

Evolution of the diagnostic criteria of antibody-mediated rejection of renal allografts: Banff classification updates

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ABSTRACT

Alloimmune rejection is one of the most common causes of both acute and chronic renal allograft dysfunction throughout the world. It is also one of the most important causes of graft loss, both in the short- and the long-term. The process of rejection of the allograft tissue is mediated predominantly by the acquired or specific alloimmune mechanisms of both humoral and T cell-mediated arms. More recently, evidence is also accumulating which supports the role of innate immunity in initiating this process. The diagnosis of the rejection process may be suspected on clinical grounds, with some support from the laboratory investigations and imaging studies, but the gold standard test for an accurate diagnosis and specifically its categorization is still the invasive procedure of renal allograft biopsy. In addition, numerous molecular markers in the serum and urine have also been investigated as non-invasive alternatives to renal allograft biopsy for the diagnosis of acute rejection, but the renal allograft biopsy provides additional valuable information over and above just the diagnosis of rejection. During early 1990s efforts began to standardize the histopathological study of renal allograft biopsies for the uniform reporting of the pathological lesions. These efforts have continued with a missionary zeal and have resulted in marked refinements in the diagnostic criteria and categories of rejection seen on allograft biopsies. The present series attempts to address the evolutionary changes

in the diagnostic criteria and the classification of the rejection process on renal allograft biopsies as these took place over the years since early 1990s. In this review, we will discuss the changes that have occurred in the diagnosis and categorization of antibody mediated rejection and the focus will be on the morphological basis of their diagnosis and categorization.

Key words: Antibody-mediated rejection; Banff classification; immunofluorescence; kidney; rejection.

The process of alloimmune injury to the graft tissue may be mediated by the cytotoxic T lymphocytes or the antibodies, or more commonly, a variable combination of both, invariably in combination with components of the innate immune system^{1,2}. Traditionally, rejection was divided on clinical grounds into hyperacute, acute, and chronic types, depending on the rapidity of rejection process development with little reference to the underlying pathogenetic mechanisms¹. Prior to 1993, there was no single universally accepted system for the diagnosis and categorization of pathological lesions on renal allograft biopsies in general and the rejection in particular^{3,4}. Different transplant centres were developing their own protocols and their own definitions of morphological features⁵⁻⁸.

The Banff schema was formulated as an international, consensus-based classification system for the

diagnosis and categorization of renal allograft biopsy pathology with a particular emphasis on the development of the morphological criteria for the diagnosis and classification of rejection^{9,10}. The first Banff conference was held in August 1991 at Banff, Alberta, Canada, and the first product that came out of that meeting was published in 1993 and is popularly known as 1st Banff classification¹¹. Subsequent Banff meetings have taken place every two years, mostly in Canada, but more recently in some other places in the world, to take cognizance of the latest developments in the field of transplant pathology. The

majority of the meetings have been followed by updates and revisions in the form of publications in international premier journals of nephrology and transplantation^{12,13}.

There have been substantial changes in both the nomenclature and the classification of rejection reaction, but the basic framework of the Banff schema has remained the same^{9,12,13}. The first major and significant modification of the original Banff classification took place in 1997 with the incorporation and merging of National Institutes of Health (NIH)-

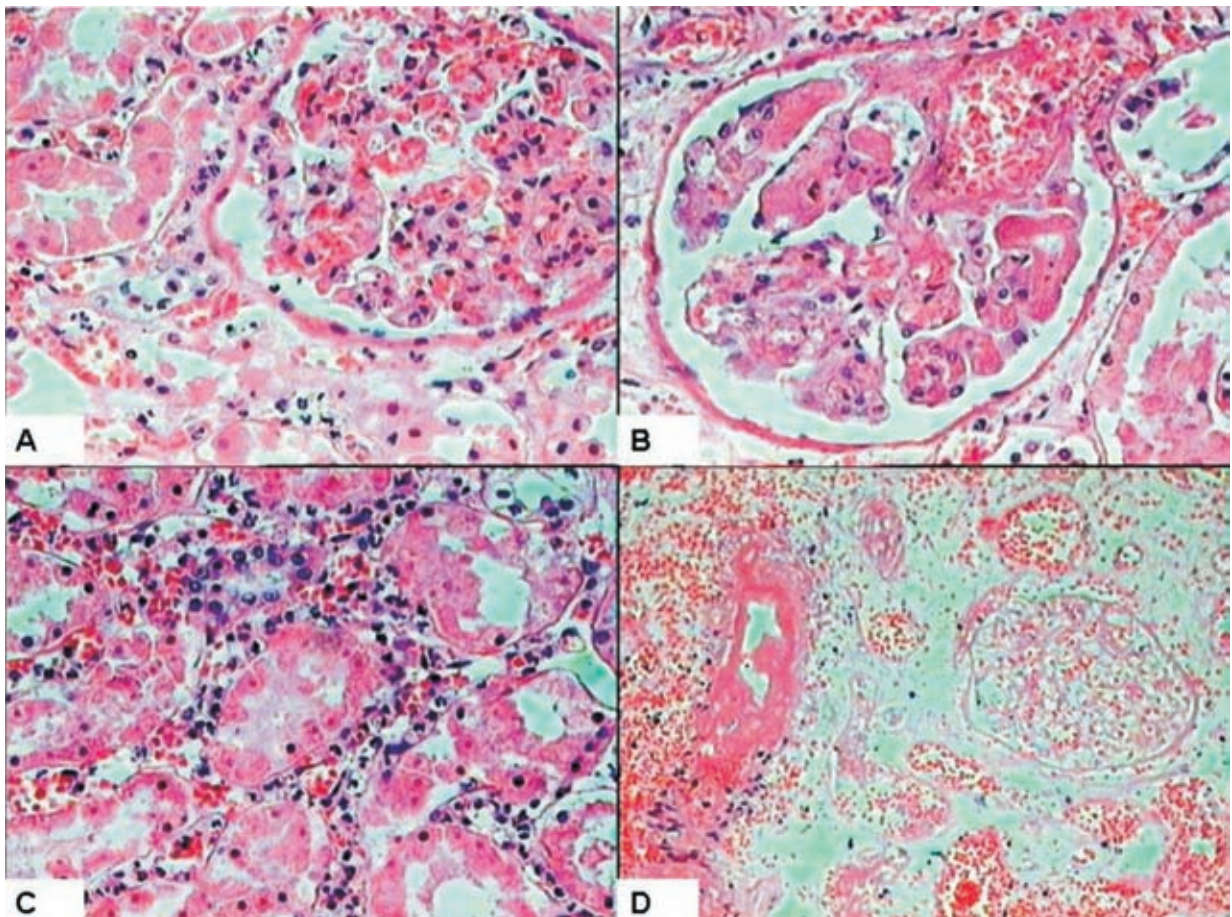


Figure 1

A-D. Key morphological features of acute antibody-mediated rejection depicted in a case of hyperacute rejection, the only case in the authors' series. A. Glomerular capillaries are congested and infiltrated by polymorphonuclear leukocytes. Similar cells are also found in peritubular capillaries in the vicinity of the glomerulus. This represents the earliest stages in the development of hyperacute rejection, the extreme form of antibody-mediated rejection. (haematoxylin and eosin (H&E), $\times 400$). B. Glomerular capillaries are filled with platelet fibrin thrombi, a slightly later stage of hyperacute rejection. (H&E, $\times 400$). C. Peritubular capillaries are congested and filled with polymorphonuclear leukocytes. There is marked acute tubular injury in the background. (H&E, $\times 400$). D. Fibrinoid necrosis involving a small artery, lesion categorized as v3 in Banff classification. There is complete parenchymal infarction of graft tissue in the background. (H&E, $\times 200$).

-sponsored Collaborative Clinical Trials in Transplantation (CCTT) classification and Banff 93-95 classification, the two most widely used classifications at that time^{14,15}. Since then, Banff 97 working classification of renal allograft pathology has served as international yardstick in the field of routine renal transplant pathology practice and the clinical trials¹³.

As regards the evolutionary changes in the diagnostic category of antibody-mediated rejection (AMR), the first Banff conference dealt with the category in a very superficial and imprecise manner. It was classified and named purely on clinical grounds as hyperacute rejection (HAR)¹¹. The clinical and pathological features of this type of rejection are so dramatic and well characterized that they rarely escape detection (Fig. 1). However, due to almost universal implementation of pretransplant antibody screening and donor-specific cross matching, this form of rejection has almost completely disappeared. It is however apparent from the pathological features of HAR that the main targets of alloantibodies are the microcirculation and the blood vessels rather than the tubules and interstitium, the latter being the prime targets of T-cell mediated rejection. The Banff 97 revised classification also dealt with this category of rejection in an imprecise manner and no attempt was made to define or classify it on the pathological foundations. The Banff 97 classification, however, identified two types of clinical presentation of the AMR and classified it into HAR and delayed (accelerated acute) forms¹⁴. The Banff 2001 classification was the first to address the issue of AMR in sufficient detail and formulated the morphological, immunopathological and serological criteria for the conclusive diagnosis of AMR¹⁶. In fact, the title of the report of Banff 2001 meeting, which was published in 2003, was reflective of this evolution. This evolution was the direct result of an exponential rise in the number of studies on AMR diagnosis in general and the discovery and widespread use of a relatively sensitive and specific marker of AMR, i.e. complement fragment of 4d (C4d)¹⁷⁻²⁸. The Banff criteria for the diagnosis of AMR are shown in Table 1 and, as alluded to previously, consist not only of the morphological changes of acute allograft injury, but also the immunopathological evidence (C4d or immunoglobulin positivity along peritubular capillary walls) and the serological evidence in the form of circulating donor-specific antibodies (DSA). The morphological features of AMR were also dealt with in detail in this updated

Table 1

The immunomorphological and serological criteria for the diagnosis of acute antibody-mediated rejection in renal allografts.

Diagnostic criteria	Findings
Morphological criteria of acute tissue injury	a. Acute tubular injury b. Capillaritis-glomerular and peritubular c. Arterial- v3 arteritis
Immunopathological criteria of antibody and complement deposition or action	a. C4d positivity in peritubular capillaries b. Immunoglobulin or complement in peritubular capillaries or arterial lesions
Serological criteria of circulating antibodies in the serum	Presence of antibodies in the serum against donor HLA or other anti-donor endothelial antibodies

classification and a pathological classification of AMR was formulated¹⁶. This represented the first pathology based classification of the process of AMR (Table 2). However, only a single category of AMR was recognized in the “Banff 97 update” classification. In 2005 Banff classification, the diagnostic category of AMR was further subdivided into 2 types: acute AMR and chronic active AMR²⁹. During subsequent Banff meetings, the criteria for C4d positivity and its scoring and the semiquantitative scoring of the inflammatory lesions of peritubular capillaritis (ptc) have also been developed, validated and incorporated into the classification³⁰⁻³². With continued expansion of literature on donor specific antibodies, it has been realized that not all antibodies present before, at or after transplantation are associated with alloimmune injury and not all antibody-mediated phenotypes inevitably lead to accelerated allograft loss. Hence, in Banff 07 classification, the term of AMR was replaced by antibody-mediated changes³⁰. The morphological features of chronic active AMR were also listed as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy (IFTA) and/or

Table 2

Pathological classification of antibody-mediated rejection (fulfilling the criteria of C4d positivity and with circulating anti-donor antibody)

Type 1	ATN-like
Type 2	Capillary-glomerulitis, peritubular capillaritis (polymorphonuclear and/or mononuclear leukocytes in peritubular capillaries)
Type 3	Arterial-transmural inflammation/fibrinoid change

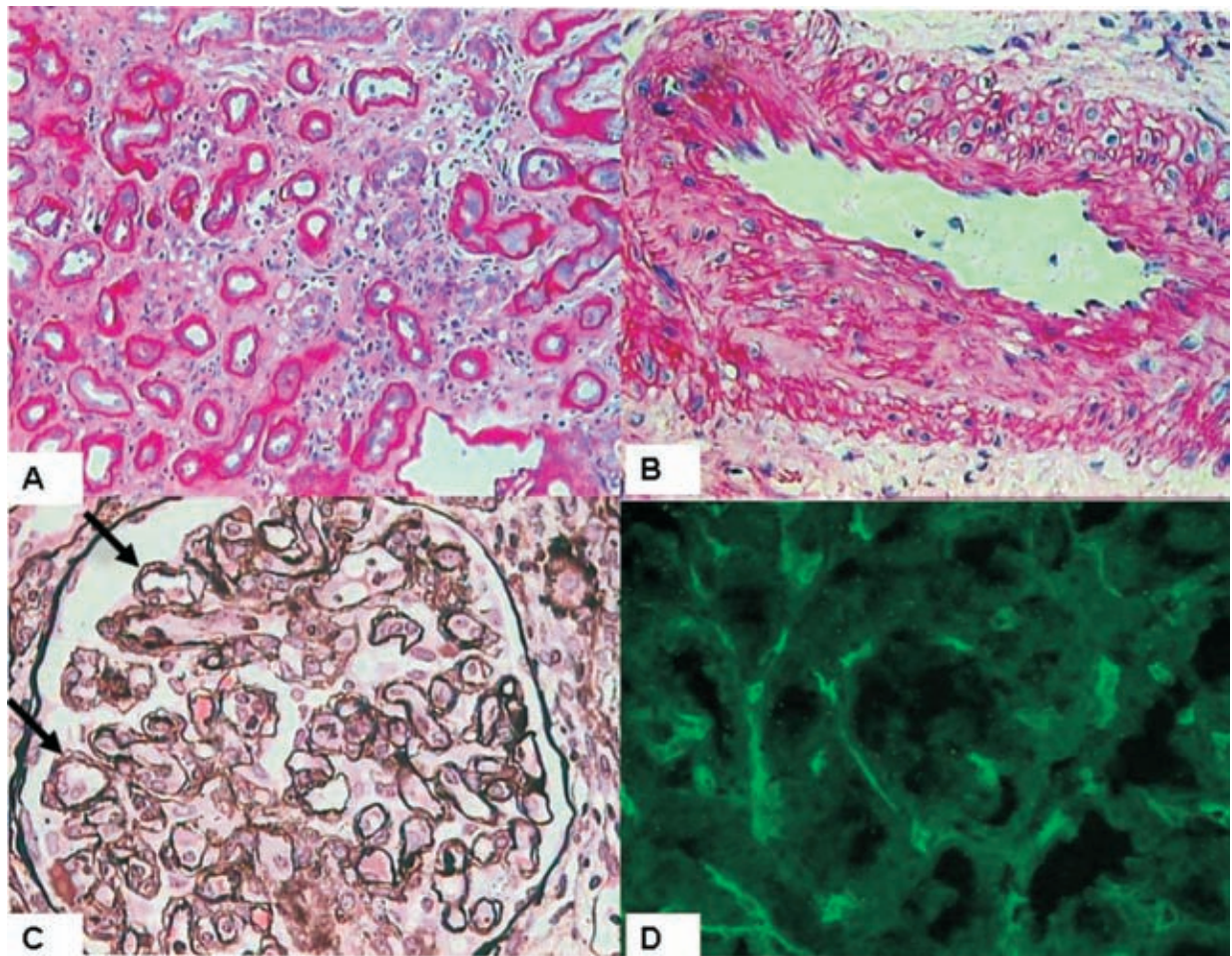


Figure 2

A-D. Key morphological features of chronic active antibody mediated rejection. A. This shows moderate degree of tubular atrophy and interstitial scarring associated with sparse lymphocytic infiltrate. Note that this is a non-specific chronic allograft scarring process and is multifactorial in origin (periodic acid-Schiff (PAS), $\times 400$). B. An interlobular size artery showing moderate degree of fibrointimal thickening. This is also a non-specific finding and multifactorial in origin. (PAS, $\times 400$). C. Widespread double-contouring of glomerular basement membranes on silver stain. Immunofluorescence was negative for immune deposits. This lesion is known as transplant glomerulopathy and is fairly characteristic for chronic active antibody-mediated rejection. (Silver stain, $\times 400$). D. C4d immunostaining showing diffuse linear positivity of the antibody along peritubular capillary walls. (Immunofluorescence for C4d, $\times 400$).

fibrous intimal thickening of arteries (Fig. 2). As is evident, the later two features are not specific for chronic active AMR and require fulfilment of all three criteria for definitive diagnosis of AMR. As a result, the category of AMR is now sufficiently characterized to allow its accurate diagnosis and management in the majority of cases. It must be pointed out here that the changes of AMR may coexist and be obscured by borderline changes, acute or chronic active T-cell-mediated cellular rejection, interstitial fibrosis/tubular atrophy and other category of the Banff classification

and none of the morphological features of AMR is completely specific³¹. Table 3 depicts the key changes that have taken place over the years in the category of AMR in Banff revisions.

With the widespread use of C4d, it has also become apparent that there are some cases which are positive for C4d without any morphological evidence of graft injury on the biopsy. For this, a category of “C4d deposition without morphological evidence of active rejection” was added in Banff 07

Table 3

The main evolutionary changes in the diagnostic category of antibody-mediated rejection as they occurred over the years in Banff classification.

Pre-Banff	1st Banff	Banff '97	Banff '97 Update	Banff '05	Banff '07
Hyperacute	Hyperacute	Antibody-mediated rejection Immediate – Hyperacute	Antibody-mediated rejection Type I: C4d+, ATN, min. inflamm	Antibody-mediated rejection Acute AMR	Antibody-mediated changes Acute AMR
		Delayed – accelerated acute	Type II: C4d+, leukocytes in PTC	Type I: C4d+, ATN, min. Inflamm	Type I: C4d+, ATN, min. inflamm
			Type III: C4d+, transmural arteritis	Type II: C4d+, leukocytes in PTC	Type II: C4d+, leukocytes in PTC
				Type III: C4d+, Transmural arteritis	Type III: C4d+, transmural arteritis
				Chronic active AMR	Chronic active AMR

AMR – antibody-mediated rejection; PTC – peritubular capillaries.

classification under the category of antibody-mediated changes³⁰. The incidence of this finding is reported as high as 25-80% on protocol biopsies in patients with ABO incompatible grafts. Only 4-12% of these patients develop features of acute AMR. Therefore, at this time the significance of this category is still largely unknown. In the 11th Banff meeting, a major outcome was the acknowledgement of the existence of the category of “C4d negative AMR” in kidney transplants³². It was also recognized that AMR is associated with heterogeneous phenotypes even within the same type of transplanted organ. It was felt that further refinement of the diagnostic criteria of AMR, especially for the category of C4d negative AMR, is 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 are expected to be presented at the 12th Banff meeting to be held in Brazil in 2013. Till that time, no changes were made in the diagnostic criteria of AMR from the earlier updates.

In conclusion, major and significant changes have occurred in the diagnostic category of AMR in the Banff classification of renal allograft pathology over the last two decades. This predominantly became possible with the discovery and widespread use of C4d antibody and the use of highly sensitive assays for the detection and characterization of DSA. However, much work remains to be done to fully define the phenotype of AMR in kidney and other solid organ transplants and Banff working groups are actively seeking the evidence-based criteria for fuller characterization of all phenotypes of AMR.

Conflicts of interest statement: None declared.

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