EDITORIAL

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Evolution of the diagnostic criteria of T-cell-mediated rejection of renal allografts: Banff classification updates II

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ABSTRACT

The allo-specific immune responses to transplanted tissues or organs represent one of the most formidable challenges in the field of transplantation. Traditionally, cell-mediated alloimmune responses were considered the preeminent cause of rejection and have remained the focus of immunosuppressive drugs during the last several decades. More recently, attention has also been directed to the alloantibody-mediated damage and the innate immune system in initiating and effecting the immune injury to the transplanted organs. As a corollary to the above considerations, the earlier Banff classifications focused more on diagnosing and categorizing cellular rejection. There have occurred some significant changes in the cell-mediated rejection in recent Banff updates, but the changes are not as drastic or widespread, as those of the antibody-mediated rejection. Acute/active cell-mediated rejection may occur early or considerably late after renal transplantation. In this context, the terms of acute and chronic are not synonymous to their traditional connotations in pathology in terms of speed or duration of reaction. Acute rejection may occur many years after transplantation, and conversely, chronic changes may be present in the graft from the outset, derived from donor changes. Acute/active cell-mediated rejection, although markedly reduced in recent years, still remains one of the common causes of both acute and chronic renal allograft injury and dysfunction throughout the world. Luckily, a vast majority of cases of acute/active cell-mediated rejection respond rapidly and completely to the conventional anti-rejection treatment. In spite of this, it remains one of the most important causes of graft loss, especially in the long-term. Renal allograft biopsy still remains the gold standard test for an accurate diagnosis and categorization of cell-mediated rejection. A standardized approach to renal biopsy study is necessary if the full benefits of this invasive procedure are to be realized. Prior to the early 1990s, there were no uniformly accepted criteria for the diagnosis and classification of renal allograft pathology in general and rejection in particular. During early 1990s, a group of dedicated nephropathologists, clinicians and basic scientists set out to standardize the histopathological study of renal allograft biopsies for the uniform reporting of the pathological lesions across the world. These efforts have continued since then and have resulted in marked refinements in the diagnostic criteria and categories of rejection observed on renal allograft biopsies. The present paper forms the second attempt of the series 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 the early 1990s. An earlier paper described in detail the changes that occurred in the category of antibody-mediated

rejection. In this paper, we will discuss the changes that have occurred in the diagnosis and categorization of cell-mediated rejection and the focus, as in previous paper, will be on the morphological findings as observed on renal allograft biopsies.

Key words: Banff schema; borderline changes; cell-mediated rejection; kidney transplantation; T cells.

The process of alloimmune rejection of the allografts represents one of the formidable challenges in the field of transplantation[1]. The rejection process may be mediated by the cytotoxic T lymphocytes or the antibodies, either solely or more commonly, in a variable combination of both. The components of the innate immune system also play an indispensable role in the rejection process at all stages of its evolution[2]. Historically, the process of allograft rejection was classified into hyperacute, acute, and chronic types, depending on the speed and timing of the rejection development with no consideration of the underlying pathogenetic mechanisms[2]. Before the early 1990s, there was no single internationally agreed upon system for the standardized reporting of the pathological lesions on renal allograft biopsies[3-9]. Different renal transplant pathologists used different approaches for the diagnosis and classification of renal allograft pathology[2-9].

The Banff classification represented the first attempt to formulate an international, consensus-based and structured classification system for the diagnosis and categorization of renal allograft biopsy pathology with a particular focus on the development of the morphological criteria for the diagnosis and classification of rejection[9-14]. In this regard, the first Banff meeting was held at Banff, Alberta, Canada on August 2-4, 1991 and the first publication that narrated the outcome of the meeting appeared in 1993 and is known as Banff 93 classification[12]. Subsequent follow-up meetings have taken place every two years, mostly in the original country of the meeting but, more recently, in some other places of the world, to fine tune and adapt the classification to the latest progresses and advances in the field of transplant pathology[13,14]. Most of the meetings have been followed by updates and revisions in the form of papers in international peer-reviewed journals of nephrology and transplantation[13-15]. There have occurred marked changes in both the nomenclature and the classification of the rejection process, but the basic structure of the Banff schema has remained the same[2,10,13-15]. The first major and significant reshuffling of the original Banff classification occurred in 1997 with the merger and combination of Banff 93-95 classification and the National Institutes of Health (NIH)-sponsored Collaborative Clinical Trials in Transplantation (CCTT) modification, the two most widely used classifications in both clinical trials and centre practice at that time[15,16]. Since then, Banff 97 working classification of renal allograft pathology has served as an international foundation for both the routine reporting of renal transplant pathology and the international clinical trials[2,14].

It is apparent from a perusal of the earlier versions of the Banff schema that the main focus of these was on the diagnosis and categorization of acute/active cell-mediated rejection[12,15]. In fact, this focus on cellular rejection overshadowed the characterization and recognition of antibody-mediated rejection (ABMR) in the earlier days of the Banff meetings[2]. However, more recently, with an increasing recognition and reporting of ABMR, major and drastic changes have occurred in the diagnostic criteria and classification of this category[2,17-21]. On the other hand, the category of cell-mediated rejection has lagged behind in this context. In fact, the most important changes in this category also occurred during the early Banff meetings[12,15,16]. More recent updates have made only minor changes in the nomenclature of the category, rather than any drastic changes in the morphological criteria or subcategorization of this entity.

As noted above, the main focus of the first Banff classification was on the diagnosis and classification of acute/active cell-mediated rejection[12]. This type of rejection is characterized by infiltration of mononuclear cells, mostly T lymphocytes and macrophages, firstly in the interstitium, followed by attack of these cells on the tubules or the larger vessels (Fig. 1).

Thus, the targets of cellular rejection are different from those of ABMR. Prior to Banff classification, the presence of a few lymphocytes anywhere in the biopsy was usually considered as an indication of rejection. However, Banff made several important and new contributions to the diagnosis and standardization of morphological criteria of rejection diagnosis[12]. It introduced for the first time a category of borderline changes. It also set a minimum threshold for a confident diagnosis of acute/active cell-mediated rejection. It also recognized the importance of the location of the inflammatory cell infiltrate in the biopsy[12,15]. It should be noted, as will become evident later on, that the above criteria and thresholds, are required for the diagnosis of tubulointerstitial or type I rejection. The rationale for creating the borderline changes category is that the morphological appearances of the rejection process develop gradually, so it is not surprising that in centres where biopsies are done early after graft dysfunction, pathologists often feel difficulty in definitively diagnosing rejection, owing to the inflammatory and tubulitis scores not

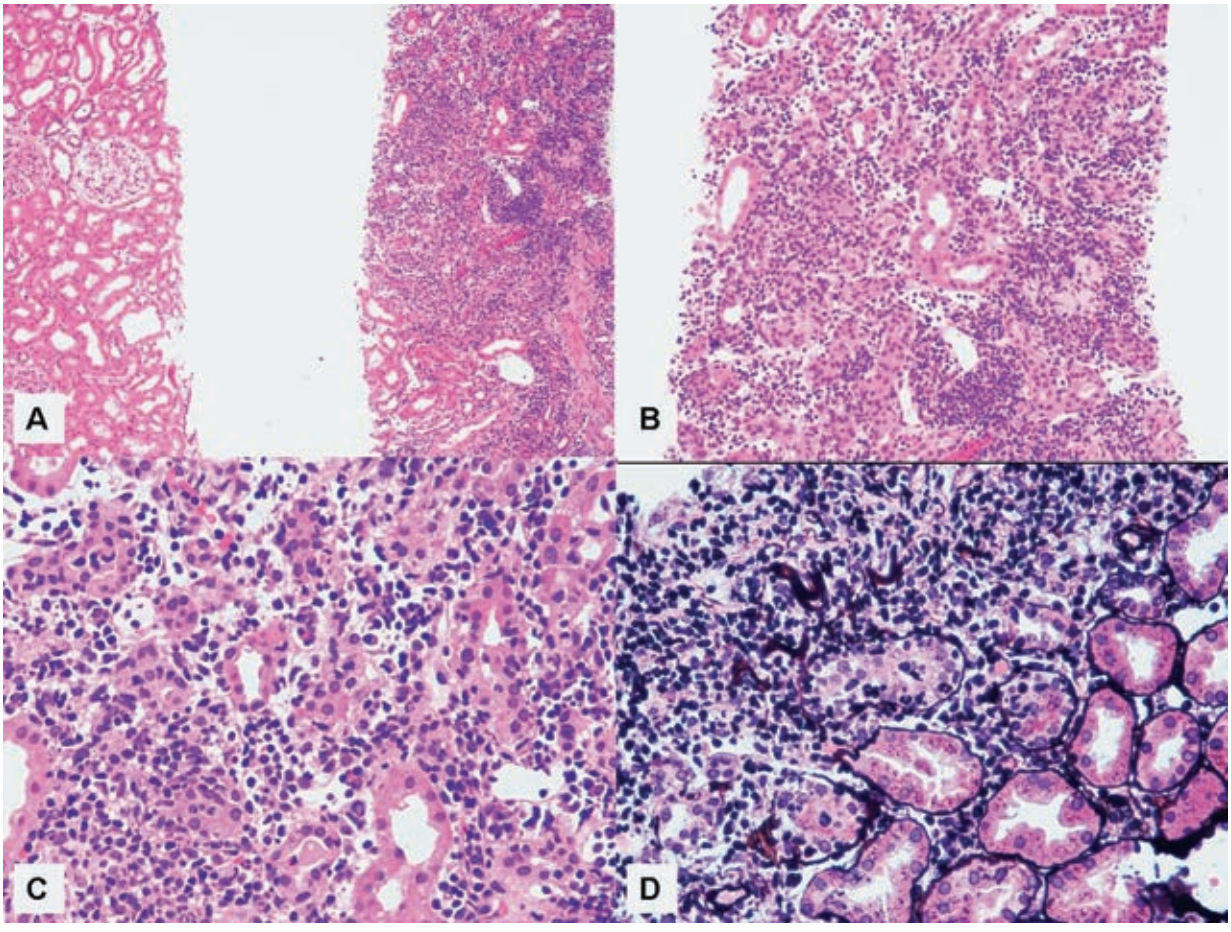

Figure 1

The morphological features of acute cellular rejection. A. Low-power view showing patchy distribution of the infiltrate. One core is heavily infiltrated by mononuclear cell infiltrate, while the other core is free of the infiltrate. (Haematoxylin and Eosin (H&E), ×100). B. Medium-power view showing the predominance of lymphocytes in the infiltrate. (H&E, ×200). C. High-power view showing occasional plasma cells and eosinophils admixed with lymphocytes in the interstitium. There is also interstitial oedema. Foci of tubulitis are present but are difficult to appreciate on H&E staining (H&E, ×400). D. High-power view showing foci of significant tubulitis in at least three tubules in the field. Tubulitis is often better appreciated on periodic-acid-Schiff (PAS) or silver stains. These stains highlight the tubular basement membranes, which facilitate identification of tubular invasion by lymphocytes (Jone's methenamine silver stain, ×400).

reaching the threshold of rejection diagnosis[22,23]. There is no borderline category for vascular or type II rejection and presence of even one lymphocyte in the intima is sufficient to diagnose a case as vascular rejection. However, the lymphocytic infiltration in the interstitium and tubulitis, especially of mild degree, are not specific for rejection and can be seen in other conditions. In order to avoid a high false positive rate of rejection diagnosis, the Banff schema set the minimum threshold of rejection diagnosis at i2 and t2, as illustrated in Fig. 2. On the other hand, higher degrees of both interstitial inflammation and tubulitis are relatively specific for rejection diagnosis[24-26].

Regarding the classification of rejection, the first Banff classification categorized acute/active rejection into three "grades" of increasing severity[12]. However, both the tubulointerstitial and vascular rejections were lumped together in this schema. The grades were: grade I or mild, grade II or moderate and grade

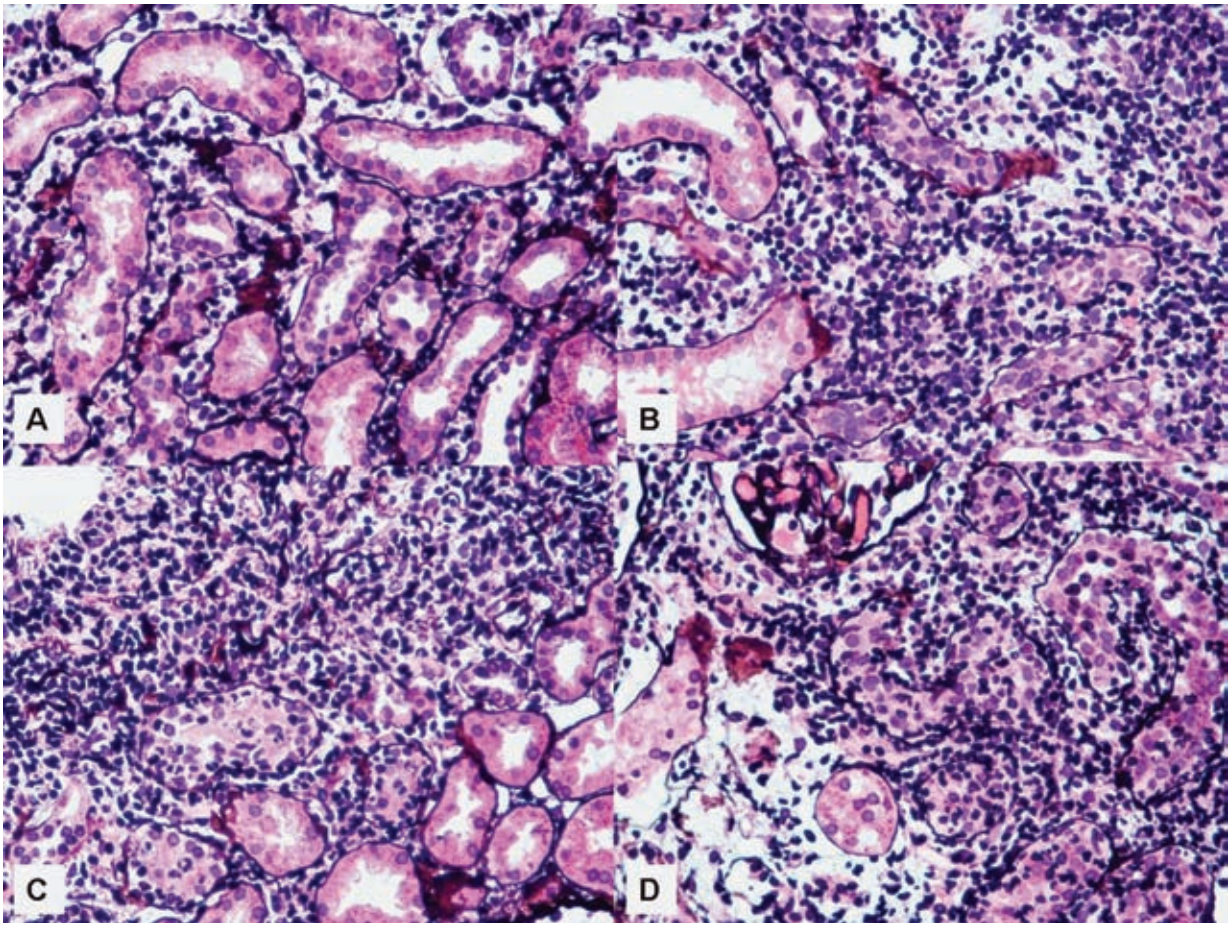

Figure 2

Different types of acute tubulointerstitial cellular rejection. A. High-power view of a representative field a biopsy showing mononuclear inflammatory cell infiltration in the interstitium but no tubulitis. If no tubulitis is seen in any of the areas with such infiltrates in the entire biopsy, the lesion is labelled as borderline changes, suspicious for acute rejection. (Jone's metheneamine silver stain, ×400). B. Another biopsy showing foci of significant tubulitis (i2) in at least two tubular cross sections with lymphocytic infiltration in the interstitium in the background. This lesion will be classified as type I A of tubulointerstitial rejection. (Jone's metheneamine silver stain, ×400). C. High-power view showing foci of severe tubulitis (t3) in at least three tubular cross sections against the background of mononuclear inflammatory cell infiltrates in the interstitium. These almost entirely consist of lymphocytes. This rejection will be classified as type I B of tubulointerstitial rejection. (Jone's metheneamine silver stain, ×400). D. High-power view of another representative area of a biopsy with severe tubulitis (t3) in many tubules. There is also interstitial lymphocytic infiltrate and oedema. Part of a glomerulus in the upper field shows congestion. (Jone's metheneamine silver stain, ×400).

III or severe (shown in Table 1). Little consideration was given to the underlying pathogenetic basis of rejection in this categorization[2,12]. The first major reshuffle in this category took place in Banff 97 meeting, when investigators using the Banff 93 classification and CCTT classification met together and adapted the Banff 97 classification with significant contributions from the CCTT classification, which emphasized the pathogenetic basis for the classification of cellular rejection[15,16]. Banff 97 classification categorized acute/active rejection into "types" and subtypes instead of grades (Table II). The major changes in Banff 97 included the separation of type I or tubulointerstitial rejection from vascular or type II rejection[15]. Type III rejection was categorized separately as in Banff 93 classification (Fig. 3). This change represented the flexibility of the Banff group to accommodate the views of investigators using CCTT classification and also assimilate the experience from newer studies showing that vasculitis *per se* has implications for the response to therapy and/or graft survival[15,16].

Banff 97-update, published in 2003, maintained the category of borderline changes, as all the subsequent updates of the classification[21]. With significant changes in the category of ABMR in this classification, however, the category of acute/active rejection was renamed as acute/active cellular rejection, to emphasize its distinction from ABMR. The typing and subtyping, however, remained the same as in Banff 97 classification[21]. No changes occurred in the nomenclature or classification of this category in Banff 2003 meeting[27]. The name of the category was again changed to T-cell-mediated rejection (TCMR) in Banff 2005 update[28]. This time, it was further divided into acute TCMR, which now included all the subtypes of acute/active cellular rejection of

Table I

The grading of acute/active rejection in Banff 93 working classification.

Category 3.	Borderline changes (suspicious for acute cellular rejection) Less than 25% inflammation (i1) with only mild tubulitis (t1), in the absence of intimal arteritis or arterial fibrinoid necrosis
Category 4.	Acute rejection
Grade I:	Mild acute rejection (AR) Cases fulfilling the criteria of significant interstitial lymphocytic infiltration, i2 (› 25% of parenchyma affected) and foci of moderate tubulitis, t2 (› 4 mononuclear cells/tubular cross section or group of 10 tubular cells).
Grade II:	Moderate AR Cases with (A) i2 and foci of severe tubulitis, t3 (›10 mononuclear cells/tubular cross section) and/or (B) mild or moderate intimal arteritis, v1 or v2.
Grade III:	Severe AR* Cases with severe intimal arteritis and/or "transmural" arteritis with fibrinoid necrosis of medial smooth muscle cells, v3.

*Recent focal infarction and interstitial haemorrhage without other obvious cause were also considered compatible with Grade III rejection.

Table II

Banff 97 classification of acute cellular rejection.

Category 3.	Borderline changes (suspicious for acute cellular rejection) Less than 25% inflammation (i1) with only mild tubulitis (t1), in the absence of intimal arteritis or arterial fibrinoid necrosis
Category 4.	Acute/active rejection
Type 1:	Tubulointerstitial type
Type 1A:	Significant interstitial inflammation, i2 (›25% of non-scarred cortex)+ moderate tubulitis, t2 (› 4 lymphocytes/tubular cross section)
Type 1B:	Significant interstitial inflammation, i2 (›25% of non-scarred cortex)+ severe tubulitis, t3 (› 10 lymphocytes/tubular cross section)
Type 2:	Vascular type, Intimal arteritis
Type 2A:	with ‹ 25% luminal occlusion (v1)
Type 2B:	with ›25% luminal occlusion (v2)
Type 3:	Severe type Transmural arteritis or fibrinoid necrosis (v3)

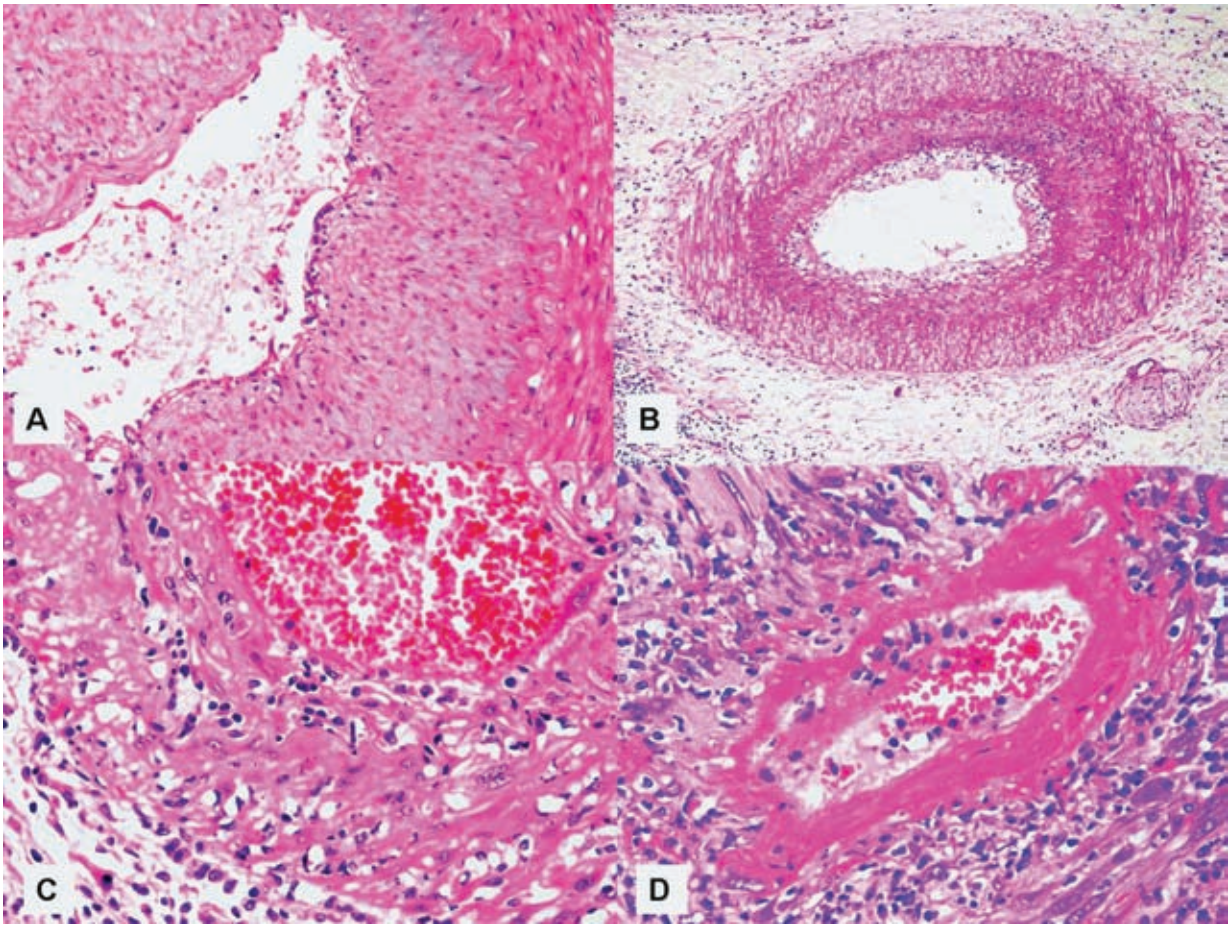

Figure 3

Different types of acute vascular rejection. A. High-power view of part of wall of an arcuate artery with foci of mild intimal arteritis (v1). This rejection will be classified as type II A. (Haematoxylin and Eosin (H&E, ×400). B. This artery shows severe intimal arteritis (v2). This lesion will be classified as type II B rejection. (H&E, ×400). C. High-power view showing an area of transmural arteritis (v3) with degenerative changes in the muscle cells of the media. No fibrinoid necrosis is seen. This lesion will be classified as type III rejection. (H&E, ×400). D. High-power view showing fibrinoid necrosis of the wall of a small artery and transmural inflammation (v3). This rejection is also classified as type III or severe rejection. Although this type of rejection may be seen in acute T-cell-mediated rejection, it is more characteristically seen in antibody-mediated rejection. (H&E, ×400).

Banff 97-update, and the chronic active TCMR. The later was defined by the presence of chronic allograft arteriopathy[28].

Banff 2007 classification added a new lesion score, termed ti (total interstitial inflammation score) to the schema. The scoring of the lesion was made optional in routine practice as the true significance of this is not known at present, but the pathologists were encouraged to note down this score in their reports. The lesion will be assessed in future meetings as the data accumulate on this variable. No change was made in lesion scoring of i-scoring[29]. A tabulated summary of the changes in the nomenclature and classification of cellular rejection is shown in Table III. Banff '09 and Banff 2011 meetings did not make any alterations in the criteria of diagnosis or classification of cellular rejection[30,31].

It is apparent from the above discussion and the illustrations that the mainstay for the diagnosis and classification of cellular rejection has been the morphology with little help from ancillary

Table III

The main evolutionary changes in the diagnostic category of T-cell-mediated rejection in Banff classification.

Pre-Banff	1st Banff	Banff '97	Banff'97 Update	Banff '05	Banff '07
Acute rejection	Acute rejection	Acute/active rejection	Acute/active cellular rejection	T-cell-mediated rejection	T-cell-mediated rejection
	Grades I, II, III	Type I A, B	Type I A, B	Acute T-cell-mediated rejection	Acute T-cell-mediated rejection
		Type II A, B	Type II A, B	Type I A, B	Type I A, B
		Type III	Type III		
				Type II A, B	Type II A, B
				Type III	Type III
				Chronic active T-cell-mediated rejection	Chronic active T-cell-mediated rejection

Note: The changes in the nomenclature and classification are highlighted by underlining the additions.

techniques of immunohistochemistry (IHC) or electron microscopy (EM). More recently, attention has been focused towards the identification of molecular markers of acute cellular rejection with promising results in single centre studies[29-31]. Multicentre trials and standardization of the methodology represent future challenges for the Banff group. The molecular data may be combined with the morphological data in the Banff classification in near future to increase the accuracy of diagnosis and classification of rejection[29-31].

In conclusion, the development of the Banff classification of the renal allograft pathology has allowed the standardization of approaches to rejection diagnosis and classification and reduced interobserver and interinstitutional variation. The mainstay of the diagnosis and classification of cellular rejection is still the morphology. Molecular profiles may help fine tune the diagnosis and classification criteria in near future.

Conflict of interest statement: None declared.

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