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.

References

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

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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 or transmural 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 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
of rejection (kappa 0.72) and the presence or absence of endarteritis (kappa 0.65). The design of this study did not intrinsically favor agreement, in that the scoring was done over several years by almost a dozen pathologists. Thus, the CCTT classification system appears to be statistically robust. The original Banff system compares unfavorably with CCTT in kappa values, it is obviously difficult to compare kappa values between these two studies, however, it is notable that the agreement rate for endarteritis was equivalent in the two studies. Since this feature is defined similarly by the two groups, this result suggests that the other marked differences in agreement are intrinsic to the classification schemes rather than the design of the studies or the skills of the pathologists.

The pathologists in this study found that the CCTT classification of the biopsies takes no more time than the usual diagnostic examination of a transplant biopsy. In contrast to Banff, little has to be quantitated: the estimated percentage of cortex involved with the infiltrate has to exceed 5% and the tubulitis occasionally has to be counted to be certain that at least three tubules are affected. Nothing else is graded: there are no “mild”, “moderate” or “severe” degrees of any lesions. As a measure of the efficiency, the review panels typically took about 5 min per biopsy.

The CCTT criteria have a sensitivity of 90% for detection of rejection in one core and a calculated sensitivity of 99% for two cores, which is quite satisfactory for clinical management. The specificity of the pathological criteria is difficult, if not impossible, to determine since the biopsy is widely regarded as the “gold standard”. When rejection was defined solely by clinical criteria and the biopsy was interpreted without any clinical information, the CCTT classification performed acceptably, with a sensitivity of 86% and a specificity of 72%. When judged by the clinical course, a significant classification performed acceptably, with a sensitivity of 86% and a specificity of 72%. When judged by the clinical course, a significant classification performed acceptably, with a sensitivity of 86% and a specificity of 72%. When judged by the clinical course, a significant classification performed acceptably, with a sensitivity of 86% and a specificity of 72%

It must be considered possible, if not likely, that these discrepancies are not due to a lack of specificity of the biopsy criteria, but rather that rejection is subclinical. Past published data do not support prognostic significance of the extent of the infiltrate or tubulitis, even if it could be accurately graded (1, 2). When the diagnostic criteria for the number of tubules with tubulitis and the percent infiltrate were varied, the greatest agreement with a clinical course consistent with rejection were using the original criteria, validating the thresholds set. Banff has a higher threshold of infiltrate for Grade I rejection (25% vs. 5%). Our results indicate that the infiltrate involves less than 25% of the cortex in 31% of the cases of Type I rejection. Thus, CCTT would classify many of the Banff borderlines in agreement are intrinsic to the classification schemes rather than the design of the studies or the skills of the pathologists. The CCTT types of rejection correlate with clinical severity. Type I rejection is more often completely steroid responsive (5).

The revised Banff classification recognizes the validity of the CCTT system and uses the same major categories (“borderline” has become “suspicious”). Major remaining issues for the future are to define more markers for active rejection versus harmless (?beneficial) infiltration in an accepted graft and to incorporate acute humoral rejection and glomerular lesions into the system.

References

**Polyomavirus infection of renal allografts**

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A morphologically manifest Polyomavirus infection of renal allografts with the BK-virus strain is a new and highly unusual complication carrying an unfavorable prognosis. Polyomavirus, a subgroup of the papovavirus family, is a double-stranded nonencapsulated DNA virus. After a mostly asymptomatic primary infection early in life, Polyomavirus frequently resides in a dormant state in the kidneys and ureters of healthy individuals. In immunocompetent hosts, it does not cause symptomatic disease. On the other hand, immunocompromised patients are at risk of a clinically manifest infection. Human disease can be caused by two Polyomavirus strains: JC and BK. JC-virus is the causative agent of progressive multifocal leukoencephalopathy. BK-virus is associated with changes in the kidney and the urothelium, i.e., "viral nephritis" and, proposed by some, hemorrhagic cystitis. However, a clinically symptomatic Polyomavirus infection is exceptional, even under immunosuppression. The kidney, a common site of dormant viruses, is hardly ever affected. In Basel we did not encounter a single case of a manifest renal allograft infection with Polyomavirus before 1996, whereas nine cases were diagnosed in the following 3 years, which points to new risk factors (1).

**Polyomavirus disease**

Polyomavirus disease defines a histologically manifest renal allograft infection with viral inclusion bodies, associated with rather varying degrees of interstitial inflammation and deterioration of graft function (i.e., an increase in serum creatinine). The initial diagnosis is made months after transplantation (range: 4-25 months) (2, 3). In man, the disease is caused by the BK-virus strain (2). The diagnosis of Polyomavirus disease is only made histologically in a graft biopsy (2). The morphological hallmark is the detec-