplant pathology, particularly rejection. In this pictorial, we aim to provide an illustrated presentation of the Banff classification categories and practical tips and tricks to identify and report the lesions. This will be useful for better understanding of renal transplant pathology for trainees and residents of nephrology and histopathology as well as for practicing pathologists and nephrologists.

Banff category 2. Antibody-mediated changes (Chronic active/inactive AMR)

In this part (part C), we will discuss the diagnosis and characterization of chronic active/chronic antibody-mediated rejection (AMR). In part A, we discussed hyperacute and accelerated acute types of AMR. In part B, acute/active type of AMR was discussed. This is the final part of AMR tutorial, in which pathological and serological features of chronic active/chronic AMR will be discussed with illustrations. As was discussed in earlier parts of AMR tutorial, during the early period of Banff classification, it was widely thought that antibodies, particularly pre-formed antibodies, cause only hyperacute and accelerated acute types of rejection and do not play any role in acute or chronic graft damage and dysfunction. The main focus of both clinicians and pathologists was on the diagnosis, classification and treatment of cellular or T-cell mediated rejection (TCMR), as reflected in earlier versions of Banff classification. However, it was soon realized that there is a form of rejection, which does not respond well to T-cell targeted therapies and manifests unusual morphologic features. At the same time, newer and sensitive antibody detection methods, and most importantly, the discovery and widespread use of C4d, renewed the interest in research for exploring the role of antibodies in causing graft damage and dysfunction beyond the immediate post-transplant period. With the help of accumulated graft pathology literature and above-mentioned ancillary techniques, criteria were developed for the diagnosis and classification of acute/active AMR during 2001 Banff meeting, which were published in 2003. For the first time, pathological criteria for the diagnosis and classification of acute/active AMR were developed and the role of antibodies in acute graft dysfunction was acknowledged. With this, the Banff classification achieved a truly multi-disciplinary character, as it not only included histopathological criteria but also immunofluorescence (IF) and immunologic criteria for complete diagnosis of AMR.

In 2005 Banff meeting, a further progress was made in the classification of AMR and a new type of AMR, chronic active AMR, was added to category 2 of original Banff. The features of chronic antibody-

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mediated injury were recognized as glomerular double contours (transplant glomerulopathy [TG] and/or peritubular capillary basement membrane multilayering [PTCBMML] and/or interstitial fibrosis/tubular atrophy [IFTA] and/or fibrous intimal thickening of arteries. In the presence of above changes, it is very important to look for features of activity, which have also evolved during following years. The features indicating activity initially included C4d positivity and the presence of donor specific antibody (DSA) in the circulation.

With widespread use of C4d, it also became apparent that there are some graft biopsies, particularly protocol biopsies, which are positive for C4d without any morphological evidence of graft injury on the biopsy. To address this, a category of “C4d deposition without morphological evidence of active rejection” was added in Banff 07 classification. In the 11th Banff meeting, a major achievement was the acknowledgement of the existence of the category of “C4d-negative AMR” in kidney transplants. It was also recognized that AMR was associated with heterogeneous phenotypes even within the same transplanted organ. It was felt that further refinement of the diagnostic criteria of AMR, especially for the category of C4d-negative AMR, were needed and for this purpose a new working group was created to define the diagnostic criteria for AMR in kidneys independent of C4d. The results of this working group were incorporated in Banff 2013 classification as additional criteria for activity diagnosis. These included: i) At least moderate microvascular inflammation ($[g + ptc] \geq 2$) and ii) Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated, as shown in Table 1. In Banff 2017 meeting, the term acute was eliminated from the category of AMR and was replaced with active. In 2019 Banff meeting, an additional category of chronic (inactive) AMR was also added.

As is apparent from the above discussion, AMR spans a whole spectrum of morphological lesions in the graft parenchyma ranging from acute to chronic (inactive) and chronic active and can involve all the four compartments of graft parenchyma. The focus of Banff classification has lately shifted to AMR diagnosis and classification and the diagnostic and classification criteria for this entity are being refined as more and more knowledge and evidence are accumulating, and this activity is likely continue at least in near future.

Table 1. The immunopathological and serologic criteria for the diagnosis of chronic active antibody-mediated rejection in kidney allografts.

Diagnostic criteria	Findings
Morphological criteria of chronic graft injury	Glomerular double contours Peritubular capillary basement membrane multilayering Interstitial fibrosis/tubular atrophy (IFTA) Fibrous intimal thickening in arteries
Criteria of current/recent antibody interaction with vascular endothelium	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 ($[g + ptc] \geq 2$) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, $ptc \geq 2$ alone is not sufficient and g must be ≥ 1 Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with AMR, if thoroughly validated
Serologic criteria of circulating antibodies in the serum	Presence of circulating antibodies in blood against donor HLA or other donor antigens such as endothelial antigens

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A series of representative images of biopsies with category 2 (chronic active/chronic inactive AMR) of Banff classification are illustrated in Figures 1 to 5.

Figure 1. High-power photomicrograph showing one large artery showing moderate fibrointimal thickening suggestive of chronic rejection, both TCMR and AMR. It is designated as *cv* in Banff classification and scores as *cv0* to *cv3*. This particular case will qualify for *cv2*. The scoring is based on the degree of luminal narrowing. The greater the narrowing of the lumen, greater the score and *vice versa*. Banff scheme does not discriminate between bland intimal fibrosis or fibrosis containing inflammatory cells. The later form is more suggestive of rejection process. (Trichrome stain, $\times 400$).

Figure 2. High-power photomicrograph of a glomerulus from the same biopsy shown in Figure 1. There is glomerulitis (*g*) as well as early glomerular basement membrane reduplications (double contouring) of some capillary loops. The later lesion is termed as chronic glomerulopathy (*cg*) or transplant glomerulopathy (TG). It is scored as *cg0* to *cg3* depending on the proportion of glomeruli showing double contouring. Scoring should be carried out on PAS or silver stains. Very early forms

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of *cg* (*cg1a*) can only be detected on transmission electron microscopy. Lesions of *cg* can be seen in chronic forms of both TCMR and AMR as well as many immune and non-immune mechanisms of injury (PAS, ×400).

Figure 3. High-power photomicrograph showing two peritubular capillaries (PTCs) with 3 or more inflammatory cells in the lumen. Among the two the one in the lower mid-field will be used as it contains maximum number of intraluminal inflammatory cells (*ptc2*). Majority of inflammatory cells are mononuclear, mostly lymphocytes. The most severely affected PTC is used for scoring the lesion. A number of other PTCs in the field show mild degrees of *ptc*. *Ptc* represents one of the components of microvascular inflammation (MVI) score. In this area, the tubules show only mild atrophic changes (Silver stain, ×400).

Figure 4. This is medium-power photomicrograph of a biopsy showing advanced changes of interstitial fibrosis and tubular atrophy (IFTA). One glomerulus is also identified showing global glomerulosclerosis. A small artery is seen showing moderate fibrointimal thickening (cv2). If the biopsy shows only such picture, it will qualify for chronic inactive AMR, provided there is prior documented history of acute or chronic active AMR (Trichrome stain, ×200).

Figure 5. This is medium-power photomicrograph of another representative area from renal allograft biopsy shown in Figure 4. Three globally sclerosed glomeruli are appreciated, but no tubules are identified. The whole field is occupied by interstitial fibrosis. This will qualify as chronic inactive AMR, provided there is history of documented active or chronic active AMR. (Trichrome stain, $\times 200$).

Further reading:

1. Racusen LC, Colvin RB, Solez K, Mihatsch MJ, Halloran PF, Campbell PM, et al. Antibody-mediated rejection criteria - an addition to the Banff 97 classification of renal allograft rejection. *Am J Transplant* 2003;3(6):708-714.
2. Mubarak M, Kazi JI. Evolution of the diagnostic criteria of antibody-mediated rejection of renal allografts: Banff classification updates. *Port J Nephrol Hypert* 2013; 27: 137-42.
3. Callemeyn J, Ameye H, Lerut E, Senev A, Coemans M, Van Loon E, et al. Revisiting the changes in the Banff Classification for antibody-mediated rejection after kidney transplantation. *Am J Transplant*. 2020 Dec 31. doi: 10.1111/ajt.16474. ePub ahead of print.
4. Loupy A, Haas M, Roufosse C, Naesens M, Adam B, Afrouzian M, et al. The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated rejection. *Am J Transplant*. 2020;20(9):2318-2331.