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## Vascular pathology in the renal transplant

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### Resumen

The availability of any pertinent information about the donor and particularly his/her vessel condition – above all the donor age – is “conditio sine qua non” for the recognition and distinction of the “inherited” donor vascular pathology from the new one acquired within the recipient.

In this paper, immunological mechanisms of Renal Vascular Pathology is reviewed in acute rejection, toxicity and vascular damage, chronic allograft dysfunction and chronic vasculopathy.

### Introduction

The renal vascular system plays a predominant physiological role through its multiple functions, including the vasa recta loop of the Henle countercurrent mechanism, the sodium/chloride exchange, the glomerular filtration and the vasomotor regulation, among others. This multiplicity of functions is reflected in the structural complexity of the vessels, involving the endothelium/intima, the vascular media and the adventitia/perivascular connective tissue associated with the veins and lymphatics as well as the topographic variability within the kidney leading to differences among vessels of the same type in different areas, in addition to the variability between arteries, arterioles and capillaries.

From a pathological point of view the following generalities can be made:

1. All forms of renal vascular pathology are both clinically and histopathologically polymorphic.
2. There are multiple pathogenetic mechanisms leading to renal vascular pathology.
3. There is a multiplicity of clinical syndromes related to vascular pathology often with overlap among them.
4. All vascular lesions follow a dynamic process starting from the acute phase that gradually evolves to the chronic stage. Any histopathological finding is a snapshot along that process and will vary accordingly.

From a histopathological point of view the evaluation of allograft vascular lesions needs to take in consideration and integrate the effects from four different sources on the renal vasculature:

- a. The preexisting donor vascular pathology.
- b. The vascular toxicity of the immunosuppressive treatment.
- c. The immunologically mediated vascular damage.
- d. The vascular damage secondary to other factors of non- immunological nature. These include the effects of ischemia, hypertension, hyperfiltration and chronic inflammatory vascular conditions – the prime example of which is atherosclerosis.

These sources of pathology do overlap at multiple levels within the same patient and at different time points. We can better capture the different sources of vascular pathology, addressing the following points:

1. The donor characteristics: Age, preexisting diseases affecting the vessels, e.g. hypertension, diabetes, etc.
2. The time point of the lesion after transplant. (early vs. intermediate vs. late).
3. The clinical presentation associated with the vascular pathology, e.g. rapidly rising creatinine with ARF vs. slowly deteriorating renal function with or without proteinuria.
4. The histopathological characteristics of the vascular lesions, e.g. endotheliitis, fibrinoid necrosis, hyalinosis or vascular sclerosis, etc.

### Donor Pathology

The availability of any pertinent information about the donor and particularly his/her vessel condition – above all the donor age – is “conditio sine qua non” for the recognition and distinction of the “inherited” donor vascular pathology from the new one acquired within the recipient. It has been amply demonstrated that several donor related factors affect both the immediate as well as the long term function of the graft, e.g. advanced donor age, arterial hypertension, diabetes with vasculopathy, CVA, smoking and asystolic donor deaths. (1, 2).

All of these preexisting donor factors are further complicated by prolonged organ ischemia and immunosuppression with anticalcineurinic agents. From a morphological (semi) quantitative point of view the presence of global glomerulosclerosis > 20%, interstitial fibrosis and above all arterial damage and arteriolar hyalinosis have been considered important not only for predicting the possibility of delayed graft function (DGF) but also as predisposing factors for acute rejection and chronic allograft failure (3) (Fig 1).

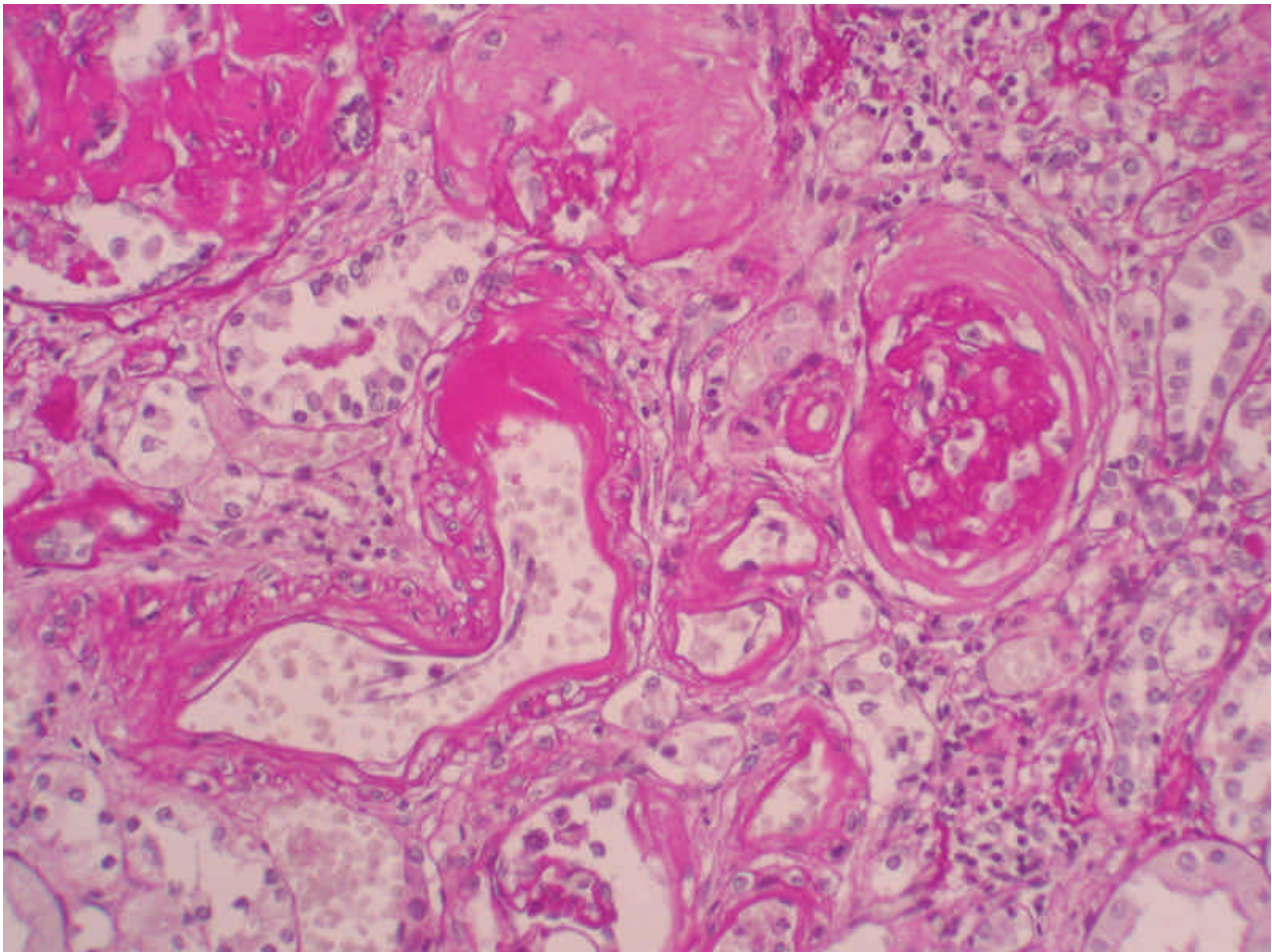


Figure nº 1.- Vascular donor pathology. Arterial sclerosis and hyalinosis arteriolar. PAS.

### Immunological mechanisms of Renal Vascular Pathology

#### Acute rejection.

The Banff schema for diagnosis and grading of acute rejection is focusing in three histopathological features:

1. Presence and degree of tubulitis.
2. Presence and extent of interstitial inflammation.
3. Vascular involvement expressed as endotheliitis or fibrinoid necrosis.

In relationship to vascular damage the acute rejection is differentiated between grade IIA – characterized by mild endotheliitis, grade IIB – characterized by moderate to severe endotheliitis, and grade III – characterized by fibrinoid necrosis. (Fig.2)

All of this – simplistically presented – vascular pathology is not related to a single pathogenetic mechanism. On the one hand the presence of endotheliitis is related to rejection, mediated by T-cells (CD4 and CD8), whereas on the other hand the fibrinoid necrosis is considered as the morphological expression of rejection mediated by antidonor antibodies and resulting Ab-Ag complexes. The endotheliitis and even more the vascular fibrinoid necrosis (grade III) have very significant prognostic value and clinopathological correlating (5-7). Patients with vascular pathology have overall a worse prognosis and particularly when they have fibrinoid necrosis they respond poorly to conventionally immunosuppression. For some authors the presence of arteritis is an independent prognostic factor for the graft loss (6, 7).

The humoral damage of vessels seems to be to a large extent related to circulating immune complexes and some authors have suggested that this mechanism is responsible for 90% of the graft losses and 25-30% of the acute rejection episodes (8).

From a histopathological point of view the problem we are facing is to correctly identify humoral rejection given its great morphological heterogeneity.

The features that are considered most characteristic are: the presence of PMNs in the peritubular capillaries, the presence of glomerulitis and the fibrinoid necrosis of the arterial wall as well as of the glomerular structures(9). The ancillary technique of demonstration of C4d – a classical complement pathway degradation fragment covalently bound in sites of activation– in peritubular capillaries is of great help. If this positivity is diffuse and intense, the diagnostic specificity for humoral rejection reaches 97% (9,10). (Fig.3)

#### Toxicity and vascular damage

– Since the introduction of Cyclosporine A, a potent immunosuppressive agent, a multiplicity of histopathological changes have been

described related to the toxicity of this family of drugs (11). The acute toxicity is centered in tubular damage and consists of the so called "isometric" vacuolization of the latter and secondarily to a mild vascular lesion which is expressed as myocytic vacuolization and/or necrosis. The latter is the precursor of the more chronic phase of this toxicity induced vasculopathy which is expressed as arteriolar hyalinosis – the cardinal feature of this toxicity (12-14). The evaluation of the acute vascular lesions is difficult, particularly the vacuolization of the vascular wall cellular elements. The arteriolar hyalinosis is also difficult to correlate with the degree of drug toxicity, particularly in kidneys with other types of pathology affecting the vasculature. Some authors consider the arteriolar hyalinosis as an exclusive result of chronic drug toxicity, which has a good clinicopathological correlation and is associated with the development of glomerulosclerosis(12) (Fig.4). This is by no means a unanimous conclusion, however, and other studies have failed to show a correlation between the degree of graft failure and the intensity of arteriolar hyalinosis (13).

In summary based on the review of the existing literature, one can say that:

1. The diagnosis of calcineurin inhibitors toxicity is a diagnosis of exclusion.
2. The severity of the nephrotoxicity lesions is not quantitatively related to the administered doses.
3. There is not constant relationship between the histopathological vascular damage and renal function.
4. It is difficult to differentiate between the lesions that are exclusively due to nephrotoxicity and those that represent the sum of diverse pathogenetic influences.

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#### **Chronic allograft dysfunction and chronic vasculopathy**

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The list of factors that have a role in the chronic deterioration of the graft function is long. In order of importance, these include: The chronic vasculopathy, the chronic drug toxicity, the arterial hypertension, the presence of arteriosclerosis, vasculitis and finally the atheroembolic disease, which has been recently considered as an admittedly rare phenomenon but nevertheless related to the development of arteriosclerosis in the graft and a potential cause of early or late graft failure (15, 18). (Fig.5)

The principal problem in the renal biopsy evaluation in the patient with chronic allograft failure is the overlap between vascular lesions of immunological nature and non-immunological processes that may coexist with the former, such as hypertensive damage, clinical nephrotoxicity and above all, the chronic effect of metabolic/inflammatory arteriosclerotic disease.

In the initial phases, but particularly in graft nephrectomies, it is not at all difficult to identify the vasculopathy of the true chronic rejection. It most characteristically involves arteries of medium caliber which show a concentric and symmetric proliferation of myofibroblasts – originating from the subintima – resulting in luminal narrowing. This neointima formation is accompanied by endotheliitis composed mostly of T-lymphocytes, but also sometimes foamy histiocytes and other proliferating macrophages (16) (Fig.6). In more advanced stages or in biopsies with limited number of arteries it is much more difficult to differentiate the immunological damage from the effects of non-immunological factors.

Another aspect of vascular pathology reflecting immunological damage are changes in the peritubular capillaries. The formation of multilamellar basal laminae in these capillaries, together with the chronic arterial vasculopathy and the transplant glomerulopathy have been considered as the specific histopathologic lesions of chronic rejection (19,20) (Fig.7) At experimental level, there has also been described an intense dilatation of the peritubular capillaries – a change that we also have observed, which does not respond to any vasoconstrictor treatment (21). These morphological changes appear to relate to chronic ischemia and to represent a critical and irreversible moment in the renal function (22).

From a morphometric point of view, attempts have been made to identify the histological elements and their changes that characterize the process towards the irreversible failure of the graft. In particular, the arteriolar hyalinosis is a predictive factor of the process to chronicity(23). However, the overall assessment of reproducibility of the histopathological factors indicating chronicity is relatively poor, with kappa values <.04 (24). The evident reason for this difficulty is that in all forms of chronic renal failure the following parameters need to be evaluated objectively: (a) the grade of vasculopathy, (b) the interstitial fibrosis, and (c) the tubular atrophy. These are the same parameters that are affected in chronic failure of the native kidney as well. In order to advance to the maximum degree of objectivity and accuracy one needs to apply judiciously morphometric methods in order to capture all the information inherent in these generalized processes. On the other hand it is necessary to consider the use of electron microscopy for the confirmation of the diagnosis of transplant glomerulopathy and the lamination of the peritubular capillary basement membranes.

Finally we need to take into account the effects immunosuppression and associated pathologies. Bacterial infections, fungal infections, e.g. angioinvasive aspergillosis can affect the intra- and extra-renal vasculature. Viral infections, like BK virus infection (25), but particularly CMV infection, have been considered to play a major role in the chronic vasculopathy in renal and cardiac transplants (26,27). Besides the bacterial, fungal and viral complications, the most constant pathology affecting the transplanted patient is the arteriosclerotic disease (28). In our review of causes of death in patients with renal transplants we found that myocardial infarction was only second after the infectious complications (29).

The longevity of patients on waiting lists and the predisposing factors inherent to chronic renal disease, together with the vasculopathic and hyperlipidemic effects of some immunosuppressive agents place the arteriosclerotic disease in a central pathogenetic role/position in the deterioration not only of the renal graft "per se" but of the transplanted patient in general (28).

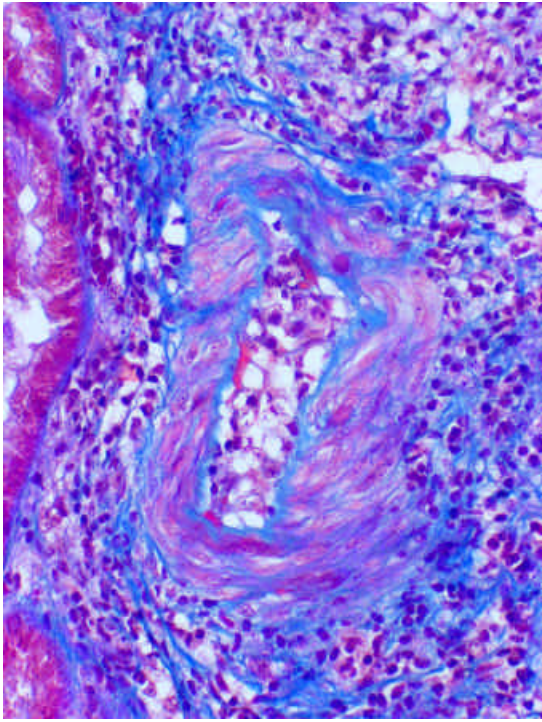


Figure nº 2.- Severe Endothelitis (grade IIB- Banff classification).

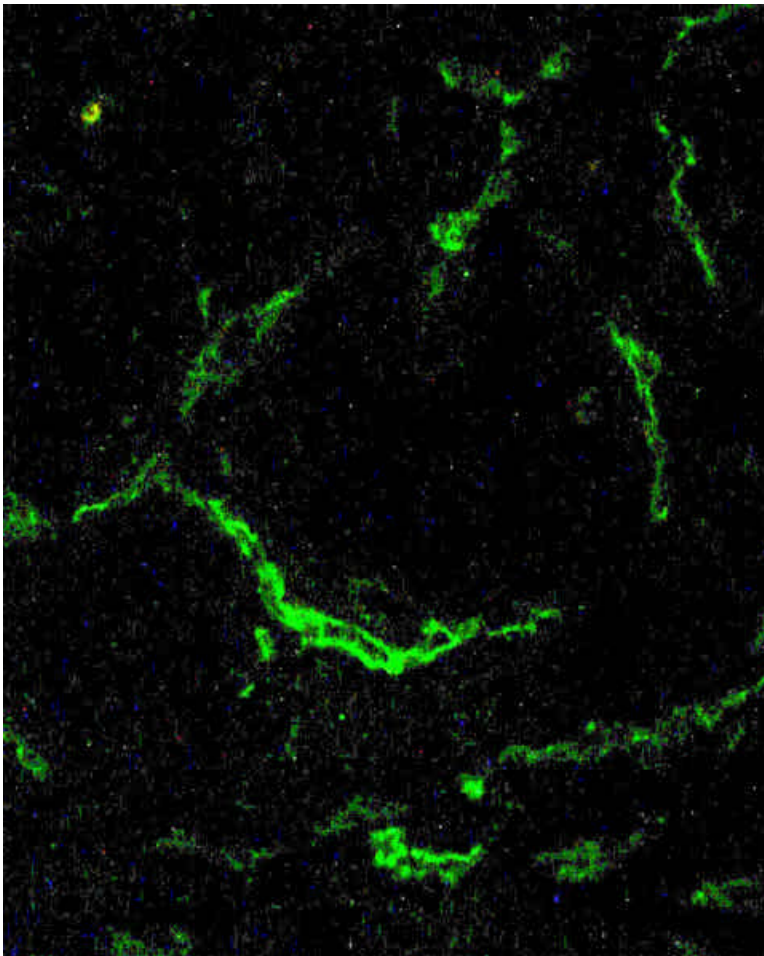


Figure nº 3.- Diffuse and intense C4d positivity.

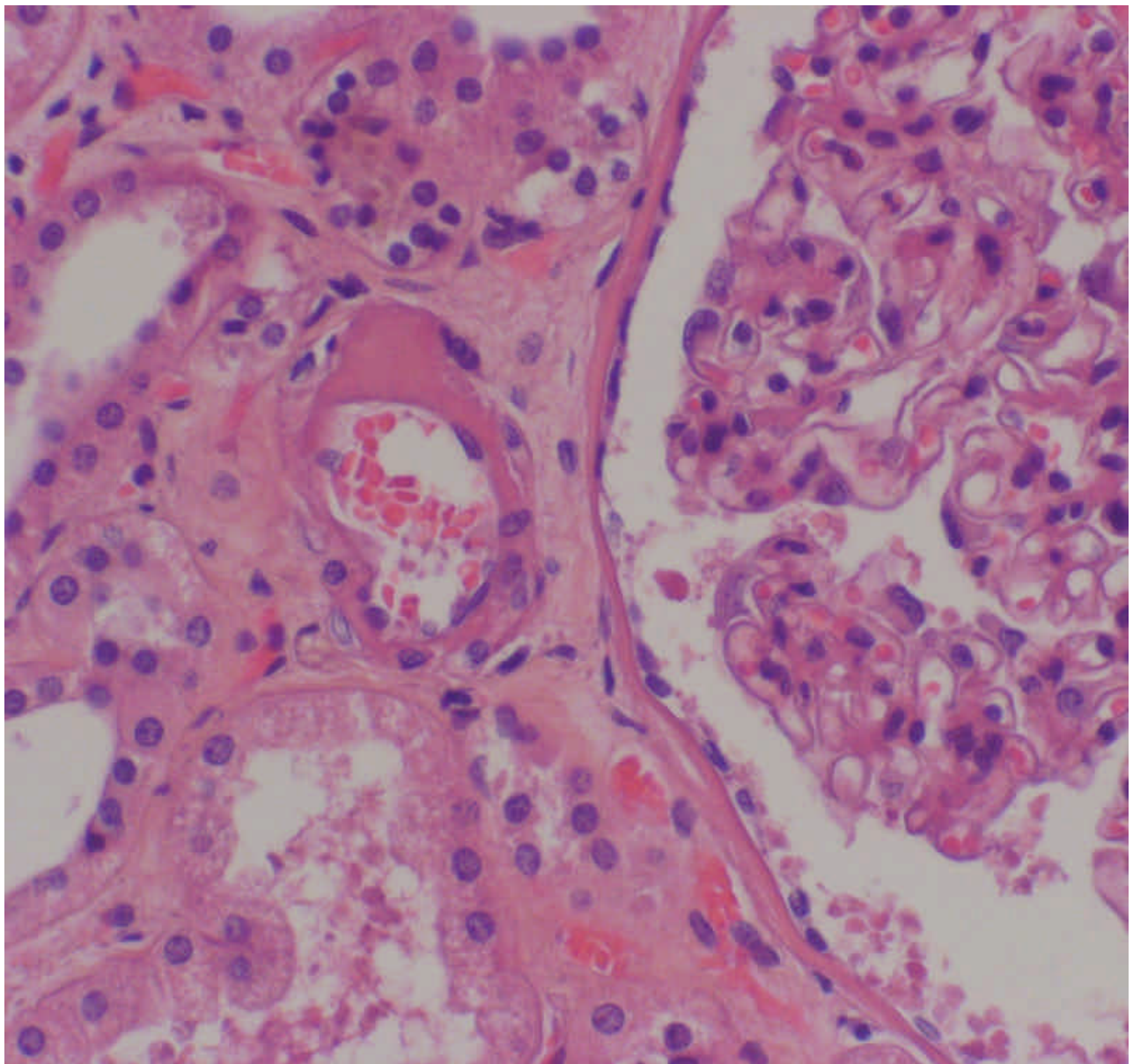


Figure nº 4.- Arteriolar hyalinosis and glomerulosclerosis related with chronic toxicity.

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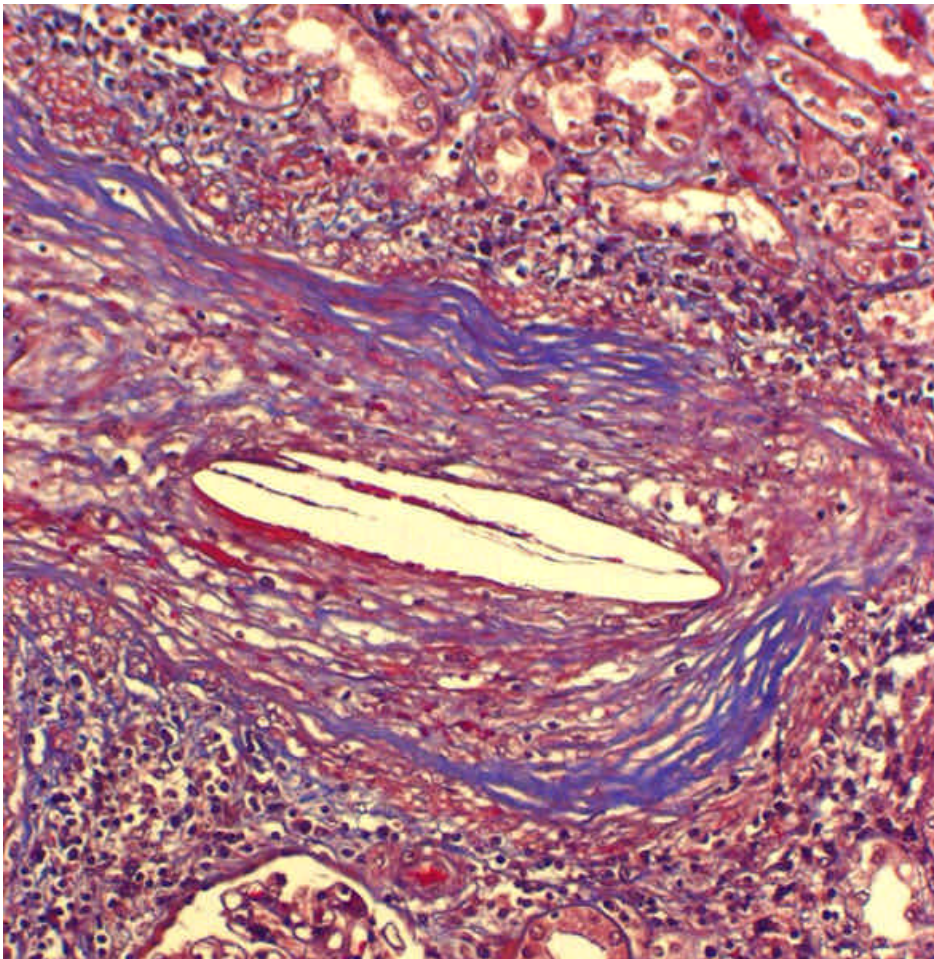


Figure n° 5.- Atheroembolic disease as a cause of allograft lost.

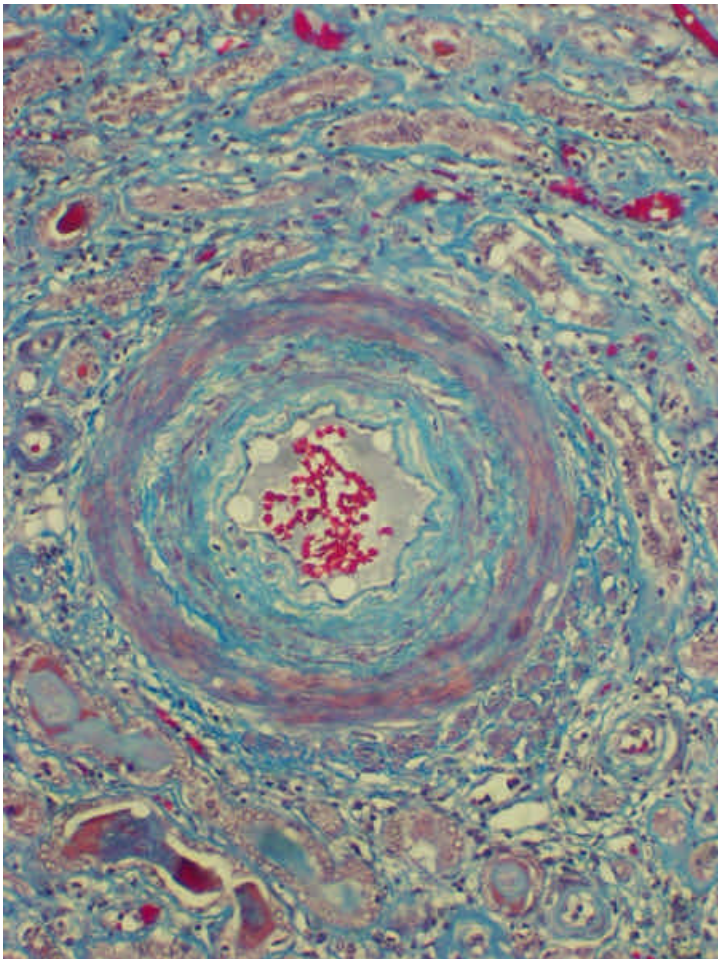


Figure nº 6.- Chronic allograft vasculopathy. Concentric and symmetric proliferation of subintima with luminal narrowing.

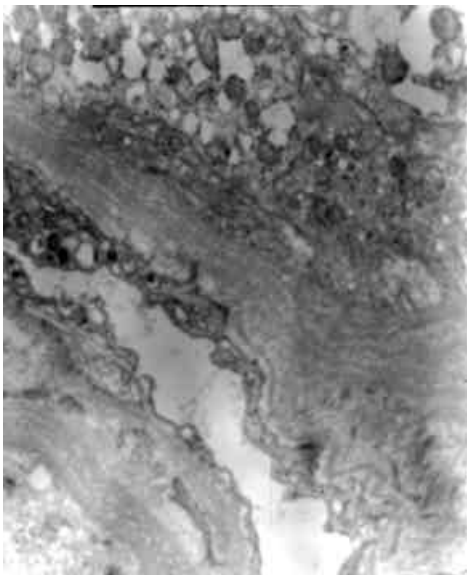


Figure nº 7.- Multilamellar basal laminae in peri-tubular capillaries.

### Conclusions

≠ Vascular Pathology in the donor kidneys particularly those from donors > 65 years old or succumbing to CVA etc., exerts a significant negative impact in the allograft prognosis. It augments the initial ischemic effect, predisposes to acute rejection and accelerates the development of chronic allograft vasculopathy in the graft.

≠ Similarly, in donors experiencing a prolonged asystole, the marked ischemic damage of the vessels can complicate the differential diagnosis from

later acquired lesions such as vascular pathology secondary to humoral immunity or myocyte necrosis in the vascular walls due to toxicity.

- ≠ The vascular damage resulting from acute vascular rejection particularly of Banff types IIB and III represent an independent poor prognostic factor for the graft. The presence of fibrinoid necrosis of the vascular wall and/or thrombotic microangiopathy is highly suggestive of humoral rejection.
- ≠ The histological presentation of chronic allograft vasculopathy in its first phase of evolution characterized by endotheliitis, and concentric subintimal fibrosis, is diagnostic of chronic vascular rejection. On the other hand, in more advanced cases these specific lesions may overlap with arteriosclerotic lesions making the differential diagnosis more problematic.
- ≠ The arteriolar hyalinosis is a lesion associated with calcineurin inhibitor treatment. Although there is a potential temporal relationship between the vasculopathy and the drug administration, there is no absolute correlation between this lesion and deterioration of graft function.
- ≠ The immunosuppressive treatment induces important lipid metabolic changes predisposing to increased arteriosclerotic changes in the allograft biopsies.
- ≠ It is important to consider in the graft vascular pathology the potential recurrence of vasculitis.
- ≠ Recently, pathogenetic consideration has been attributed to additional forms of arteriosclerosis such as the atheroembolic disease, which can lead to graft loss during the early post-transplant periods as well as during the later ones.

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