



Jovan DIMITRIJEVIĆ¹
Aleksandar DUJIĆ²
Ljubica ĐUKANOVIĆ³
Rajko HRVAČEVIĆ²
Radmila BLAGOJEVIĆ³
Ivica MILOSAVLJEVIĆ¹
Goran BRAJUŠKOVIĆ¹
Anastasija ALEKSIĆ²

¹INSTITUTE OF PATHOLOGY, MILITARY MEDICAL ACADEMY, BELGRADE, YUGOSLAVIA

²CLINIC OF NEPHROLOGY, MILITARY MEDICAL ACADEMY, BELGRADE, YUGOSLAVIA

³INSTITUTE OF UROLOGY AND NEPHROLOGY, UNIVERSITY CLINICAL CENTER, BELGRADE, YUGOSLAVIA

The place and role of a pathologist in the transplant team

ABSTRACT

Renal allograft biopsies have been used as a good method for monitoring the evolution of kidney transplants for at least 20 years. With the increase in renal transplantation at almost every medical center, the pathologist is being called upon to evaluate renal transplant biopsies from patients with allografts and to determine: whether there is evidence of allograft rejection, cyclosporine A nephrotoxicity, or some other unrelated lesion and if rejection is present, to predict whether the lesions present are potentially reversible with therapy. Recent experience point out the importance of allograft biopsy in evaluating allograft function and appropriate therapy administration in 30% to 50% renal transplanted patients. Up to 1998 in our country 559 kidney transplantations with consecutive biopsies were performed. Heart, lungs and liver transplantations were registered in single cases. The histology analysis of renal allograft biopsies is obligatory guided by frequently modified Banff classification with positive effects to work of clinicians and pathologist and their cooperation, and progressive contribution in transplant team functioning.

KEYWORDS: Biopsy; Organ Transplantation; Kidney Transplantation; Physician's Role

INTRODUCTION

Renal allograft biopsies have been used as a good method for monitoring the evolution of kidney transplants for at least 20 years. Histological analysis permits differential diagnosis of the causes of allograft dysfunction to be made. With the increase in renal transplantation at almost every medical center, the pathologist is being called upon to evaluate renal transplant biopsies from patients with allografts and to determine: whether there is evidence of allograft rejection, cyclosporine A nephrotoxicity, or some other unrelated lesion and if rejection is present, to predict whether the lesions present are potentially reversible with therapy. The clinician usually needs a quick diagnosis to permit administration of necessary therapeutic measures. Many pathol-

ogists like to process the whole biopsy specimen with a fast embedding method. Immunofluorescence (IF) and electron microscopy (EM) are frequently not performed. In our opinion the transplant biopsy should be processed as a regular renal biopsy. From the snap-frozen part of the biopsy, sections should be cut and stained with haematoxylin-eosin (H&E), Periodic acid-Schiff (PAS), and possibly trichrome staining. Frozen sections usually do not have a good structure, yet the signs of interstitial or vascular rejection may easily be recognized in most cases, and a preliminary diagnosis can be made within an hour. Recent experience points out the importance of allograft biopsy in evaluating allograft function and appropriate therapy administration in 30% to 50% renal transplanted patients (1). Up to 1998 in our country 559 kidney transplantations with consecutive biopsies were performed (2). Heart, lungs and liver transplantations were registered in single cases.

MATERIALS AND METHODS

Theoretically, renal transplant biopsy specimens should not be handled differently from native kidney biopsies; however the special circumstances and the need for quick diagnosis frequently require some special procedures. In the diagnosis of rejection, IF and particularly EM are of limited value. Thus, in many centers the entire renal transplant biopsy specimen is embedded in paraffin. However, the transplant kidney may show pathologic changes unrelated to rejection, such as de novo or recurrent glomerular disease, the diagnosis of which requires IF and EM. In cases in which rapid processing for a prompt diagnosis of acute rejection is desired, frozen sections may provide the fastest answer. However, the histology of frozen sections may not be adequate (3,4). From a practical point of view, the best alternative is perhaps to do rapid processing by automated dehydration by continuously distilled acetone, allowing paraffin-embedded sections to be prepared within 3 to 4 hours of biopsy. The advantage of this procedure over snap-freezing of the tissue is that preservation is superior; however, it is still not as good as with routine processing. Because of recurrent or de novo renal disease the specimens should undergo regular processing, or at least IF should be performed. Several types of classification have been proposed. The most widely accepted classification developed historically, as the clinicopathologic correlation was becoming increasingly clear during the rejection. It is based on a combination of pathogenetic, morphologic, and clinical data. Recently, a new classification has been proposed by the group of prominent pathologist, transplant surgeons, and nephrologists after a meeting in Banff, Canada. Hence, this classification is referred to as the Banff classification (5).

ALLOGRAFT PATHOLOGY

Histologic analysis of renal allograft biopsies is obliged guided by the frequently modified Banff classification with positive effect to work of clinicians and pathologist and their cooperation, and progressive contribution in transplant team functioning. This classification includes diagnostic categories for renal allograft biopsies combined with the differential diagnoses of "other" categories and the definitions provide a reproducible system which maximizes the clinical utility of the biopsy (6-8). Recent Banff 97 working classification refines earlier schemas and represents an input from two classifications most widely used in clinical rejection trials and in clinical practice worldwide (5). Major changes include the following: rejection with vasculitis is separated from tubulointerstitial rejection; severe rejection requires transmural changes in arteries; "borderline" rejection can only be interpreted in a clinical context; antibody mediated rejection, and lesion scoring focuses on most severely involved structures (9). It is necessary to recognize the following histologic changes that suggest a poor renal allograft prognosis: fibronoid necrosis in arteries, infarcted areas, intimal arteritis, obliterative arteriopathy, interstitial hemorrhage, transplant glomerulopathy, glomerulitis, many eosinophil cells in the infiltrate. The Banff 97 combined classification of renal allograft pathology includes acute/active rejection, chronic/sclerosing nephropathy, and other

Address correspondence to:
Dr Jovan Dimitrijević, Institute of Pathology, Military Medical Academy, Crnotravska 17, 11000 Belgrade, Yugoslavia

The manuscript was received: 14. 03. 2000.

Accepted for publication: 17. 04. 2000..

morphologic findings, including de novo and recurrent diseases, toxic changes, and infection (10-12).

The first human liver transplantation was first performed in 1963. Numerous advances since that time led to enhanced graft and patient survival. As the clinical practice of organ transplantation continues to evolve, it is appropriate to inquire whether causes of mortality are also changing. Postmortem examination of liver transplant recipients can more firmly establish the cause(s) of death, occasionally revealing causes that were not clinically suspected, and can document the extent and organ distribution of the disease. Liver transplantation is an established treatment for multiple end-stage liver disease, yet little information is available on the autopsy-determined causes of death in liver transplant recipients. Infections were the most frequent cause of death, present in 64% of the total. Overall, the infections were bacterial in 48% of the cases, fungal in 22% and viral in 12% (13).

Heart transplantation has established itself as an effective treatment for end stage cardiac disease. The morphologic pattern shown by the endomyocardium may vary, depending on the time elapsed since the transplantation, and is divided in immediate changes, early changes, intermediate changes and late changes. Moreover, there are changes not related to the elapsed time but that can be observed early as well as late. Until now, histologic interpretation of the endomyocardial biopsy and scoring of intensity and extent of the lymphocytic infiltrate and myocyte damage are still the cornerstones of cardiac transplant pathology. One should however realize that lymphocytes, in spite of a similar morphology, may have entirely different properties and one should also keep in mind that other cells than lymphocytes may also play a role in the effectivity and efficiency of the local immune reaction in the grafted heart (14).

The grafted lungs have a high incidence of acute rejection when compared to other solid organ allografts and this is most reliably diagnosed by transbronchial biopsy. The lung rejection study group of the International Society of Heart Lung Transplantation (ISHLT) has recommended that at least five pieces of alveolated lung parenchyma are examined to confidently grade acute pulmonary rejection. In practical terms, the bronchoscopist should submit more than 5 biopsies in order to provide this minimum number of parenchymal pieces. The biopsy fragments can be gently agitated in formalin to inflate them and may be processed according to a two-hour schedule if urgent. Sections from at least 3 levels of the paraffin block should be examined with H&E stains. This is however a minimum standard and many centers, examine multiple serial sections of the pulmonary biopsies. Connective tissue stains are essential for the diagnosis of airway and vascular fibrosis when chronic rejection is suspected and silver stains are mandatory for fungi and pneumocystis in all biopsies. Acute pulmonary rejection is manifested by perivascular infiltrates, which increase in density and frequency with increasing severity. A standard nomenclature for its grading was established in 1990 by the lung rejection study group of the ISHLT and this been modified in 1995 in the light of experience of several large lung transplant centers (15).

The evaluation of transplant biopsies is a challenging task for the pathologist. The diagnosis should be made as soon as possible because of urgent therapeutic consideration. Over/or underdiagnosis of rejection, cyclosporine nephrotoxicity, and other factors may result in inappropriate treatment that can adversely influence the outcome of transplantation and cause unwanted complications (e.g., infections because of increased immunosuppression). The optimal scenario for both the pathologist and the transplant team is to evaluate the biopsy together in the form of a clinicopathologic cooperation (1,8).

REFERENCES

1. Nadasdy T. Transplantation In: Renal biopsy. Silva GF, Vivette D, Agaty D, Nadasdy T, eds. New York: Churchill Livingstone, 1996:373-401.
2. Đukanović Ljubica et al. Annual report on regular dialysis and transplantation. Belgrade: Clinical Center of Serbia, 2000.
3. Mazzali M et al. Percutaneous renal graft biopsy: a clinical, laboratory and pathological analysis. *Rev Paul Med* 1999;117(Suppl 2):57-62.
4. Dimitrijević J et al. Značaj biopsije bubrega za kliničko-patološku procenu stanja transplantiranog. *Acta Medica Medianae* 1997;XXVI(Suppl.1):120-2.
5. Racusen LC et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999;55:713-23.
6. Seron D et al. Early protocol renal allograft biopsies and allograft outcome. *Kidney Int* 1997;51:310-6.
7. Dimitrijević J et al. Pathohistological finding in renal graft with changes not considered to be due to rejection. *Archive of Oncology* 1998;6(Suppl.2):104.
8. Dimitrijević J et al. Renal graft histology: Relationship between transplant rejection and changes not considered to be due to rejection. *Medicinska istraživanja* 1999;33:89-93.
9. Schweitzer EJ et al. Significance of the Banff borderline biopsy. *Am J Kidney Dis* 1996;28:585-8.
10. Mihatsch JM et al. Morphological criteria of chronic rejection: Differential diagnosis, including cyclosporine nephropathy. *Transplant Proc* 1993;25:2031-7.
11. Isoniemi HM et al. Histopathologic chronic allograft damage index accurately predict chronic renal allograft rejection. *Transplantation* 1994;58:1195-8.
12. Nickerson P et al. Identification of clinical and histopathologic risk factors for diminished renal function 2 years post-transplant. *J Am Soc Nephrol* 1998;19:482-7.
13. Torbenson M et al. Causes of death in autopsied liver transplantation patients. *Mod Pathol* 1998;11(Suppl.1):37-46.
14. Slootweg PJ et al. Developments in cardiac transplant pathology. Short course: Developments in Transplantation Pathology. XVI European Congress of Pathology, Maastricht, 1997.
15. Stewart S. New developments in lung transplant pathology. Short course: Developments in Transplantation Pathology. XVI European Congress of Pathology, Maastricht, 1997.