Kidney Pathology Series: Kidney Transplant

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# Kidney Transplant Pathology Series-VI: Banff Category 5 –
## Interstitial fibrosis and tubular atrophy (IFTA), no evidence of any specific etiology

**Dr. Muhammed Mubarak**

**Professor of Pathology and HOD**
**JIK Department of Histopathology,**
**Sindh Institute of Urology and Transplantation (SIUT),**
**Karachi, Pakistan.**
***DOI: 10.53778/pjkd61193***
Email address: drmubaraksiut@yahoo.com
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Banff classification of kidney allograft pathology has evolved considerably over the past 30 years and has undergone significant changes in many of the original diagnostic categories. With this evolution, it has increased in complexity and level of difficulty. To make it user friendly, this series of tutorials has been planned. 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 kidney transplant pathology for trainees and residents of nephrology and histopathology as well as for practicing pathologists and nephrologists.

### Banff category 5. Interstitial fibrosis and tubular atrophy (IFTA), no evidence of any specific etiology

This category of Banff classification of kidney allograft pathology was created to denote, classify and grade (or stage) chronic changes in the kidney allografts resulting from a variety of causes. Many important changes have also taken place in this category over the past three decades of evolution of Banff classification process. In this tutorial, we will discuss these and will elaborate on the reasons behind these changes.

As is well known, the most pressing problem in the field of kidney transplantation since the beginning of this activity is the development of chronic, progressive, sclerosing changes in the allograft and is still a challenging issue. The chronic changes occur almost universally in all kidney allografts at a rate of 2-4% per year. Interestingly, chronic sclerosing changes are also quite prevalent in well functioning grafts, as revealed by protocol biopsies. The chronic changes may involve any or all of the four compartments of the kidney graft parenchyma, i.e., the glomeruli, blood vessels, tubules and interstitium, albeit in variable proportions and combinations. Among these, glomerular and vascular changes are relatively more specific but are more prone to sampling error, especially the blood vessels. They help in defining the "causes" of chronic changes, especially chronic rejection. On the other hand, the tubulointerstitial changes are less specific, but importantly are less prone to sampling error. Hence, these are used for grading the severity of chronic changes in the Banff classification. In the management of kidney transplant patients, not only the identification, classification and grading of severity of acute changes is

important, but also of the chronic changes is vitally important in guiding the treatment and predicting the long-term graft outcome.

As already described in our previous tutorials on the Banff classification, prior to 1991, there was no internationally agreed upon system for uniform reporting of pathological lesions on kidney allograft biopsies. The Banff working classification represented the first step towards formulation of an international, consensus-based and structured classification system for the diagnosis and categorization of kidney allograft biopsy pathology. The Banff schema not only addressed the issue of acute pathological lesions, but also dealt with the chronic sclerosing changes in sufficient detail. Although the basic framework of the schema and the semiquantitative lesion scoring have largely remained the same, there have occurred significant changes in both the nomenclature and the classification of the original diagnostic categories including category 5 which deals with the chronic sclerosing changes in the allograft.

The evolution of the Banff classification schema regarding the nomenclature and classification of chronic sclerosing changes in the allograft reflects our continued and improved understanding of the pathophysiology of these changes. It is important to clarify that the terms "acute" and "chronic" in the context of kidney transplant pathology do not mirror their usual pathological connotations. For example, some "chronic changes" including fibrous intimal thickening and tubular atrophy may be present in kidney allograft biopsies even at the time of transplantation; these constitute the so-called donor-related changes. Conversely, an "acute rejection" may occur many years after transplantation.

During pre-Banff era, the term "chronic rejection" was used for all causes of chronic allograft dysfunction. This was unscrupulous, in that the chronic changes in the allograft are not only caused by alloimmune mechanisms but also by the non-immune mechanisms and differentiation among these is important for proper treatment. In fact, these non-immune mechanisms may be more prevalent than the alloimmune mechanisms in many cases. The Banff formulation introduced the term chronic allograft nephropathy (CAN) in 1991 as a generic alternative to the then popular and misleading term of "chronic rejection". The Banff 93 classification divided CAN into three grades based on the degree of tubular atrophy and interstitial fibrosis (Figures 1 to 3). No division of CAN category was made and all causes of chronic changes were lumped together in this one category. This again was unfortunate in that this prompted the transplant pathologists to render the diagnosis of CAN with little effort to look for specific features of diseases affecting the graft. In addition, many morphological features of, for example, chronic antibody-mediated rejection, were not known at that time.

In Banff 1995 report, chronic allograft nephropathy index (CADI) was integrated with the CAN category to grade the severity of chronic changes. No subclassification of CAN was however made in this update of the classification.

In Banff 97 classification, an attempt was made toward sensitizing the pathologists to look carefully for specific features of chronic changes in the allograft and identify and document these changes. A subdivision of each of the grades of rejection into "a" and "b" category was done depending on the absence or presence of specific features related to "chronic rejection", respectively. The grading

of the CAN category however remained the same as in previous classifications. No changes in the nomenclature or grading of CAN were made in 97-update classification (Banff 2001 meeting) or Banff 2003 meeting reports.

Although the original intent of introducing the CAN terminology was that it is a non-specific and non-committal category describing the chronic sclerosing changes involving the graft, its widespread use, resulted in the misconception that this is a specific disease entity. A need was felt to remove the category. However, the term remained in use for a good period of 14 years before it was eliminated in 2005 Banff meeting. A major change in the category of chronic sclerosing changes thus occurred in the Banff 2005 meeting with the result that the term CAN was eliminated and replaced by interstitial fibrosis/tubular atrophy (IFTA), no evidence of specific etiology. The causes of "a" subcategory of CAN in previous classifications were moved to the "other" category, while the chronic alloimmune causes were included in the respective categories of antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR) as chronic active or chronic (inactive) types. These will be discussed in more detail in future tutorials. Thus, category 5 in the Banff 2005 and all subsequent updates, now includes only those cases of chronic changes for which no specific etiological features can be found on the biopsy (Table 1).

**Table 1. The principal evolutionary changes in the diagnostic category of chronic changes in Banff classification.**

| Pre-Banff | 1st Banff | Banff '97 | Banff '97 Update | Banff '05 | Banff '07 |
|---|---|---|---|---|---|
| Chronic rejection | 5.CAN*<br>Grade I: mild<br>Grade II:moderate<br>Grade III :severe | 5. CAN*<br>Grade I: mild<br>Grade II: moderate<br>Grade III: severe<br>Classification:<br>a<br>b | 5.CAN*<br>Grade I: mild<br>Grade II:moderate<br>Grade III: severe<br>Classification:<br>a<br>b | 5. IFTA @,<br>no specific etiology<br>Grade I: mild<br>Grade II: moderate<br>Grade III: severe | 5.IFTA@<br>no specific etiology<br>Grade I: mild<br>Grade II: moderate<br>Grade III: severe |

*Chronic allograft nephropathy. @ Interstitial fibrosis and tubular atrophy

Starting from Banff 2009 meeting, a new initiative was started in the form of establishment of Banff Working Groups (BWGs) to address the problematic areas of the Banff classification in more focused approach. A working group was also established to assess the problems of the definition, interpretation and quantification of fibrosing injury in the kidney allografts and native kidneys.

Preliminary results by the BWG have shown a good correlation between the visual fibrosis scoring using the trichrome stain with the computer and immunohistochemical (IHC) stain-based image analysis methods. The group is further refining the diagnostic criteria and testing various staining methods and techniques to further improve the interobserver reproducibility and the predictive value of the chronic sclerosing changes for the ultimate improved graft outcome.
It is worth emphasizing here that the category of chronic sclerosing changes can co-exist with any of the other categories of kidney allograft pathology, except 1, which is normal. It is important to document both the acute and chronic pathological lesions on the biopsies to guide the treatment and inform the prognosis.

**In conclusion,** the nomenclature, categorization and classification of chronic changes have undergone significant changes during the last three decades of the Banff consensus process. More recently, the focus is on the identifying the early specific features relevant to the causes of chronic allograft damage, so that its progress may be halted with intervention. This has been facilitated by the ancillary techniques of immunohistochemistry and electron microscopy. In future, molecular profiling may help pinpoint the causes of chronic allograft damage and this will ultimately help in the optimal long-term graft outcome.

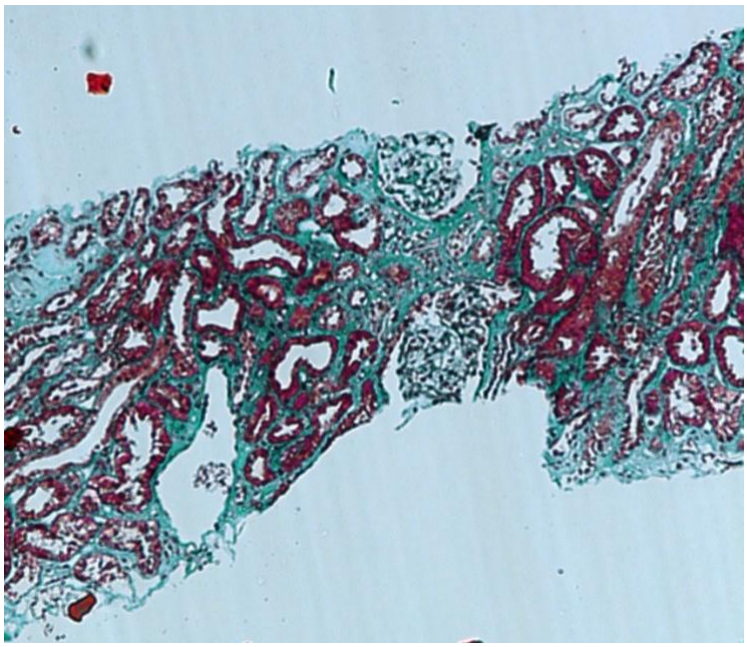

**Figure 1**. Early chronic changes with patchy mild interstitial fibrosis (fibrous tissue stains green with this special stain) and tubular atrophy (IFTA, grade I). The glomeruli are relatively normal. No artery is included in this field. The tubulointerstitial changes are used to grade teh severity of chronic changes, as these compartments are less prone to sampling error. (Trichrome stain, ×100).

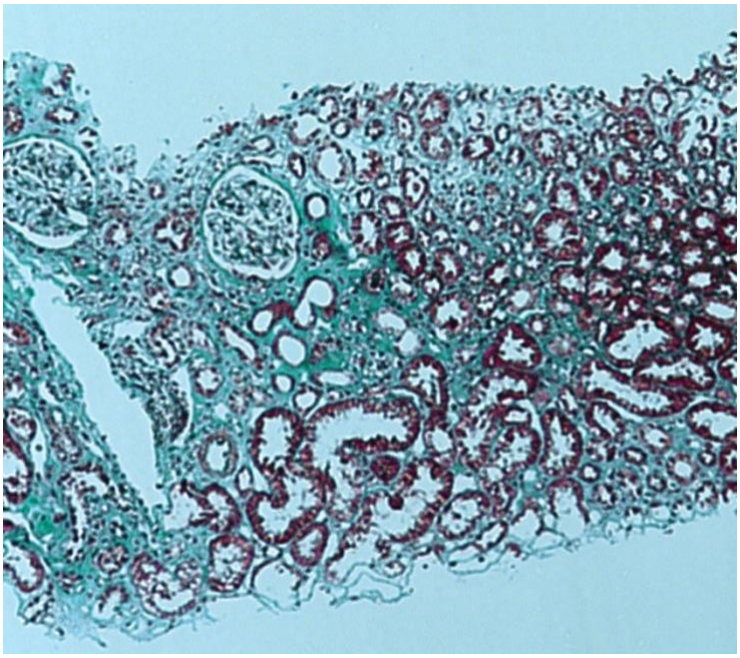

**Figure 2.** Another kidney allograft biopsy showing moderate degree of interstitial fibrosis (fibrous tissue stains green with this special stain) and tubular atrophy (IFTA, grade II). The glomeruli are intact. No glomerulitis or chronic changes are seen. No artery is included in this field. The tubulointerstitial changes are used to grade teh severity of chronic changes, as these compartments are less prone to sampling error. (Trichrome stain, ×100).

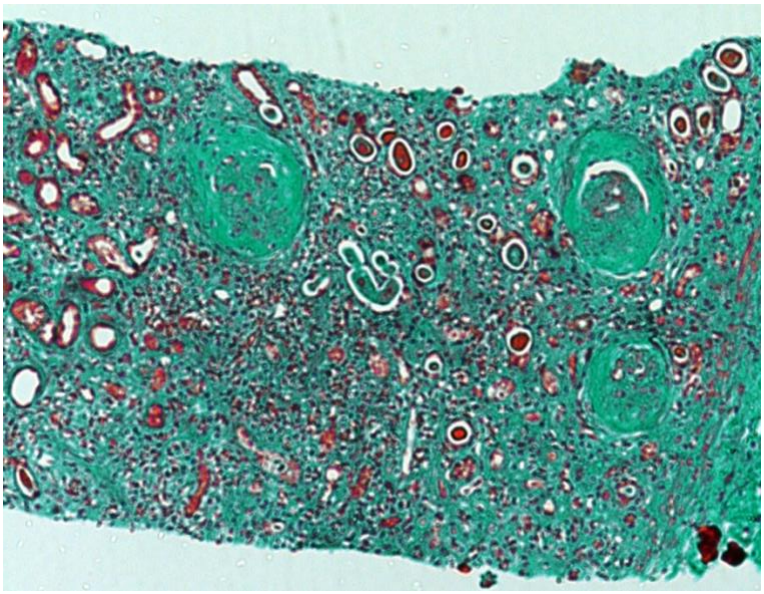

**Figure 3.** Advanced chronic changes with severe degree of interstitial fibrosis and tubular atrophy (IFTA) with global glomerulosclerosis of all three included glomeruli. This will be graded as severe IFTA or grade III. (Trcihrome stain, ×100).

## Further reading:


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