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Relevant topics in pathology of transplantation

Chairperson M J Mihatsch *Switzerland* **Co-chairpersons:** R B Colvin *USA* and P Furness *UK*

The Banff 97 classification of renal allograft pathology

P.N. Furness

Dept. of Pathology University of Leicester, UK.

Introduction

The original Banff classification was developed at a meeting held in Banff, Canada in 1991, organized principally by Professor Kim Solez. Its stated aim was to facilitate international standardization of nomenclature and evaluation of renal transplant biopsies "to guide therapy in transplant patients and to help establish an objective rejection endpoint in clinical trials" (1). This schema has become widely accepted. It has been used in numerous clinical trials and has become incorporated into routine clinical practice in many transplant centers. However, it was always viewed as a "working classification", with the intention that further changes and improvements would be incorporated as time went on. Inevitably, evidence of problems emerged and suggestions for improvements were put forward. This process was facilitated by the subsequent series of meetings at Banff (2) and by the ground-breaking use of the Internet as a discussion tool in the development of histopathological consensus. Some relatively major changes were agreed upon at the fourth Banff conference in 1997. At the time of writing these have not yet become available in conventional published form (3) but in the interim a "pre-print" is available on the Internet (4). The purpose of this paper is to present the main features of the new classification and to discuss some of the problems which have arisen.

Changes in the classification

The most important changes are in the classification of acute rejection changes. The original classification (Banff 93) fused "cellular" and "vascular" rejection, and Grade 2 rejection included cases with severe tubulitis (2a) and mild intimal arteritis (2b), The meeting accepted evidence from several large studies that this fusion was probably a mistake, as vascular changes indicate a poorer prognosis and response to therapy (5, 6). Tubulitis in atrophic tubules is now specifically excluded as a criterion for rejection. Other minor changes were incorporated, but arguments for inclusion of new features, such as infiltration by eosinophils, neutrophils or plasma cells were not accepted; such features may be recorded, and noted with an asterisk on the "i" score, but do not form part of the classification.

The scoring of lesions most relevant to acute rejection is now as follows:

Tubulitis ("t") score (applied only to tubules which are no more than mildly atrophic)

t0 No mononuclear cells in tubules;
ti Foci with 1 to 4 mononuclear cells per tubular cross section or 10 tubular epithelial cells;
t2 Foci with 5 to 10 mononuclear cells per tubular cross section or 10 tubular epithelial cells;
t3 Foci with 1 to 4 mononuclear cells per tubular cross section or 10 tubular epithelial cells "disappearing tubules" in at least 2 places and t2 elsewhere

Intimal arteritis ("v" score)

v0 No arteritis;
vi Mild to moderate intimal arteritis in at least one cross section. (Lymphocytes must be beneath endothelium in arteries. Venulitis is not included, nor is mononuclear adherence to endothelium);
v2 Severe intimal arteritis with at least 25% luminal area lost in at least one cross section;
v3 Arteritis with fibrinoid change and/or transmural arteritis with smooth muscle necrosis;

These changes make it necessary to be clear whether one is using Banff 93 or Banff 97. Partly to emphasize this, and partly to emphasize the recognition that arterial changes are qualitatively different, "borderline" has been replaced with "suspicious for acute rejection" and "grades" of acute rejection have been replaced with "types".

Severity of acute rejection

No acute rejection.
Suspicious for acute rejection: ti present, v0.
Acute/active rejection:

Type IA Mild tubulitis with interstitial infiltration (t2, at least i1, v0)
Type 1B Severe tubulitis (t3, at least i1, v0)
Type 2A Mild to moderate intimal arteritis (vi)
Type 2B Severe intimal arteritis (v2)
Type 3 Arterial fibrinoid/smooth muscle necrosis (v3)

Other changes in definitions of specimen adequacy, chronic allograft nephropathy grading etc. are documented in detail elsewhere (3, 4, 7).

These changes have been viewed by some as an inconvenience, but they should be seen as evidence of strength in a system which is capable of adaptation and development in order to avoid obsolescence. It is recognized that in some circumstances, such as ongoing clinical trials, it may be necessary to continue to use the Banff 93 formulation until the trial is complete.

Drawbacks of the classification

The Banff classification is widely perceived as a success in the context of clinical trials, in harmonizing approaches and in facilitating meaningful communication. There is evidence that it has improved reproducibility of assessment, and it is particularly popu-

lar with pathologists who are relatively inexperienced in renal transplant pathology, as it provides a clear framework for evaluation. However, evidence of improvement in the management of individual patients has been harder to find, In the author's personal opinion, this stems largely from an inappropriate rigidity in the application of the schema to individual patients.

Firstly, as a simple example: the scheme provides a clear definition of specimen adequacy. Adequate for what? A definition is clearly necessary in the context of clinical trials, but when dealing with an individual patient, flexibility is needed. If a specimen does not fulfill the criteria for adequacy, this should be clearly stated, but the pathologist should not refuse to make any assessment. Even a sample which contains only medulla may be adequate for patient management if there is clear evidence of acute rejection, though it remains inadequate for grading of the severity of the rejection. Medulla alone obviously cannot be adequate to exclude rejection.

The basis of the decision to treat acute rejection has been the subject of much controversy, largely because of over-rigid implementation. The Banif classification attempts to grade the severity of changes within the needle biopsy; but we know that biopsies sometimes fail to sample evidence of rejection, and conversely histological evidence of "rejection" may be present in protocol biopsies from completely stable grafts (8). Attempts to define a clear point in the schema at which treatment is justified should not be made in the absence of clinical data. The original Banif paper stated: "Clearly individual centers will develop their own clinical strategies for dealing with various biopsy findings" (1), and this needs to be reemphasized. Studies in this area are fraught with hidden dangers from differences in practices and populations in different centers, which may not be immediately apparent. For example, we recently developed a computer-based system which integrated 12 different histological variables to produce a highly reliable system for the diagnosis of very early acute rejection (9). When the pathologist whose observations had been used to "train" the system moved from the UK to Pakistan, he found that it no longer worked; it required retraining with data from his new institution. The inference is that although a system to grade acute rejection is valuable, attempts to impose a single "action point" for treatment are likely to fail unless the characteristics of the local institution are taken into account.

Recommendations

The appropriate course of action, when reporting renal transplant biopsies, is first to give a description of the histological changes which includes the Banff grading system. This aspect of the report is most important in clinical trials. However, the pathologist is also a physician, so the conclusion should include a recommendation for appropriate management which is based not only on the Banff classification, but also on the clinical features and experience of local conditions and practices. It may also be appropriate to consider "minor" histological features of acute rejection, which although less reliable than tubulitis and intimal arteritis may be of assistance in difficult cases (9).

At the time of writing the 1999 Banff conference has not been held. It is anticipated that a brief report of this meeting, to be held in June 1999, will be incorporated into the presentation in Barcelona in September 1999.

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A simplified classification system for acute renal allograft rejection (CCTT)

R.B. Calvin

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

Introduction

A simplified, standardized scoring system for acute renal allograft rejection was sought which would avoid some of the perceived limitations of the Banff system. This description is excerpted and updated from that report (1) and a recently published review (2).

A panel of renal pathologists participating in the National Institutes of Health supported Cooperative Clinical Trials in Transplantation program (CCTT) defined and tested the clinical utility of the three following categories of acute rejection (1):

Type I: At least 5% of the cortex must have interstitial mononuclear infiltration with at least two of the three following features present: edema, tubular degeneration/injury or reactive lymphoblasts. Tubulitis must be present, with at least three tubules affected in 10 serial high power fields (40x) from the areas with the most infiltrate.

Type II: Arterial mononuclear endothelial inflammation (endarteritis or endothelialitis) is present (with or without features of type I).

Type III: Arterial fibrinoid necrosis ortransmural inflammation in present and may be accompanied by thrombosis, parenchymal necrosis/recent infarction or hemorrhage.

In contrast to Banff (3), CCTT adds criteria that reflect ongoing parenchymal injury (edema, tubular injury) or immunological activity (activated lymphocytes) to help separate active rejection from inactive infiltrates. CCTT excludes the subcapsular area for scoring (which often shows mild inflammation and fibrosis) and does not score tubulitis in areas of tubular atrophy (where it is often seen nonspecifically). CCTT regards the presence or absence of endarteritis as potentially more fundamental and it therefore is the basis of separating Type I from Type II.

Interobserver reproducibility of the CCTT classification showed 91% agreement on the presence or absence of rejection (0.80 kappa score) (1). The agreement was almost as good for the type