Chronic renal graft disease

E. Vázquez Martul

Servicio Anatomía Patológica. Hospital Universitario Juan Canalejo. A Coruña.

Nefrología 2008; 28 **(4)** 373-380

INTRODUCTION

Chronic graft nephropathy (CGN) has been conceptually defined as a progressive kidney function impairment unrelated to discontinuation of immunosuppressive treatment, disease recurrence, and vascular or urological complications.[1] The current decrease in the incidence of acute rejection is one of the reasons explaining that CGN is the second leading cause of graft loss, the first cause being patient death.[2] Fifty percent of patients lose the graft at 5 years.[3] The search for the main etiopathogenetic mechanisms, the detection of predictive histopathological lesions, and a better understanding of prognostic criteria are the main current discussion factors.[4-6]

Since the 8th Banff conference held in Edmonton (Canada) in 2005,[7] a consensus was reached by clinical and pathologists not to use the term CGN as a diagnostic term because its generic use conceals other multiple immune or non-immune causes,[5,8] preventing a more specific diagnosis and, thus, appropriate treatment. The concept of chronic graft disease secondary to an immune mechanism should therefore be distinguished from those other chronic diseases unrelated to an immune process. Among these diseases, particular mention should be made of high blood pressure, chronic toxicity, obstruction, reflux, and/or bacterial chronic interstitial nephritis, as well as viral interstitial nephritis.[7] This multiplicity of causes with different but imbricate or overlapped etiopathogenetic mechanisms is one of the main difficulties for making an adequate histopathological study and finding clinical correlations.

MAIN HISTOPATHOLOGICAL CHARACTERISTICS

The prior concept of CGN, as modified in Banff 2005,[7] consists of slowly progressive functional impairment of the graft whose histopathological substrate is characterized by interstitial fibrosis, tubular atrophy, arteriolar hyaline disease, and glomerulosclerosis. It should be reminded that this concept is fully descriptive and non-specific, because all these histopathological characteristics suggesting chronicity are common to any chronic renal condition in which the proportion of glomerular sclerosis, fibrosis, and tubular atrophy is also related to the degree of renal failure, irreversibility of the process, and therefore a poorer prognosis. In order to establish a clinical correlation and suggest therapeutic schemes, a search for the etiopathogenetic mechanisms involved is required.

Correlation between histopathological damage and prognosis has led since the 90s to the search for objective and reproducible parameters, in which special mention should be made to two protocols or study groups, Banff[7] and the CADI system,[9] pursuing a same objective, namely quantification of different histopathological parameters of chronicity, including glomerular disease, grade and extent of interstitial fibrosis, tubular atrophy, and vascular lesion. Three grades with a clinical correlation are classified based on this methodology, with grade III cases having a poorer prognosis (table I).

Despite these diagnostic guidelines, however, in the attempts made to ascertain the interobserver degree of specificity and reproducibility, kappa indices in these biopsies have been very low, less than 0.40.[10] This fact could be explained by multiple reasons, including inconsistent interobserver experience, the negative role of inconsistent quality and representativeness of the biopsy, overlapping of different diseases, particularly at vascular level, and finally, absence of morphometric studies limiting a significant subjectivity burden on observers.[11]

It should be noted that the chronic graft phase is the evolutionary product of a dynamic biological fact in which intercurrent immune and non-immune factors, such as infectious, toxic, and ischaemic factors making assessment of each patient difficult may coincide and coexist. As already discussed by

Table I. Chronic graft disease with no evidence of known etiology (Banff, 2005 meeting report. *Am J Transplant* 2007; 7: 518-526)

Grades:

I. Interstitial fibrosis and mild tubular atrophy (< 25% of cortical area).
II. Interstitial fibrosis and moderate tubular atrophy (26%-50% of cortical area).
III. Fibrosis and severe tubular atrophy (< 50%).

Non-especific vascular lesion (atherosclerotic type and/or hypertensive vascular disease) as well as % glomerulosclerosis may be included.

Correspondence: *E. Vázquez Martul*
Servicio Anatomía Patológica
Hospital Universitario Juan Canalejo
15006 As Xubias. A Coruña
evazmar@canalejo.org

Furness,[12] paradoxically «… we may have abundant data but a limited understanding of what is happening in the patient».

However, it has been documented that a severe grade of chronicity (Banff's grade III) with extensive interstitial fibrosis, tubular atrophy, arteriolar hyalinosis, and a high percentage of glomerulosclerosis has an adverse influence on graft prognosis, with a very low 10-year survival. Only in 57.9% of grade II cases graft survival was longer than 10 years with a significant p value ($p < 0.01$), By contrast, low chronicity rates involving mild atrophy and interstitial fibrosis and no vascular disease were associated to 10-year survival of more than 80% of grafts.[13]

It has been recommended to include among histopathological parameters to be quantified in the biopsy in chronic stages the concept of chronic «active» nephropathy, encompassing the coexistence of focal or diffuse subcapsular or perivascular interstitial inflammatory infiltrates and vascular disease with intimal lesion.[7,14] When the prognostic impact is assessed, it is important to distinguish this active phase from the inactive phase, characterized by interstitial fibrosis, tubular atrophy, vascular sclerosis, and glomerular sclerosis only. This information should therefore be included in the pathological report for better clinical information.

This information would however be inadequate if, when assessing biopsy diagnostic criteria, other significant and controversial factors related to graft prognosis in this evolutionary period are not considered.

- Donor kidney disease secondary to advanced age, arteriosclerosis, diabetes, or hypertension.
- Subclinical rejection demonstrated by the protocol biopsy.
- Relationship to antibody-mediated humoral rejection.
- Cell type of inflammatory infiltrate and/or cell subpopulations.
- Calcineurin inhibitor-induced chronic nephrotoxicity.
- Relationship between transplant glomerulopathy, chronic vascular disease, and immune mechanism.

DONOR FACTORS INVOLVED IN CHRONIC GRAFT NEPHROPATHY

The social pressure exerted by the long waiting lists of patients pending transplantation has led in recent years to the use of less strict criteria for donor selection. Patients over 60 years of age, with diabetes or hypertension, and kidneys from people dying from a cerebrovascular accident (CVA) and in asystole with warm ischaemia are currently being accepted as donors. However, it has been documented that a history of hypertension, smoking, death from CVA, serum creatinine higher than 150 mL/dL, asystole, and atherosclerotic vascular disease together with very prolonged cold ischaemia has an impact on both poor early function and predisposition to graft acute rejection and chronic failure.[15-18]

These wider donor selection criteria make it advisable to perform a biopsy before implantation to ascertain the histological status of the graft.[19] Such biopsy has been shown to be useful and to be associated with a better prognosis as compared to groups where no prior biopsy was performed.[20] It is generally accepted that greater than 20% glomerulosclerosis, diffuse and concentric arteriolar hyalinosis, and a significant interstitial fibrosis would mark the limit to contraindicate such grafts, not only because of the poor early function and increased morbidity, but also because of the great probability of development of chronic graft disease.[21-23] An additional significant reason for requesting a donor kidney biopsy is to facilitate subsequent assessment of the condition during the transplant course.

Thus, the earliest damage that may be seen in the first graft biopsy, and that should be histologically assessed, is a damage, either vascular, tubulointerstitial or glomerular, «inherited» from the donor.

In a study conducted on our prior patients where 66 cases of CGN, with biopsy assessment after the sixth post-transplant month were reviewed, lesions characterizing chronic disease, such as fibrosis and tubular atrophy, were related to grafts with no initial function and with a higher percentage of glomerulosclerosis.[24]

SEARCH FOR PREDICTIVE LESIONS: SIGNIFICANCE OF PROTOCOL BIOPSY

The possibility of knowing the early lesion stages at times when the pathological process has not reached an irreversible level has been and continues to be the main objective for indicating protocol biopsies that allow us for detecting in sufficient advance a given histopathological lesion and monitoring its course and response to treatment. Protocol biopsies performed in patients with stable function have been shown to allow for detecting subclinical rejections that may be treated, as well as the presence of «tubulitis», fibrosis, and vascular disease in biopsies from patients with no kidney function impairment.[25,26] Some series where protocol biopsies were performed found rejection criteria in up to 30% of patients with stable kidney function.[27] Performance of these biopsies has shown a relationship of several histopathological parameters such as interstitial fibrosis, glomerulosclerosis, and mononuclear infiltrate with progressive kidney function impairment.[28] Protocol biopsies also appear to have shown a direct relationship of recurrent rejection episodes, as well as acute rejection after the fourth month, with development of chronic nephropathy.[29]

However, histopathological assessment may be difficult in these early stages because minimal lesions and/or lesions classified as borderline, usually focal in character, with little histopathological impact, of uncertain significance, and even with different response to treatment are more commonly seen.[30,31] This limits the validity of the results, which together with increased costs and ethical problems, are the factors argued by some authors to advise against performance of these biopsies.[32]

CHRONIC GRAFT VASCULAR DISEASE (CGVD)

Together with arteriolar hyalinosis, a sign of chronicity and poor graft evolution,[13] CGVD continues to be an objective and specific histological marker of chronic rejection mediated by an immune mechanism.[33] CGVD has traditionally been considered as a characteristic histopathologic lesion of chronic

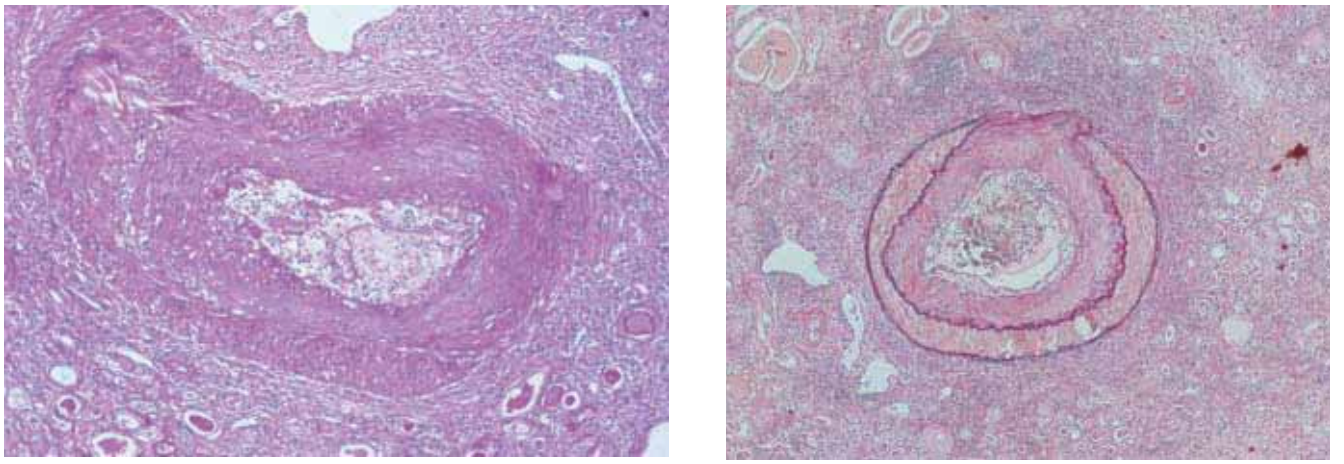

Figure 1. Chronic graft vascular disease. Proliferation of the arterial intima layer not associated with concentric reduplication of the internal elastic lamina (PAS and Verhoeff's stain).

graft rejection, together with transplant glomerulopathy (TG).[34,35] Histopathological features of CGVD include a reduction in vessel lumen size caused by a concentric myointimal proliferation in which a cell component, preferentially consisting of CD3-positive lymphocytes, macrophages, foamy histiocytes, and myofibroblastic cells, is seen[36] (fig. 1). This lesion progresses and becomes more sclerosing, with a trend to an increased luminal occlusion and intimal signs of sclerosis. At this more advanced stage, differential diagnosis with lesions secondary to hypertensive vascular disease and/or advanced atherosclerotic lesions is more difficult. A useful histological key to differentiate both lesions consists of the existence of a concentric, segmental reduplication of the internal elastic lamina in cases of atherosclerosis and/or peripheral vascular disease, which does not occur when the vascular lesion results from CGVD, when the internal elastic lamina remains unchanged. However, it should always be reminded that the vascular lesion is a dynamic event, and chronic vasculopathy lesions of an immune origin may be overlapped with atherosclerotic and/or hypertensive lesions.

In addition to lesion of medium-sized muscular arteries, arteriolar involvement should also be assessed. Arteriolar sclerosis and hyalinosis is a significant histological marker of chronic nephropathy,[13,37] but as occurs with arterial pathology, it may be result from multiple causes, not only atherosclerosis, hypertension, and diabetes, but also calcineurin inhibitor toxicity.

CALCINEURIN INHIBITOR-INDUCED CHRONIC TOXICITY

The continued toxic action of calcineurin inhibitors is one of the main causes of chronic graft failure.[37] Since cyclosporin A (CyA) started to be used as a potent immunosuppressant, multiple histological changes related to the toxicity of this drug class have been reported.[37-40]

Acute toxicity is limited to tubular damage consisting of the presence of microvacuolization of an identical size, hence the term of «isometric» microvacuolisation, and to a slight vascular damage, not always evident at this first stage.[37] Necrosis of arteriolar smooth muscle cells and nodular hyalinosis has been considered as a lesion characteristic of CyA toxicity,[41] but it should be admitted that such hyalinosis is a non-specific finding in itself.

Another histological feature reported consists of interstitial fibrosis and glomerulosclerosis,[38-41] characteristics that are common to chronic renal graft evolution regardless of the cause. In order to identify specific signs that allow for differentiating this toxicity from that due to other causes, it should be noted that there are studies that appear to show that fibrosis induced by CyA shows a lower proportion of collagen III than chronic rejection biopsies.[42] Some authors think that arteriolar hyalinosis is a highly consistent characteristic and the one having a greatest impact on prognosis.[43] By contrast, there are other conclusions not showing a clear relationship between the grade of renal failure and the severity of arteriolar hyalinosis attributed to toxicity.[43]

To sum up, we may conclude that:

1. Histopathological diagnosis of calcineurin inhibitor-induced chronic toxicity is an exclusion diagnosis.
2. In patients with chronic kidney disease, lesions due to nephrotoxicity only are difficult to separate from those caused by atherosclerosis, hypertension, or chronic rejection.
3. Arteriolar hyalinosis, together with glomerulosclerosis, should be considered as poor prognostic criteria not always related to the degree of kidney function impairment.
4. Arteriolar hyalinosis and glomerulosclerosis are the most commonly reported histological lesions.

TRANSPLANT GLOMERULOPATHY (TG)

TG is a histological form of glomerular lesion not previously described in native kidneys, consisting of a diffuse thicke-

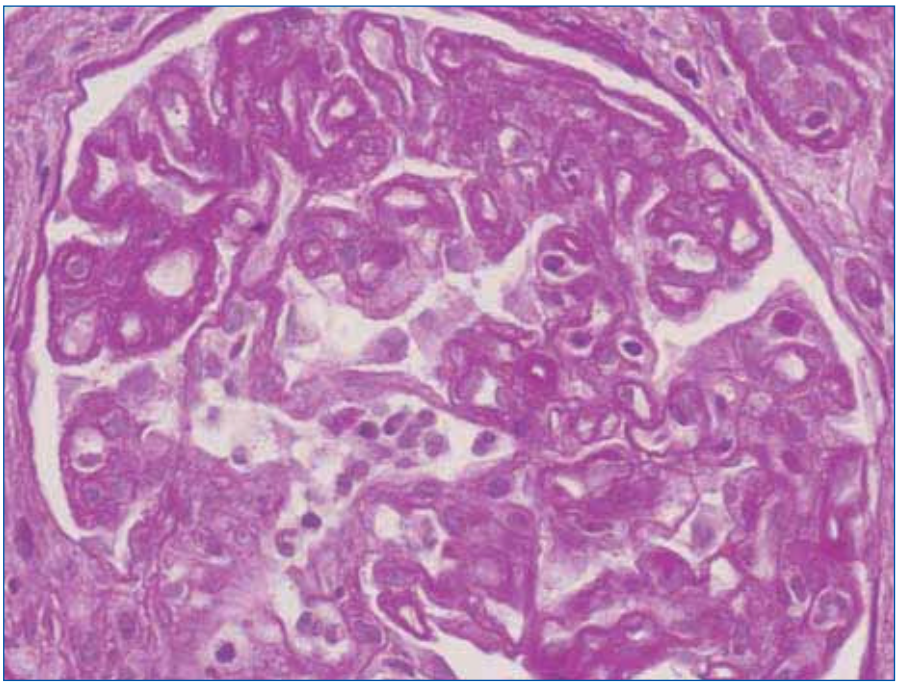

Figure 2. Chronic graft disease. Transplant glomerulopathy. Double contours of the glomerular capillary wall (PAS stain).

ning of the glomerular capillary wall with formation of double contours, basement membrane lamellation, subendothelial electron-lucent area with no or minimal electron-dense deposits, increase and widening of the mesangial space, and finally «mesangiolysis»[34,44,45] (fig. 2).

TG incidence ranges from 7% if all transplant pathology is included and more than 25% if chronic graft disease or patients biopsied after the third month are only analysed.[46,47] In our review of more than 1,114 biopsies from transplant patients accumulated from 1985 to 2008, and including glomerular disease only, TG is the most common and leading glomerular graft disease, including *de novo* and recurrent glomerulonephritis, with an incidence of 37.2%. In some reviews of protocol biopsies in grafts with no impaired kidney function, incidence may be up to 49%.[48] In another review conducted by us of all biopsies from patients with chronic kidney function impairment after the sixth month, TG was found in 11% (personal experience).

One of the main problems for diagnosing TG is its high degree of heterogeneity, as it is common to find in evolved cases coexisting ischaemic glomerular lesions alternating with segmental or global sclerosis in a setting of chronic disease (personal experience).

Because of the presence of double contours in the glomerular basement membrane (GBM), differential diagnosis should consider two very similar conditions, mesangiocapillary glomerulonephritis (MCG, *de novo* or relapsing) and chronic thrombotic microangiopathy (TMA). Differential diagnosis requires a study with electron microscopy and immunofluorescence. MCG is characterised by abundant C·3 deposits located in mesangium and capillary walls, particularly at subendothelial level, that should not be present in TG or TMA, in which deposits are usually focal or absent.[49]

Both with light microscopy and electron microscopy and immunofluorescence, a great similarity exists between TG and chronic TMA, as described in the adult haemolytic uremic syndrome (HUS),[49,50] and both conditions are completely superimposable from the light microscopy, immunofluorescence, and ultrastructural viewpoints. This fact has led to postulate that both conditions may have a common etiopathogenetic mechanism. The most significant differences are multilamellation of the lamina densa in electron microscopic studies in TG[51] and, clinically, the absence of a haemolytic uremic syndrome. However, TMA is not always associated to HUS in series of transplant patients,[52] nor the absence of multilamellation rules out a diagnosis of TG.

Classical studies on MCG pathogenesis[53] reported that endothelial cell necrosis, cleavage, and lesion lead to a regenerative process resulting in formation of a new GBM and GBM reduplication. If a hypothetic «accomodation» phenomenon of the graft to an immune mechanism of repeated, subclinical chronic humoral rejection is accepted, we could also accept the possibility of a phenomenon of «accomodation» and endothelial subclinical lesion not triggering a HUS secondary to endothelial damage. Such «accomodation» events would allow for a chronic evolution of the graft, preventing massive lysis of endothelial cells from being able to trigger complement and coagulation activation as occurs in HUS. To support this hypothesis, a factor H deficiency has been reported in the acute phase of TG, in which a significant endothelial impairment highly superimposable to what occurs in TMA exists. Endothelial damage promoted by T lymphocytes in the acute phase of TG would predispose to intraglomerular platelet aggregation and TMA development.[54]

HUMORAL REJECTION AND RELATIONSHIP WITH TRANSPLANT GLOMERULOPATHY AND CAPILLAROPATHY

Many reports state that factors related to a poor prognosis of renal graft are related to the presence and/or persistence of specific anti-donor antibodies together with histological markers consisting of glomerulitis, capillaritis of the peritubular capillary (PTC), presence of vascular fibrinoid necrosis, and diffuse C4d deposits in PTC (Table II). All these signs are required to be present to diagnose antibody-mediated acute rejection or humoral rejection.[7,14,55,56] In review studies, anti-donor antibodies are detected in up to 96% of patients who have experienced acute rejection, a relationship being found with chronic rejection.[57]

Table II. Acute humoral rejection (Banff, 2005 meeting report. *Am J Transplant* 2007; 7: 518-526)

Grades:
I. Lesions such as acute tubular necrosis, C4d+, minimum inflammation.
II. Capillary margination of white blood cells and/or thrombosis, C4d+.
III. Arterial disease. Severe endothelitis (v3), C4d+.

Table III. Chronic active humoral rejection (Banff, 2005 meeting report. *Am J Transplant* 2007; 7: 521)

a) Double contour of glomerular basement membrane and/or
b) Multilamellation of peritubular capillary basement membrane and/or
c) Interstitial fibrosis/tubular atrophy C4d+ and/or
d) Regular thickening of arterial intima.

TG, whose etiopathogenesis is not well known, has traditionally been considered a glomerular form of chronic rejection.[7] There were already reports relating TG with a humoral mechanism of rejection. In an experimental study conducted in 1994 on different mouse strains to show the type of histological lesion related to anti-donor antibodies, glomerular lesions superimposable to TG were reported.[58] Recent data support the hypothesis of the involvement of an antibody-mediated immune mechanism (humoral rejection) in chronic graft disease and TG.[57-59] This hypothesis is mainly based on the finding of C4d deposits in the basement membrane of the peritubular capillary in 30% to 74% of patients with specific anti-donor antibodies.[60,61] Our own review revealed highly positive C4d deposits in PTC in 10 out of 21 biopsies from 17 patients with TG (personal communication pending publication) (fig. 3). There are studies relating multilamellation of GBM, described as a typical ultrastructural lesion in TG, and PTC[62,63] to C4d deposits and reporting that such deposits preceded TG[64] (fig. 4).

There is thus a connection between humoral rejection and C4d deposits, TG, and capillaropathy supporting a same etiopathogenesis where a primary change in endothelial cells would trigger lesions in the glomerular basement membrane and PTC, including multilamellation. However, while this immune theory is very attractive, it should be noted that a change in the basement membrane of PTC consisting of thickening and «rarefaction» related to an ischaemic mechanism has been reported.[65]

To sum up, after reviewing the literature and in accordance with the Banff criteria for identification of an immune mechanism causing chronic graft failure, we think that the following criteria should be met (table III):

- Presence of specific anti-donor antibodies, and/or
- TG with double contours and/or multilamellation in GBM, and/or
- Significant multilamellation of the PTC basement membrane, and/or
- Chronic vascular disease based on arterial myointimal proliferation, and/or
- Presence of diffuse C4d deposits in PTC.

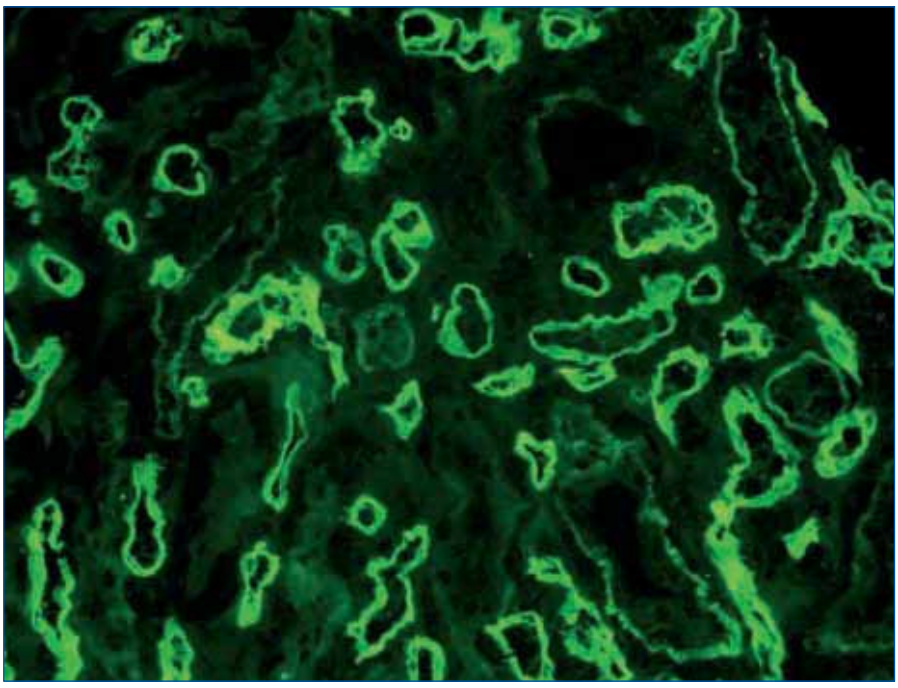

Figure 3. Diffuse C4d deposits in the wall of peritubular capillaries (immunofluorescence technique).

CELL SUBPOPULATIONS IN THE SETTING OF CHRONIC GRAFT DISEASE

Since the early histopathological studies of graft biopsies, an attempt has always been made to correlate the severity and type of inflammatory infiltrate with prognosis. Classical studies reported that severity of such infiltrates and a decreased T4/T8 ratio, as well as changes of this ratio in peripheral blood, involved a poorer prognosis.[66,67] While the T-lymphoid component is the leading element in the histological picture of acute cell rejection, involvement of B cell population, plasma cells, and macrophages, highly correlated to graft prognosis and chronic evolution, cannot be forgotten. Presence of B cells has been associated to a poorer graft prognosis and steroid resistance.[68] Because of the possibility that this type of rejection with predominance of B lymphocytes may be treated with another type of immunosuppressant (rituximab), it could be advisable to study cell subpopulations using immunohistochemistry procedures, particularly in patients with interstitial lymphocyte infiltrates

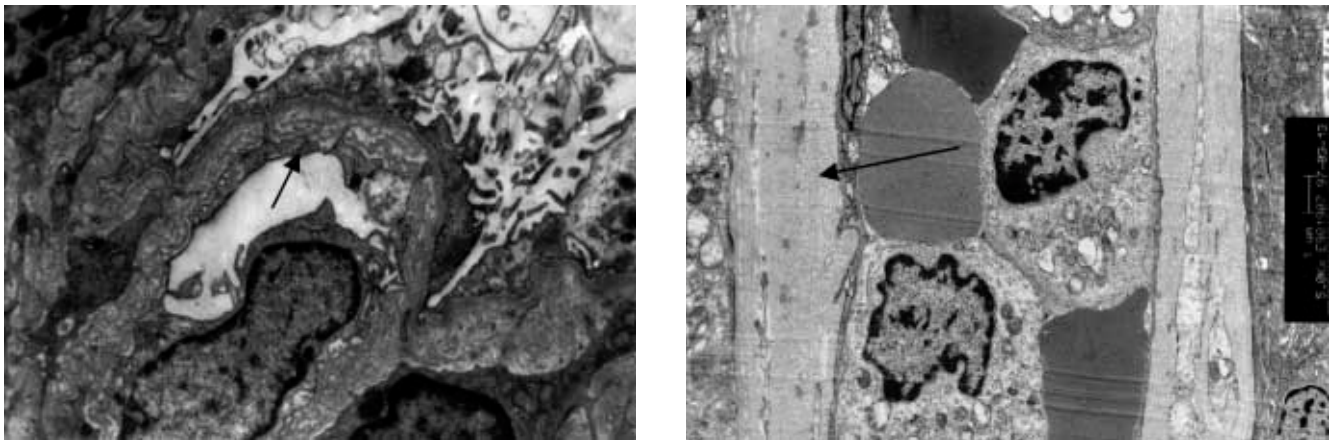

Figure 4. Electron microscopic study of the glomerular capillary basement membrane and a peritubular capillary. Note the thickening and multilamellation (arrow).

resistant to standard immunosuppressive therapy. The correlation of macrophages and plasma cells with a poorer prognosis has already been discussed in the literature, and their presence should be noted in diagnosis or the biopsy report.[7,14,69,70,71] Some authors found, in biopsies taken more than six months after transplant, a relationship between C4d deposits in peritubular capillaries and plasma cell infiltrates in up to 52% of cases, whereas only 13% of biopsies negative for C4d had a population of plasma cells.[72] A comparison of protocol biopsies from two patient populations dependent on immunosuppressive therapy, either cyclosporine A or tacrolimus, showed lower proportions of CD45, CD3, and CD68 in the tacrolimus group.[73]

As regards inflammatory cell populations, it may therefore be concluded that identification of populations rich in CD20 cells, in addition to involving a poorer prognosis, may have an impact on the therapeutic approach. Inflammatory infiltrates with a population of plasma cells and macrophages, particularly after the sixth month, are associated to a poorer prognosis. Finally, there is a clear evidence of the relationship of plasma cell and macrophage populations to humoral rejection, and also to a chronic evolution and a poor prognosis of the graft.

CONCLUSIONS

• CGN should not be used as a diagnostic term because it encompasses multiple histopathological conditions secondary to different immune and non-immune ethiopatogeneses and pathophysiological mechanisms.

• This term should be replaced by a designation describing interstitial fibrosis, tubular atrophy, and glomerular sclerosis when an etiology is not known and an etiopathogenetic mechanism cannot be established.

• Among non-immune factors, inherent donor pathology, particularly vascular lesions, and continued toxic damage induced by calcineurin inhibitors have a preponderant role.

• Transplant glomerulopathy (TG), as well as PTC capillaropathy, chronic vascular disease, and C4d deposits in PTCs, suggest a humoral rejection mechanism mediated by anti-donor antibodies.

• Identification of the type of interstitial inflammatory population associated to chronic lesions is important because of the poor prognosis associated to macrophages and plasma cells.

• The protocol biopsy may predict for graft evolution and allow for early treatment. There is, however, an ongoing controversy about cost/benefit and ethical issues.

• Pathologists facing a biopsy of a transplant patient with chronic kidney function impairment should try and establish the main etiopathogenetic mechanism, for which a C4d study, electron microscopy, and analysis of cell subpopulations in the event of late acute rejection or a poor response to treatment should be performed.

REFERENCES

1. Ponticelli C, Villa M, Cesana B, Montagnino G, Tarantino A. Risk factors for late kidney allograft failure. *Kidney Int* 2002; 62 (5): 1848-54.
2. Matas AJ, Humar A, Gillingham KJ et al. *Kidney Inter* 2002; 62: 704-714.
3. Flechner SM, Modlin CS, Serrano DP, Goldfarb DA, Papajcik D, Mastroianni B, Goormastic M, Novick AC. Determinants of chronic renal allograft rejection in cyclosporine-treated recipients. *Transplantation* 1996; 62 (9): 1235-41.
4. Kreis HA, Ponticelli C. Causes of late renal allograft loss: chronic allograft dysfunction, death, and other factors. *Transplantation* 2001; 71 (11 Supl.): SS5-9.
5. Paul L. Chronic allograft nephropathy: and update. *Kidney Int* 1999; 56: 783-793.
6. Colvin RB. Chronic allograft nephropathy. *N Engl J Med* 2003; 394 (24): 2288-90.
7. Solez K, Colvin RB, Racusen LC, Sis B, Halloran PF, Birk PE, Campbell PM, Cascalho M, Collins AB, Demetris AJ, Drachenberg CB, Gibson IW, Grimm PC, Haas M, Lerut E, Liapis H, Mannon RB, Marcus PB, Mengel M, Mihatsch MJ, Nankivell BJ, Nickeleit V, Papadimitriou JC, Platt JL, Randhawa P, Roberts I, Salinas-Madriga L, Salomon DR, Seron D, Sheaff M, Weening JJ. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy («CAN»). *Am J Transplant* 2007; 7 (3): 518-26.
8. Fellström B, Backman U, Larsson E, Zezina L. Immunologic and nonimmunologic risk factors of chronic rejection. *Transplantation* 2001; 71: SS10-16.
9. Isoniemi H, Taskinen E, Häyry P. Histological chronic allograft damege index accurately predicts chronic renal allograft rejection. *Transplantation* 1994; 58: 1195-1198.
10. Furness P, Taub N, Assmann K et al. International variation in histologic grading is large and persistent feedback does not improve reproductibility. *Am J Surg Pathol* 2003; 27: 805.

11. Furness PN, Philpott CM, Chorbadjian MT, Nicholson ML. Protocol biopsy of the stable renal transplant: a multicenter study of methods and complication rates. *Transplantation* 2003; 76 (6): 969-73.
12. Furness PN. Predicting allograft survival: abundant data, but insufficient knowledge? *Transplantation* 2007; 83 (6): 68.
13. Nankivell BJ, Borrows RJ, Fung CL et al. The natural history of chronic allograft nephropathy. *N Eng J Med* 2003; 349: 2326-33.
14. Solez K, Colvin RB, Racusen LC et al. Banff 07 Classification of Renal Allograft Pathology: Updates and Future Directions. *Am J Transplant* 2008.
15. Pratschke J, Wilhelm MJ, Lusaka M et al. Brain death and its influence on donor organ quality and outcome after transplantation. *Transplantation* 1999; 67: 343-348.
16. Herrero JC, Andrés A, Praga M, Morales E, Domínguez-Gil B, Carreño A, Hernández E, Morales JM. *Transplant Proc* 1999; 31 (6): 2281-2.
17. Terasaki PI, Gjerston DW, Cecka JM et al. Significance of the donor age affect on Kidney transplant. *Clin Transplant* 1997; 11: 366.
18. Pessione F, Cohen S, Durand D, Hourmant M, Kessler M, Legendre C, Mourad G, Noel C, Peraldi MN, Pouteil-Noble C, Tuppin P, Hiesse C. Multivariate analysis of donor risk factors for graft survival in kidney transplantation. *Transplantation* 2003; 75 (3): 361-7.
19. Randhawa P. Role of donor kidney biopsies in renal transplantation. *Trasplantation* 2001; 71: 1361.
20. Remuzzi G, Cravedi P, Perna A, Dimitrov BD, Turturro M, Locatelli G, Rigotti P, Baldan N, Beatini M, Valente U, Scalamogna M, Ruggenenti P. Long-term outcome of renal transplantation from older donors. *N Engl J Med* 2006; 354 (4): 343-52.
21. Moreso F, Serón D, Gil-Vernet S et al. Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients. *Nephrol Dial Transplant* 1999; 14 (4): 930-5.
22. Gaber LW, Moore LW, Alloway RR et al. Glomerulosclerosis as a determinant of posttransplant function of older donor renal allografts. *Transplantation* 1995; 60 (4): 334-9.
23. Karpinski J, Lajoie G, Cattran D et al. Outcome of kidney transplantation from high-risk donors is determined by both structure and function. *Transplantation* 1999; 67 (8): 1162-7.
24. Vázquez-Martul E, Mosquera JM, Rivera CF, Hernández AA, Pertega S. Histological features with clinical impact in chronic allograft nephropathy: review of 66 cases. *Transplant Proc* 2004; 36 (3): 770-1.
25. Seron D, Moreso F. Protocol biopsies in renal transplantation: prognostic value of structural monitoring. *Kidney Int* 2007.
26. Mengel M, Gwinner W, Schwarz A, Bajeski R, Franz I, Brocker V, Becker T, Neipp M, Klempnauer J, Haller H, Kreipe H. Infiltrates in protocol biopsies from renal allografts. *Am J Transplant* 2007; 7 (2): 356-65.
27. Rush DN, Henry SF, Jeffery JR. Histological findings in early routine biopsies of stable renal allograft recipients. *Transplantation* 1994; 57: 208-211.
28. Nankivell BJ, Borrows RJ, Fung CL et al. Delta análisis of postransplantation tubulointerstitial damage. *Transplantation* 2004; 78: 434-441.
29. Shishido SA, Nakai HM, Nakai H. The impact of repeated subclinical acute rejection on the progression of chronic allograft nephropathy. *JASN* 2003; 14: 1046-1052.
30. Saad R, Gritsch HA, Shapiro R et al. Clinical significance of renal allograft biopsies with «borderline changes» as defined in the Banff Schema. *Transplantation* 1997; 64: 992-995.
31. Schweitzer EJ, Drachenberg C, Anderson L et al. Significance of the Banff borderline biopsy. *Am J Kid Dis* 1996; 28: 585-588.
32. Ponticelli C, Banfi G. The case against protocol biopsies. *Transplantation Proc* 2002; 34: 1716-1718.
33. Morris RE. Vascular and cellular mechanisms of chronic renal allograft dysfunction. *Transplantation* 2001; 71: SS 37-41.
34. Habib R, Antingnac C, Hinglais N et al. Glomerular lesions in the transplanted kidney in children *Am J Kidney Dis* 1987; 3: 198-207.
35. Solez K. Internacional standardization of criteria for histologic diagnosis of chronic rejection in renal allografts. *Clin Transplant* 1994; 8: 345-350.
36. Mihatsch MJ, Nickeleit V, Gudat F. Morphologic criteria of chronic renal allograft rejection. *Transplant Proc* 1999; 31: 1295.
37. Nankivell JS, Borrows RS, Gund CL et al. Calcineurin inhibitors nephrotoxicity: longitudinal assesment protocol histology. *Transplantation* 2004; 78: 557.
38. Mihatsch MJ, Kyo M, Morozumi K et al. The side-effects of ciclosporyne A. and tacrolimus. *Clin Nephrol* 1998; 49: 356.
39. Takeda A, Vchida K, Haban T et al. Chronic cyclosporine nephropathy; long term effects of cyclosporine on renal allograft. *Clin Transplant* 2001; (Supl. 5): 22.
40. Falkehain ME, Cosio FG, Sedmak DD. Progressive histologic injury in kidneys from heart and liver transplant recipients receiving cyclosporine. *Transplantation* 1966; 62: 364.
41. Andoh TF, Bennet WM. Chronic cyclosporine nephrotoxicity. *Curr Opin Nephrol Hypertens* 1998; 7: 265-270.
42. Bakker RC, Koop K, Sijpkens YW. Early interstitial accumulation of collagen type I discriminates chronic rejection from chronic cyclosporine nephrotoxicity. *JASN* 2003; 14: 2142-2149.
43. Kambham N, Nagarajan S, Shah S et al. A novel, semiquantitative, clinically correlated calcineurin inhibitor toxicity score for renal allograft biopsies. *Clin Am Soc Nephrol* 2007; 2: 135-142.
44. Maryniak RK, First MR, Weis MA. Transplant glomerulopathy: evolution of morphologically distinct changes. *Kidney Int* 1985; 27: 799.
45. Habib R, Zurowska A, Hinglais N et al. A specific glomerular lesion of the graft: allograft glomerulopathy. *Kidney Int* 1993; SS 104-111.
46. Habib R, Broyer M. Clinical significance of allograft glomerulopathy. *Kidney Int* 1993; 43: S95-8.
47. Gloor JM, Sethi S, Steqall MD et al. Transplant glomerulopathy: subclinical incidence and association with alloantibody. *Am J Transplant* 2007; 7: 2124-2132.
48. Andresdort MB, Assmann KJ, Koene RA et al. Immunohistological and ultastructural diffrerences between recurrent typeI membranoproliferative glomerulonephritis and chronic transplant glomerulopthy. *Am J Kidney Dis* 1998; 32: 582-588.
49. Morel-Maroger L. Adult hemolytic uremic syndrome. *Kidney Int* 1980; 18: 125-134.
50. Vázquez Martul E, Valdés C, Alonso A et al. Síndrome hemolítico urémico del adulto: características histopatológicas, ultrastructurales y de inmunofluorescencia. *Nefrología* 1984; 4: 271-280.
51. Ivanyi B. Transplant capillaropathy and transplant glomerulopathy: ultrastructural markers of chronic renal allograft rejection. *Nephrol Dial Transplant* 2003; 18 (4): 655-60.
52. Baid S, Cosimi AB, Tolkoff-Rubin N, Colvin RB, Williams WW, Pascual M. Renal disease associated with hepatitis C infection after kidney and liver transplantation. *Transplantation* 2000; 70 (2): 255-61.
53. Zamurovic D, Churg J. Idiopathic and secondary mesangiocapillary glomerulonephritis. *Nephron* 1984; 38 (3): 145-53.
54. Fortín MCH, Schürch W, Cardinal H, Hérbert MJ. Complement factor H deficiency in acute allograft glomerulopathy and post-transplant haemolytic uremic syndrome. *Am J Transpl* 2003; 4: 270-273.
55. Racusen LC, Halloran PF, Solez K. Banff 2003 meeting report: new diagnostic insights and standards. *Am J Transplant* 2004; 4 (10): 1562-6.
56. Racusen LC, Haas M. Antibody-mediated rejection in renal allografts: lessons from pathology. *Clin J Am Soc Nephrol* 2006; 1 (3): 415-20.
57. Terasaki. Humoral Theory of Transplantation [Article]. *American Journal of Transplantation* 2003; 3 (6): 665-673.
58. De Heer E, Davidoff A, Van der Wal A et al. Chronic renal allograft rejection in the rat. *Transplantation* 1994; 70: 494-502.
59. Poduval RJ, Kadambi PV, Josephson M, Cohn R et al. Implications of immunohistochemical detection of C4d along peritubular capillaries in late allograft rejection. *Transplantation* 2005; 79 (2): 228-235.
60. Sis B, Campbell PM, Mueller T, Hunter C, Cockfield SM, Cruz J, Meng C, Wishart D, Solez K, Halloran PF. Transplant glomerulopathy, late antibody-mediated rejection and the ABCD tetrad in kidney allograft biopsies for cause. *Am J Transplant* 2007; 7 (7): 1743-52.

61. Regele H, Bohmig GA, Habicht A, Gollowitzer D, Schillinger M, Rockenschaub S, Watschinger B, Kerjaschki D, Exner M. Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: a contribution of humoral immunity to chronic allograft rejection. *J Am Soc Nephrol* 2002; 13 (9): 2371-80.
62. Monga G, Mazzucco G, Motta M et al. Intertubular capillary changes in kidney allografts: a morphologic investigation on 61 renal specimens. *Mod Pathol* 1992; 5: 125-30.
63. Ivanyi B. Transplant capillaropathy and transplant glomerulopathy: ultrastructural markers of chronic renal allograft rejection. *Nephrol Dial Transplant* 2003; 18 (4): 655-60.
64. Aita K, Yamaguchi Y, Horita S, Ohno M. Thickening of the peritubular capillary basement membrane is a useful diagnostic marker of chronic rejection in renal allografts. *Am J Transplant* 2007; 7: 923-929.
65. Basile DP. Rarefaction of peritubular capillaries following ischemic acute renal failure: a potential factor predisposing to progressive nephropathy. *Curr Opin Nephrol Hypertens* 2004; 13 (1): 1-741.
66. Sanfilippo F, Kolbeck PC, Vaugh WK, Bollinger RR. Renal allograft cell infiltrates associated with irreversible rejection. *Transplantation* 1985; 40: 679-684.
67. Stelzer GT, McLeish KR, Lorden RE et al. Alterations in T lymphocyte subpoblations associated with renal allograft rejection. *Transplantation* 1984; 37: 261-264.
68. Kayler LK, Lakkis FG, Morgan C, Basu A et al. Acute cellular rejection with CD20-positive lymphoid clusters in kidney transplant patients following lymphocyte depletion. *AmJ Transplant* 2007; 7: 949- 954.
69. Charney DA, Nadasdy T, Lo AW, Racusen LC. Plasma cell-rich acute renal allograft rejection. *Transplantation* 1999; 68 (6): 791-7.
70. Desvaux D, Le Gouvello S, Pastural M et al. Acute renal allograft rejections with major intertitial oedema and plasma cell-rich infiltrates: hihg gamma interferron expression and poor outcome. *Nephrol Dial Transplant* 2004; 19: 933-939.
71. Colvin RB. Transplant Mac attack: humor the macrophages. *Kidney Int* 2003; 63 (5): 1953-4.
72. Magil AB. Infiltrating cell types in transplant glomerulitis: relationship to peritubular capillary C4d deposition. *Am J Kidney Dis* 2005; 45 (6): 1084-9.
73. Seron D, O'Valle F, Moreso F, Goma M, Hueso M, Grinyo JM, García del Moral R. Immunophenotype of infiltrating cells in protocol renal allograft biopsies from tacrolimus-*versus* cyclosporine-treated patients. *Transplantation* 2007; 83 (5): 649-52.