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Review Article

Arterial and Arteriolar Lesions in Renal Allografts: A Differential Diagnostic Approach

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Abstract

Renal allograft pathology is quite a complex issue and has been addressed in many monographs and book chapters. Renal allografts can fail secondary to rejection, but recurrent renal diseases and de novo diseases affecting the allograft may also contribute to the demise of the transplanted kidney. As a pathologist, one needs to examine the four compartments of the kidney (glomeruli, tubules, interstitium, and vasculature) separately and integrate the histology with the clinical presentation. Although glomerular and tubulointerstitial changes can be quite relevant in terms of renal allograft outcome and prognosis, correct evaluation of arterial/arteriolar changes in a renal allograft is crucial in making the appropriate diagnosis and the arterial/arteriolar changes may provide relevant prognostic information.

The pathologist should very carefully study and describe the vascular changes in a renal allograft and correlate them with clinical findings. If arteries are not present, or if only a single or two small terminal interlobular arteries are seen, the biopsy report should indicate this and draw attention to possible sampling errors and to limited informative value of the specimen.

In this review, we will try to provide a short review on vascular changes in renal allografts with a differential diagnostic approach.

INTRODUCTION

Renal allograft pathology is quite a complex issue and has been addressed in many monographs and book chapters. Renal allografts can fail secondary to rejection, but recurrent renal diseases and de novo diseases affecting the allograft may also contribute to the demise of the transplanted kidney.

As a pathologist, one needs to examine the four compartments of the kidney (glomeruli, tubules, interstitium, and vasculature) separately and integrate the histology with the clinical presentation. Although glomerular and tubulointerstitial changes can be quite relevant in terms of renal allograft outcome and prognosis, perhaps the most important prognostically relevant changes are seen in the vasculature. Vascular pathology can be the result of acute or chronic rejection, but of course other etiologies that can be seen in native kidneys should also be taken into consideration. If the intrarenal arteries show widespread and severe obliterative changes, the oxygen supply to the renal allograft will suffer, and eventually the graft will fail. In this review, we will try to provide a short review on vascular changes in renal allografts with a differential diagnostic approach (Algorithm 1 and 2).

VASCULAR CHANGES SECONDARY TO REJECTION

Acute vascular rejection

Pathologic Change

In the Banff classification, changes of acute vascular rejection are graded as v0, v1, v2, and v3 [1]. V0 means no arterial inflammation. In a v1 lesion, there is mild intimal arteritis with obvious subendothelial

inflammatory cells in the thickened edematous intima, which causes less than 20% luminal compromise (Figure 1A-D). In a v2 lesion, there is prominent intimal arteritis with circumferential involvement of the thickened intima causing over 25% luminal narrowing (Figure 2A-C). In a v3 lesion, there is transmural inflammation of the entire arterial wall; not only the arterial intima is inflamed, but also the smooth muscle layer of the artery. Alternately, if fibrinoid necrosis involves the arterial wall associated with inflammation, the lesion is also graded as v3 (Figure 3A-C). The inflammatory cells in the thickened intima are mainly lymphocytes and macrophages [1]. In severe cases, complete obliteration of the arterial lumen may occur with associated fibrin thrombi. If this happens, anemic infarcts of the renal cortex may develop.

The diagnosis of vascular rejection is easy if renal arteries with characteristic inflammatory lesions are present in the biopsy specimen. However, one has always to consider sampling issues and remember that the distribution of vascular inflammatory lesions within the renal allografts can be somewhat uneven. Therefore, if only one or two cross-sections of unremarkable small arteries are seen in the biopsy specimen, and if other signs of severe rejection, such as interstitial hemorrhage, are seen, one always has to consider a sampling error.

Differential Diagnosis

The histologic signs of acute vascular rejection are quite obvious; the only problematic differential diagnosis can be thrombotic microangiopathy (TMA) with vascular wall necrosis and thrombi (this will be discussed under the heading of TMA). Theoretically, recurrent vasculitis affecting the arteries could also cause inflammation, but in practice this situation is exceptional, and usually other signs of vasculitis (such as crescents) should be evident. Rare cases of cryoglobulinemic vasculitis may develop in renal allografts. In such cases, the presence of glomerular hyaline thrombi with glomerular hypercellularity (mainly intracapillary monocytes/macrophages) helps in the differential diagnosis.

Occasionally, in milder forms of acute rejection, inflammatory cells may be attached to the arterial endothelium. We prefer not to diagnose Banff grade v1 acute vascular rejection in such cases, but again the possibility of sampling error does exist.

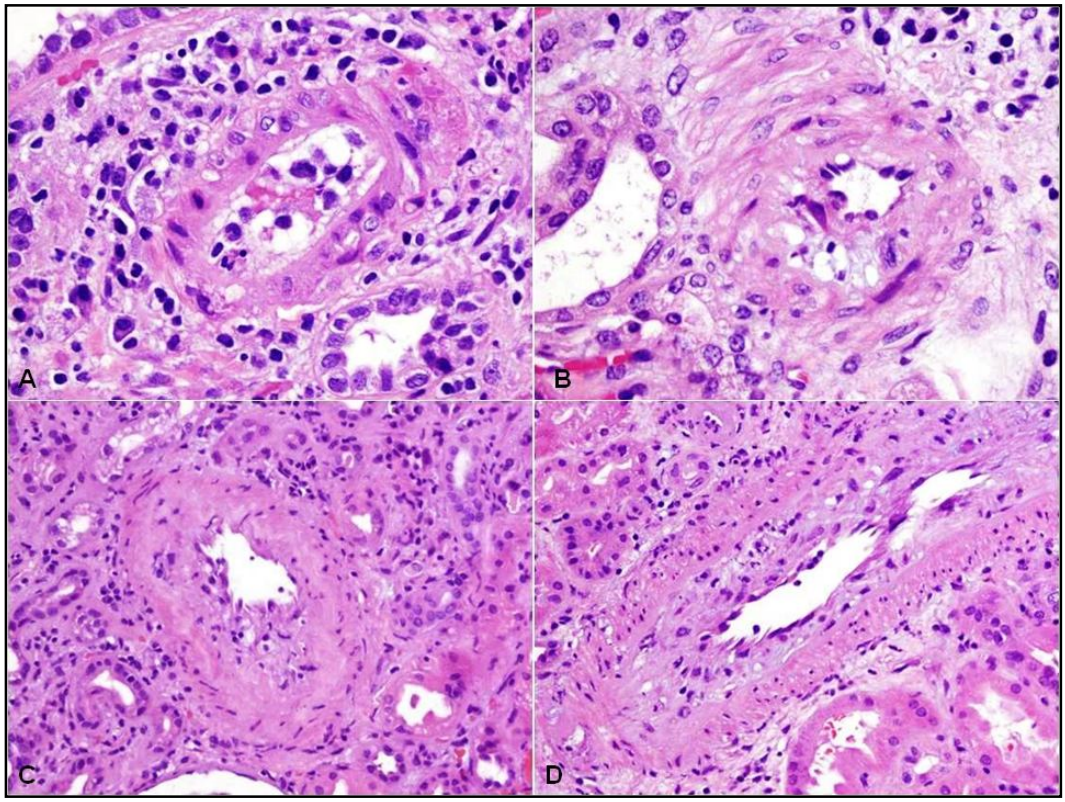


Figure 1: Arterial lesions in Banff Grade IIA renal allograft rejection (v1 lesion), showing mild intimal arteritis with subendothelial inflammatory cells in the thickened edematous intima, causing less than 20% luminal compromise (H&E, x400 for A and B; x200 for C and D).

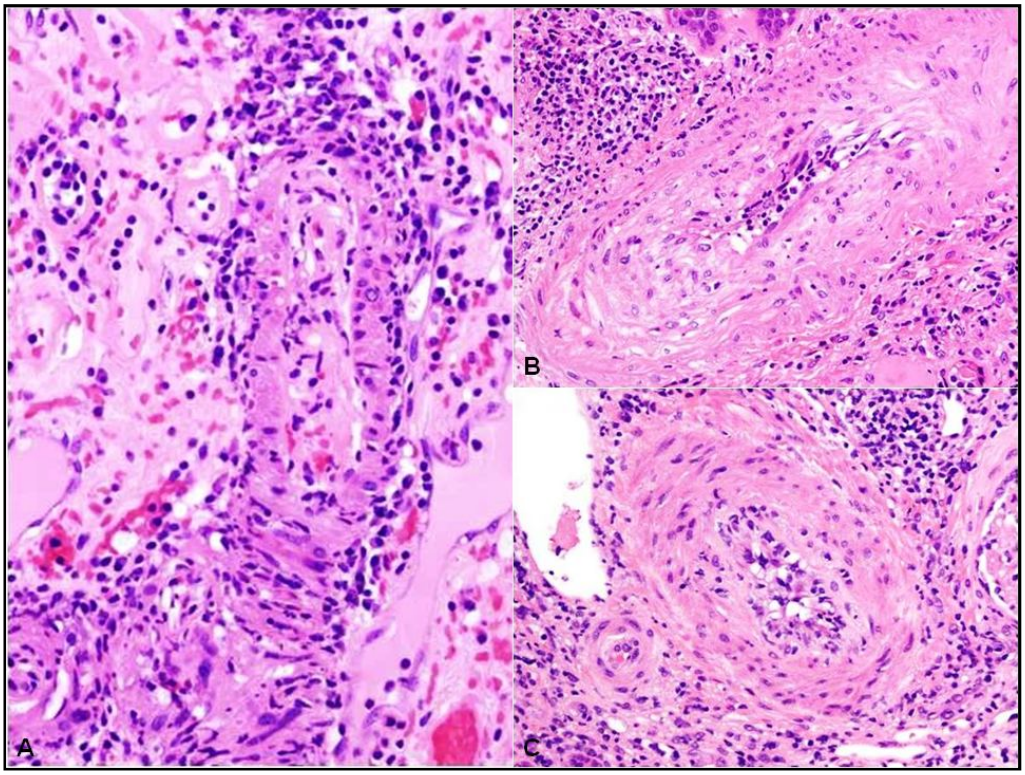


Figure 2: Arterial lesions in Banff Grade IIB renal allograft rejection (v2 lesion), showing prominent intimal arteritis with circumferential involvement of the thickened intima causing over 25% luminal narrowing (H&E, x200 for all).

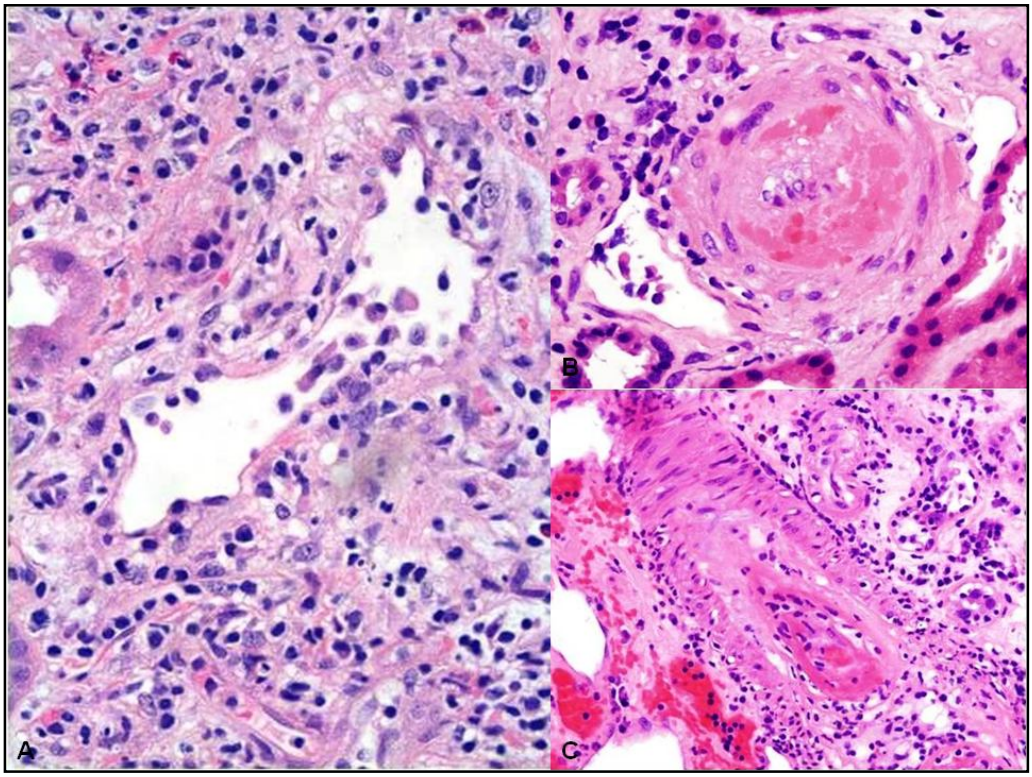


Figure 3: Arterial lesions in Banff Grade III renal allograft rejection (v3 lesion), there is transmural inflammation of the entire arterial wall; not only the intima, but also the smooth muscle layer of the artery. Alternately, there is fibrinoid necrosis involving the arterial wall associated with inflammation. The inflammatory cells in the thickened intima are mainly lymphocytes and macrophages. In severe cases, complete obliteration of the arterial lumen may occur with associated fibrin thrombi (H&E, x400 for A and B; x200 for C).

Pathogenesis

Acute vascular rejection, even Banff grade v3 vascular rejection, can be related both to cellular and antibody-mediated rejection. Although severe v3 vascular lesions with vascular fibrinoid necrosis are more commonly associated with circulating donor-specific antibodies than less severe v1 and v2 vascular lesions, in our experience only approximately 50% of our biopsies with Banff grade v3 lesions have demonstrable circulating donor-specific antibodies and associated peritubular capillary C4d staining. It is possible that the procoagulant activity of the macrophages would induce the fibrinoid necrosis in the vasculature.

Clinical Course and Outcome

Cases with severe acute vascular rejection, particularly with Banff grade v3 acute vascular rejection, show poor response to treatment and have usually a poor long-term outcome [2, 3]. However, a recent paper from Japan on a small series of patients with vascular rejection states that with aggressive antirejection therapy, better outcome is possible [4, 5].

Obliterative transplant arteriopathy in chronic rejection

Pathologic changes

In the Banff classification, arterial fibrointimal thickening (cv) is graded from cv0 to cv3. Obviously, cv0 means normal artery with no fibrous intimal thickening. In cv1, the fibrous intimal thickening causes less than 25% of luminal narrowing. In cv2, the luminal narrowing is between 26-50%. In cv3, over 50% of the lumen is obliterated by the fibrointimal thickening [1]. To determine the percentage of luminal narrowing can be quite difficult and subjective, in our experience. Therefore, we use a slightly different approach [6]. If the intimal thickening does not exceed the thickness of the media, we grade it as mild. If the intimal thickening exceeds the thickness of the media but is less than twice the thickness of the media, we grade it as moderate. If the intimal thickening exceeds twice the thickness of the media, we grade it as severe. It is important to measure media thickness at the point of the artery which is not tangentially cut and is representative. An example of chronic transplant arteriopathy is shown in Figure 4. It is very common to see some infiltrating inflammatory cells in the thickened intima in chronic rejection; however, in burned-out cases, the fibrointimal thickening can be very difficult to distinguish from intimal thickening of nonimmunologic causes (see below). Occasionally, intimal foam cells may be present in the thickened intima. Sometimes in advanced stages of obliterative transplant arteriopathy, a new smooth muscle layer can form in the thickened intima around the narrowed lumen (vessel-in-vessel phenomenon).

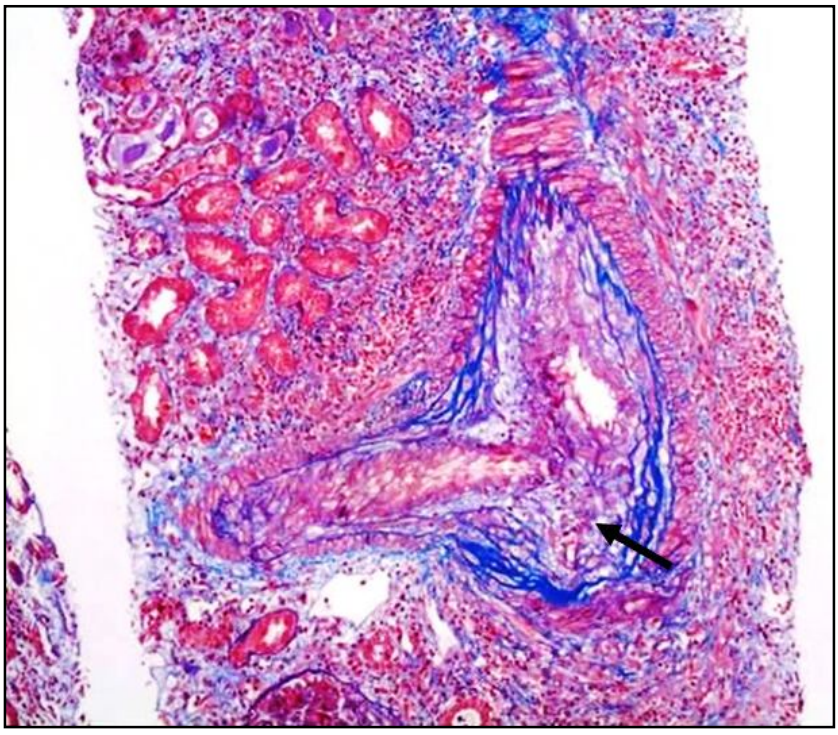


Figure 4: Artery with chronic transplant arteriopathy. There is fibrointimal thickening of the artery (arrow) with few inflammatory cells in the thickened intima (Periodic Acid Schiff – Trichrome stain, x200).

Differential Diagnosis

If there are infiltrating inflammatory cells (usually T cells and macrophages) in the thickened intima, the differential diagnosis is usually easy. However, in older burned-out cases, the appearance of the intimal thickening can be very similar to that of arterial intimal thickening of non-immunological reasons such as hypertension, arteriosclerosis, or chronic-stage TMA (see later sections).

Pathogenesis

As with acute vascular rejection, chronic obliterative transplant arteriopathy can be associated both with cell-mediated and antibody-mediated rejection processes. Well-developed obliterative transplant arteriopathy is rarely seen within the first six months after transplantation, but, in our experience, it may occur particularly in presensitized patients.

Clinical Course and Outcome

Usually, the more prominent the obliterative intimal thickening in the arteries is, the worse the outcome. The presence of active inflammatory cell infiltrate in the thickened intima is an indicator of ongoing, even more progressive active disease process. If such changes are associated with features of antibody-mediated rejection (such as transplant glomerulopathy, peritubular capillaritis, peritubular capillary C4d staining), the progression may be even more rapid.

THROMBOTIC MICROANGIOPATHY (TMA)

The diagnosis of thrombotic microangiopathy (TMA) in renal allografts can be quite difficult; therefore, we will discuss this entity more in detail. TMA is a histopathologic term referring to severe microvascular injury characterized by microvascular thrombi, fibrinoid necrosis of the wall of small arteries, amorphous material admixed with fibrin in the widened subendothelial space and lumina of glomerular capillaries, fragmented red blood cells within the thickened damaged arterial wall and/or glomeruli, and, in later stages, severe mucoid to concentric thickening of the small arteries [7, 8]. Clinically, TMA is associated either with hemolytic-uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) [8-11]. HUS is characterized by nonimmune hemolytic anemia, thrombocytopenia, and renal failure. In TTP, nonimmune hemolytic anemia and thrombocytopenia are associated with central nervous system symptoms rather than renal disease; however, overlaps are common. Most cases of HUS represent the typical form caused by shiga-like toxin-producing E. coli. In typical HUS, the renal disease follows hemorrhagic colitis and diarrhea, and most cases completely recover [9]. In contrast, atypical HUS (aHUS) is a heterogeneous disease complex with a variety of underlying etiologies, and the outcome is usually poor [8-13].

TMA in a renal allograft can either be recurrent or de novo [14]. Most cases of recurrent TMA are related to genetic abnormalities or sometimes autoimmune diseases, whereas de novo TMA is usually secondary to immunosuppressive medications, allograft rejection, and rarely other causes, such as infection. Shiga-like toxin-producing E. coli-associated typical HUS is very rare in renal allografts. In TMA affecting the transplant kidney, systemic signs of HUS are not always present.

Recurrent TMA

It is important to note that recurrent TMA can only be diagnosed if the native kidney disease is correctly diagnosed as TMA. The recurrence rate of TMA in renal allografts is reported to be between 4% and 60% [11, 14-20]. One reason for this wide range could be that different series include TMA cases with different etiologies. Because typical diarrhea-positive, shiga-toxin-like, E. coli-related HUS does not recur in renal allografts, studies including such patients report a low recurrence rate. On the other hand, studies that include only patients with aHUS report recurrence rates around 60% or higher [14, 15].

It appears that patients with aHUS secondary to mutations in complement regulatory genes have a higher incidence of recurrence and also a worse outcome than other forms of TMA. This is particularly true for patients who have complement factor H or complement factor I gene mutations [14, 16, 21, 22]. Mutations in genes encoding complement factor H regulatory proteins, complement factor B, C3, and membrane cofactor protein (MCP) can also be associated with recurrent TMA [14, 22]. Recurrent TMA may also be related to autoantibodies (anti-factor H antibodies, anti-ADAMTS13 antibodies, antiphospholipid antibodies) and autoimmune diseases, such as scleroderma, systemic lupus erythematosus.

De novo TMA

Although TMA has a high recurrence rate in renal allografts, the great majority of transplant TMA is de novo disease. The reported rates of de novo TMA varies from 1.1% to 14% [23]. A recent study, reports only a 1.1% rate of de novo TMA; however, these authors excluded every patient who had some evidence of antibody-mediated rejection [24]. Variable diagnostic criteria (clinical and histologic) may also partially explain these large differences. The great majority of de novo TMA in renal allografts can be attributed either to rejection, drug toxicity, or both. De novo TMA frequently occurs early, within the first month post transplant, but it may also develop later [23-26].

Pathologic changes

The diagnosis relies on the clinical presentation but mainly on renal biopsy findings. Clinical and laboratory findings include thrombocytopenia and evidence of microangiopathic hemolysis, such as presence of schistocytes in the peripheral blood smear, low haptoglobin levels, elevated lactate dehydrogenase (LDH) levels, and decrease in the hematocrit. These laboratory findings may not be present in renal allograft recipients with TMA in the transplant kidney [26].

The gold standard of the diagnosis of TMA in renal allografts still remains the renal biopsy (Figure 5A-D). The characteristic histologic signs include:

- Fibrin/platelet thrombi in arteries/arterioles and/or glomeruli with or without associated fibrinoid necrosis of the vasculature (Figure 5C and D).
- Amorphous material and swollen endothelial cells filling glomerular capillary lumina in numerous glomeruli ("bloodless" glomeruli).
- The presence of fragmented red blood cells within thickened arterial/arteriolar walls or in the amorphous glomerular material, sometimes even in the interstitium.
- Severe mucoid, sometimes concentric thickening of the small arteries/arterioles (Figure 5A and B).

If any of the above four lesions occur prominently, or in combination, in a renal allograft biopsy, we do not hesitate to diagnose TMA.

Unfortunately, in many instances, these changes can be subtle or focal. In a small allograft biopsy specimen with limited amount of renal cortex, the diagnosis of TMA can be missed. We like to see at least four small interlobular arteries, numerous arterioles, and at least 10 glomeruli in two separate biopsy cores before we say that TMA is an unlikely cause of graft dysfunction. Evaluating these histologic changes is somewhat subjective, as diagnostic histopathologic criteria are not established, which is probably at least partially responsible for the wide variation in the reported incidences of de novo TMA in renal allografts. Novel molecular methodologies such as microarray methodology may soon provide quick and detailed workup of the kidney biopsy enabling more disease-specific accurate diagnosis, particularly if correctly interpreted with additional laboratory and clinical data [27, 28].

Differential Diagnosis

Sometimes it can be very difficult distinguishing between acute vascular (Banff grade III) rejection and TMA. Both can be associated with fibrinoid necrosis of the vascular wall and luminal fibrin/platelet thrombi. Endothelial injury secondary to anti-MHC antibodies can be severe enough to induce endothelial and vascular wall necrosis with subsequent thrombosis [29]. However vascular wall necrosis can also occur in severe cellular rejection in the absence of detectable circulating anti-MHC antibodies. If the vascular fibrinoid necrosis and vascular thrombi are associated with other signs of acute rejection, including intimal arteritis, interstitial inflammatory cell infiltrate and tubulitis, we favor the diagnosis of acute rejection. If features of TMA, such as fragmented red blood cells in the vasculature, are also noted, we diagnose acute (Banff grade III) vascular rejection with features of TMA. If other evidence of acute rejection is not seen and the vascular and glomerular changes are consistent with TMA, we do not hesitate to make the diagnosis of TMA involving the renal allograft. In antibody-mediated rejection, the vascular damage can be serious enough to induce morphologic changes of TMA in the absence of obvious morphologic signs of acute cellular rejection [25].

Glomerular changes of active TMA may be helpful in the differential diagnosis; however, there are growing data indicating the overlap of glomerular TMA and transplant glomerulopathy [30, 31]. Baid-Agrawal et al. [31] reviewed 25 renal allograft biopsies which met morphologic criteria of transplant glomerulopathy, and 32% of them had evidence of TMA [32]. The glomerular changes in chronic-stage glomerular TMA and transplant glomerulopathy probably reflect a common pathogenic pathway, with endothelial damage due to a variety of antibodies and changes in prothrombotic and antithrombotic activities in the microcirculation [29, 30, 33].

Pathogenesis

Calcineurin Inhibitors

It is widely accepted that cyclosporine and tacrolimus are associated with de novo TMA in renal allografts [34-38]. Calcineurin inhibitors cause arteriolar vasoconstriction probably through multiple mechanisms, including upregulation of endothelin and thromboxane and downregulation of vasodilators [such as prostaglandin and nitric oxide]. Increased procoagulant activity may also play a role [38-40].

mTOR Inhibitors

There is increasing evidence that mTOR inhibitors, including sirolimus and everolimus, can be associated with post-transplant de novo TMA [23, 41]. After a review of USRDS database, Reynolds et al. [23] found that the incidence of TMA was 18.1 episodes/1000 person-years in patients on initial maintenance therapy with sirolimus versus 5.0 episodes/1000 person-years

in patients who were on calcineurin inhibitors [23]. Le Quintrec et al. [22] report that patients on mTOR inhibitor-based immunosuppression have a significantly higher risk for recurrence of aHUS than patients on calcineurin inhibitor-based treatment. These studies suggest that mTOR inhibitors are more commonly associated with de novo TMA in renal allografts than calcineurin inhibitors. MTOR inhibitors, inhibit endothelial cell proliferation and delay reendothelialization of vascular stents [42-44], theoretically delaying endothelial regeneration in the microvasculature.

Antibody Mediated Rejection

Donor-specific antibody-mediated endothelial injury can be associated with TMA in renal allografts [14, 25, 45]. We reviewed a six-year period at our institution and identified 59 patients with de novo TMA in their renal allografts. In 55% of them, the biopsy showed peritubular capillary C4d staining, and in 84% of these, circulating anti-MHC antibodies were detectable at the time of the biopsy [25]. Meehan et al. [45] from the University of Chicago identified 37 renal allograft biopsies with TMA, and six of them (16.2%) had peritubular capillary C4d staining. This is a substantially lower incidence however, both Meehan et al. and our group agree that antibody mediated rejection-associated TMA cases in renal allografts have worse outcome than antibody-mediated rejection alone without evidence of TMA [25, 45].

Other Etiologies

Rarely, de novo TMA in renal allografts has been associated with hepatitis C virus infection and anticardiolipin antibodies [32, 46, 47], pregnancy [48], parvovirus B19 infection [49-51], and cytomegalovirus infection [52, 53]. It is likely that uncontrolled hypertension may contribute to severe vascular damage with features of TMA. Coagulation abnormalities, including antiphospholipid antibodies, may also present a risk [13, 32, 46, 47]. Le Quintrec et al. [54] examined 24 kidney transplant recipients with de novo TMA. Seven of the 24 patients (29%) had mutations in the gene encoding factor H or factor I. Therefore, patients who have subclinical complement regulatory gene abnormalities may be at high risk for de novo TMA in the renal allografts.

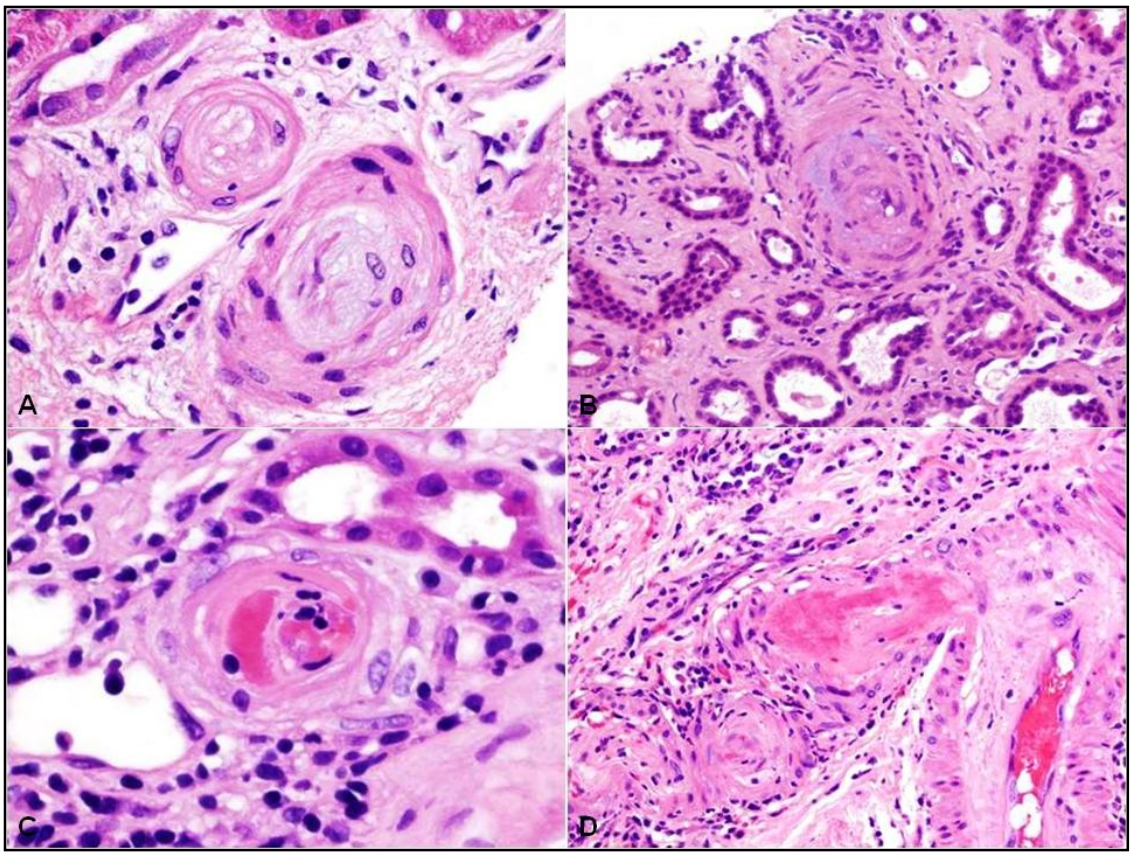


Figure 5: Thrombotic microangiopathy (TMA). Associated with a spectrum of histologic features. A and B (H&E, x400) show mucoid intimal thickening with obliteration of arterial lumina. C and D (H&E, x400 and x200 respectively) show fibrinoid necrosis of the intima with inflammatory cells and obliteration of the lumina.

Clinical Course and Outcome

Most cases of recurrent TMA are diagnosed within the first month of transplantation [14, 15]. Occasionally TMA may reappear within days, but sometimes the recurrence is delayed and can happen up to two years following transplantation. Graft outcome is poor; according to one review, 91.6% of patients with recurrent TMA secondary to aHUS developed graft failure within a year [15]. Recent data indicate that Eculizumab, a monoclonal antibody that blocks C5, can effectively treat complement regulatory protein deficiency associated TMA [55]. In de novo TMA the underlying etiologic factor should be eliminated, if possible. If the TMA is related to immunosuppressive medications (calcineurin inhibitors or mTor inhibitors) the drug should be stopped. In antibody mediated rejection-associated TMA treating the rejection (e.g., plasmapheresis and IVIg) can be effective [25]. Although successful treatment of de novo TMA is possible, the prognosis is still poor.

OBLITERATIVE ARTERIAL CHANGES OF OTHER ETIOLOGIES

Variable degree of fibrous intimal thickening is a common finding in renal allografts and could be related to hypertension, arteriosclerotic lesions, or chronic graft ischemia secondary to main renal artery stenosis (adaptive intimal thickening in the renal arteries). Such changes may develop in the post-transplant period, but it is not unusual that arterial intimal thickening is already present in the donor kidney, particularly if the donation is cadaveric. Performing a baseline kidney biopsy during the transplant surgery can be important to decide whether arterial obliterative changes were already present in the donor; however, many times the baseline allograft biopsy is a superficial wedge and does not contain at least arcuate sized arteries, which are usually present in a somewhat deeper renal cortex. Performing baseline biopsies with a biopsy needle is more preferable, but most surgeons find it easier performing the biopsy with the scalpel during surgery.

It is practically impossible to differentiate intimal thickening not related to chronic transplant rejection to intimal thickening secondary to inactive chronic rejection if the intima does not contain inflammatory cells. In such instances, previous episodes of acute rejection, circulating donor-specific antibodies, presence of transplant glomerulopathy may provide a clue that at least some of the intimal thickening could be related to true chronic rejection.

Occasionally, cholesterol emboli may occur in renal allografts [56, 57]. Cholesterol emboli in the renal allografts may develop at the time of the transplant surgery and may originate from the donor or from the recipient if the recipient as atherosclerotic iliac artery. Based on our limited experience, we found that if the cholesterol embolization is coming from the recipient, graft survival may not be so dismal [56]. Obviously, cholesterol embolization may be overlooked in a kidney biopsy specimen because of sampling issues. Rarely, thromboemboli may also develop in renal allografts, particularly if the patient has atrial fibrillation or a coagulation abnormality. Thromboemboli usually get stuck in arcuate-sized arteries and undergo recanalization. They should not be mistaken as thrombotic microangiopathy. In thromboemboli, usually the underlying endothelium is intact, at least initially.

As mentioned above, recurrent vasculitis in the renal allograft is exceptionally rare, and if inflammatory lesions are present in an artery, acute vascular rejection should be the primary consideration.

ARTERIOLAR CHANGES IN RENAL ALLOGRAFTS

Although, strictly taken, arterioles are not arteries, it is difficult not to discuss arteriolar changes briefly in the context of a review describing arterial pathology in renal allografts. Afferent arterioles connect the interlobular arteries to the glomeruli; therefore they will be affected by many changes involving the intrarenal arteries. Arterioles do not have an internal elastic membrane, therefore, a well-formed intima. Because of these structural differences between an artery and the arteriole, there will be some differences in the pattern of injury induced by a given pathogenetic factor (E.g. arterioles have no intimal arteritis, but endothelial injury/dysfunction in the arterioles is frequently associated with the deposition of “thick” lipid rich proteinaceous material inspissated from the serum [hyalin] between the arteriolar smooth muscles). A simplified differential diagnostic approach to arteriolar lesions in renal allografts is provided in Algorithm 2.

Because of the structural differences from arteries and probably because of the small size of the arteriole, arteriolar inflammatory changes in acute rejection are rare, but in severe forms of acute vascular rejection, arteriolar necrosis associated with some inflammation may develop. In contrast, in TMA, arteriolar changes are usually prominent with arteriolar fibrin thrombi frequently associated with arteriolar wall necrosis but with no inflammation.

In chronic calcineurin inhibitor nephrotoxicity, the arterioles can display a peculiar form of nodular hyaline change localized primarily to the periphery of the arterioles (Figure 6) [34, 58, 59]. Mucoid thickening of the arterioles is also a common finding in chronic calcineurin inhibitor nephrotoxicity. Circumferential hyaline change in the arterioles may

also occur in chronic calcineurin inhibitor nephrotoxicity; however, this type of hyaline change is quite nonspecific and may be seen frequently in patients with diabetes, hyperlipidemia, and hypertension. Performing a baseline allograft biopsy at the time of transplantation can be very helpful in evaluating the arteries because some degree of arteriolar hyaline change is commonly found already in donor kidney biopsies, and in such instances the arteriolar hyaline should not be interpreted as a characteristic sign of chronic calcineurin inhibitor nephrotoxicity.

Concentric thickening of the arterioles or prominent mucoid thickening of the arterioles may happen in chronic-stage TMA secondary to any etiology (including de novo or recurrent TMA in renal allografts).

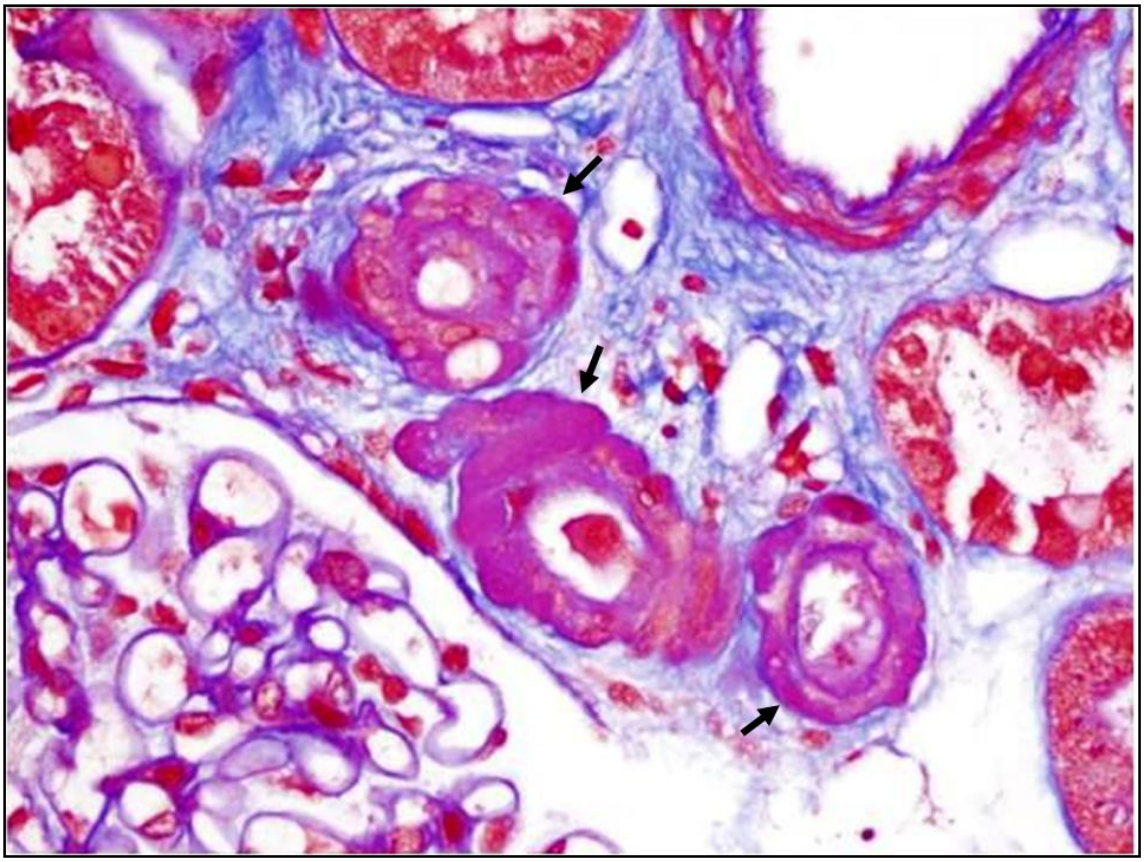


Figure 6: Nodular arteriolar hyaline deposits along the outer circumfernce of the arterioles (arrows) frequently seen in association with chronic calcineurin-inhibitor toxicity (Periodic acid Schiff - Trichrome stain, x400).

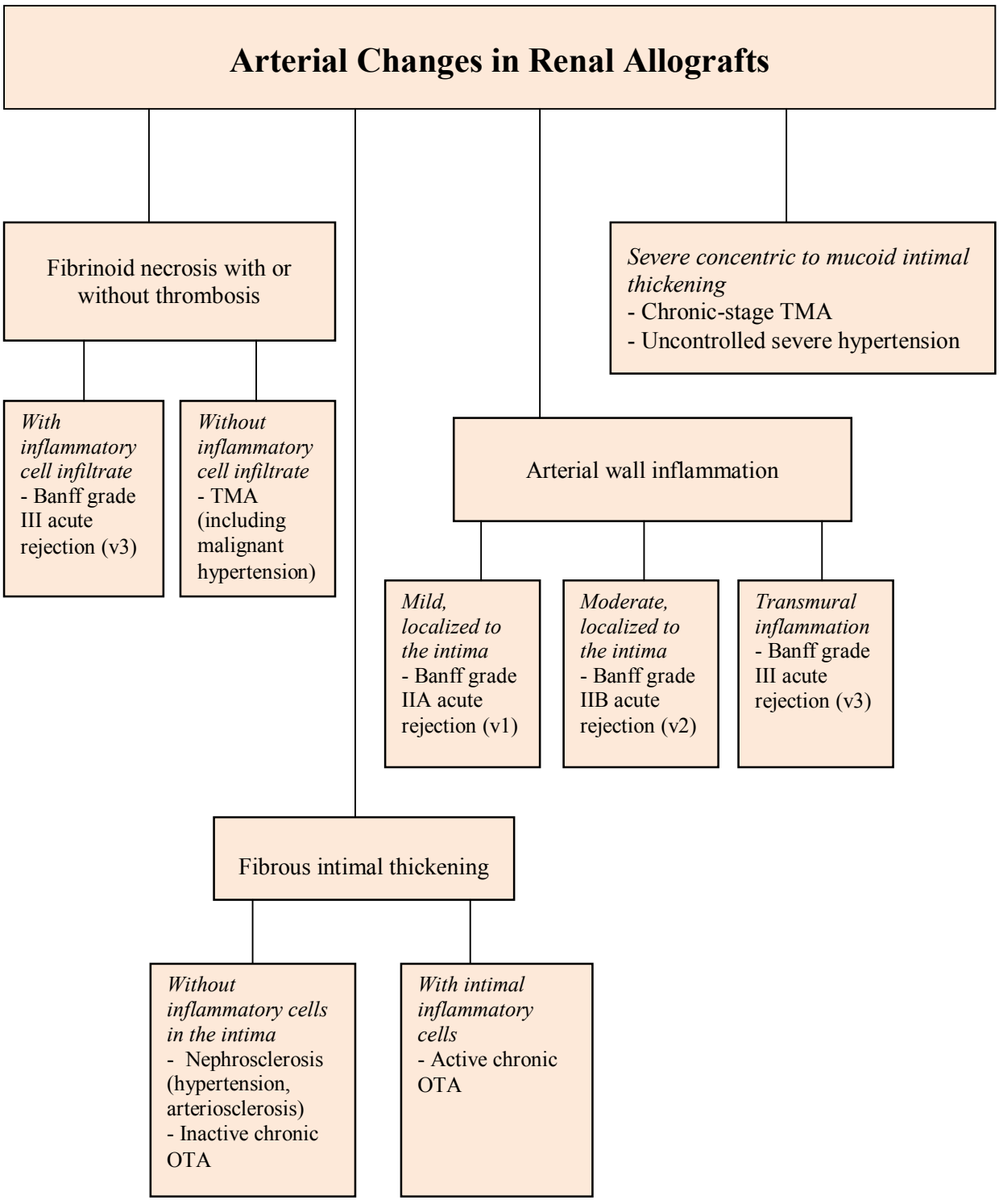
CONCLUSION

Correct evaluation of arterial/arteriolar changes in a renal allograft is crucial in making the appropriate diagnosis and the arterial/arteriolar changes may provide relevant prognostic information. The pathologist should very carefully study and describe the vascular changes in a renal allograft and correlate them with clinical findings. If arteries are not present, or if only a single or two small terminal interlobular arteries are seen, the biopsy report should indicate this and draw attention to possible sampling errors and to limited informative value of the specimen.

CONFLICTS OF INTEREST

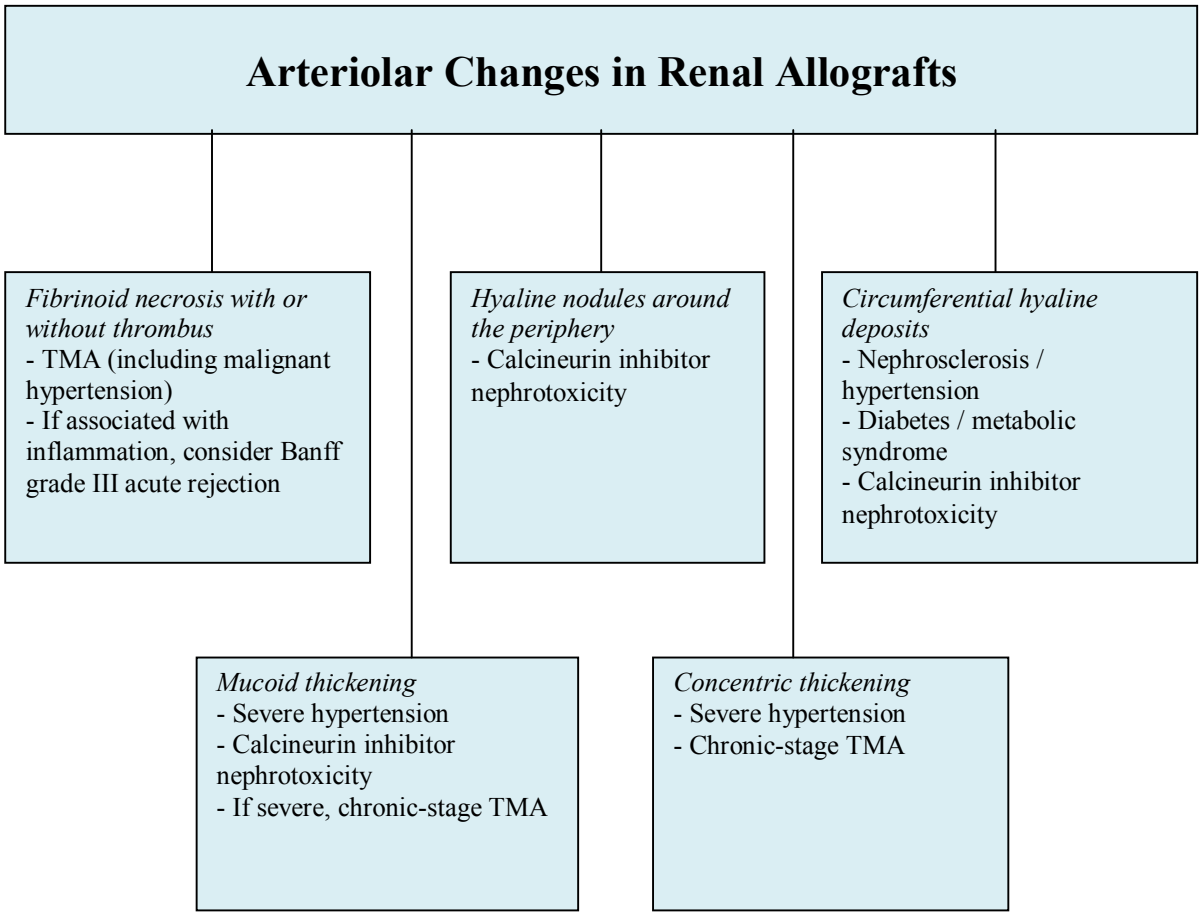
The authors declare that they have no conflict of interest.

Algorithm 1



TMA: thrombotic microangiopathy; OTA: obliterative transplant arteriopathy

Algorithm 2


Arteriolar Changes in Renal Allografts
Fibrinoid necrosis with or without thrombus
- TMA (including malignant hypertension)
- If associated with inflammation, consider Banff grade III acute rejection
Hyaline nodules around the periphery
- Calcineurin inhibitor nephrotoxicity
Circumferential hyaline deposits
- Nephrosclerosis / hypertension
- Diabetes / metabolic syndrome
- Calcineurin inhibitor nephrotoxicity
Mucoid thickening
- Severe hypertension
- Calcineurin inhibitor nephrotoxicity
- If severe, chronic-stage TMA
Concentric thickening
- Severe hypertension
- Chronic-stage TMA

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