Kidney Pathology Series: Kidney Transplant

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Kidney allograft interstitial fibrosis and tubular atrophy (IFTA) due to specific causes: Chronic calcineurin inhibitor toxicity

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Chronic scarring in the graft parenchyma represents the most formidable challenge to the field of kidney transplantation. In fact, in most of the studies, it has emerged as one of the most prevalent causes of late graft loss. Chronic changes in the graft result from a variety of causes including both alloimmune and non-immune factors (Table 1). A complex and often synergistic interaction among these complicates the matter further. Often, more than one causes contribute to chronic injury to the graft. It is important to identify all causes and their relative contributions to graft scarring if these are to be treated effectively. The role of graft biopsy and renal transplant pathologist is very important in this context. All of the specific causes of IF/TA can and should be recognized by the pathologist (Table 2). While some investigators argue that the renal allograft biopsy is not useful in analyzing graft dysfunction after 1 year, published literature reveals that the allograft biopsy leads to a change in management that improved renal function in 8% to 38% of patients.

Chronic changes due to rejection were discussed previously in relevant categories of Banff classification in this Banff tutorial. Chronic non-specific category of chronic changes (IFTA, NOS) was discussed in the preceding issue of this journal.

In this issue, we discuss again the chronic changes caused by certain specific forms of allograft injury, eg. hypertension, calcineurin inhibitor toxicity, etc. This may result in some repetition of material, but given the importance of chronic scarring of the graft, it is worthwhile to do so.

Table 1. Common specific causes of chronic allograft dysfunction

Chronic alloimmune rejection
T cell mediated
Antibody mediated
Chronic calcineurin inhibitor toxicity
Infection (e.g., polyomavirus nephropathy)
Development of recurrent glomerular or other diseases
Development of de novo diseases (e.g., diabetic nephropathy)
De novo arteriosclerosis (hypertensive vascular disease)
Renal artery stenosis
Progression of donor disease (arteriosclerosis, fibrosis)

Chronic calcineurin inhibitor (CNI) toxicity

The long-term effects of CNI on the renal allograft are nonspecific renal scarring with interstitial fibrosis, tubular atrophy (IFTA), which may be either "stripped" ischemic or diffuse in distribution, glomerulosclerosis and arteriolar hyalinosis. A definite diagnosis of chronic CNI toxicity is rarely made on renal allograft core biopsies alone but some features can help in raising suspicion of CNI toxicity as a possible cause of chronic graft injury. These features include the following:

Table 2. Morphological features of specific diseases excluding alloimmune rejection causing chronic fibrosing changes in the kidney allograft.

Specific diseases	Morphologic features
Calcineurin inhibitor toxicity	New onset transmural nodular arteriolar hyalinosis and/or progressive increase in the absence of hypertension or diabetes. Medial vacuolization of arterioles. Tubular cell injury with isometric vacuolization, dystrophic calcification. IFTA with stripped or diffuse fibrosis.
Chronic hypertension	Fibrointimal thickening of arteries with reduplication of internal elastic lamina (fibroelastosis). IFTA.
Bacterial pyelonephritis	Intratubular and peritubular neutrophils, lymphoid follicle formation, and plasma cells.
Viral infection	Chronic interstitial inflammation and fibrosis. Viral inclusions on light microscopy and immunohistochemistry and/or electron microscopy.
Chronic obstruction	Relative glomerular sparing, atubular glomeruli. Marked tubular dilation. Large Tamm – Horsfall protein casts with extravasation into interstitium.
Recurrent/de novo glomerulopathies	Specific pathological features in the glomeruli.

Arteriolar hyalinosis:

Arteriolar hyalinosis (Figures 1, 2) is common in chronic CNI toxicity but in isolation is not specific. Features suggesting that it represents CNI toxicity include (1) new onset of arteriolar hyalinosis, and (2) a nodular, transmural and eccentric pattern, in the absence of significant preexisting donor injury, diabetes mellitus, or hypertension. In the latter two entities, arteriolar hyalinosis is more subendothelial in location and circumferential in distribution, and may involve arteries and arterioles. Another morphological feature that is also commonly seen in CNI toxicity consists of medial vacuolization of smooth muscle cells in arteriolar wall (Figure 3).

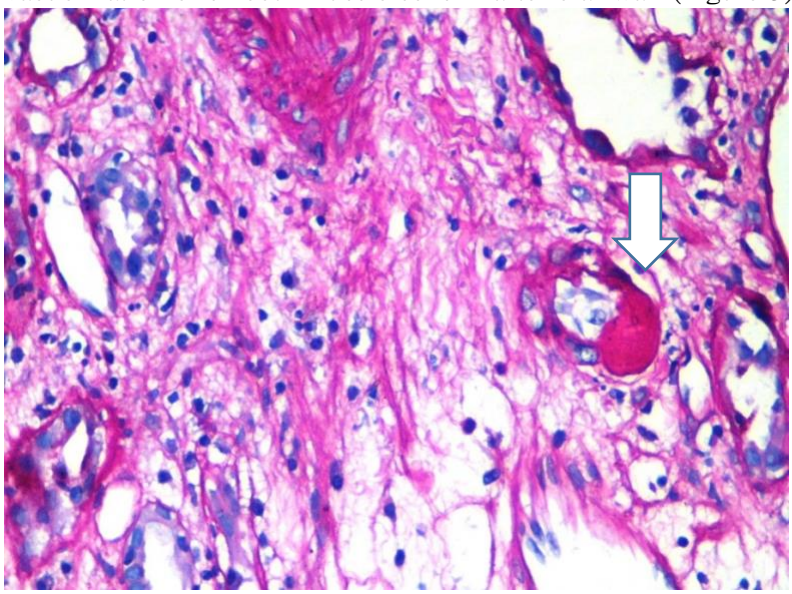

Figure 1. Morphological features suggestive of calcineurin inhibitor (CNI) toxicity. A nodular arteriolar hyalinosis (arrow) is strongly suggestive of CNI toxicity. In the background, interstitial fibrosis can be seen (Periodic acid-Schiff (PAS) stain, ×400).

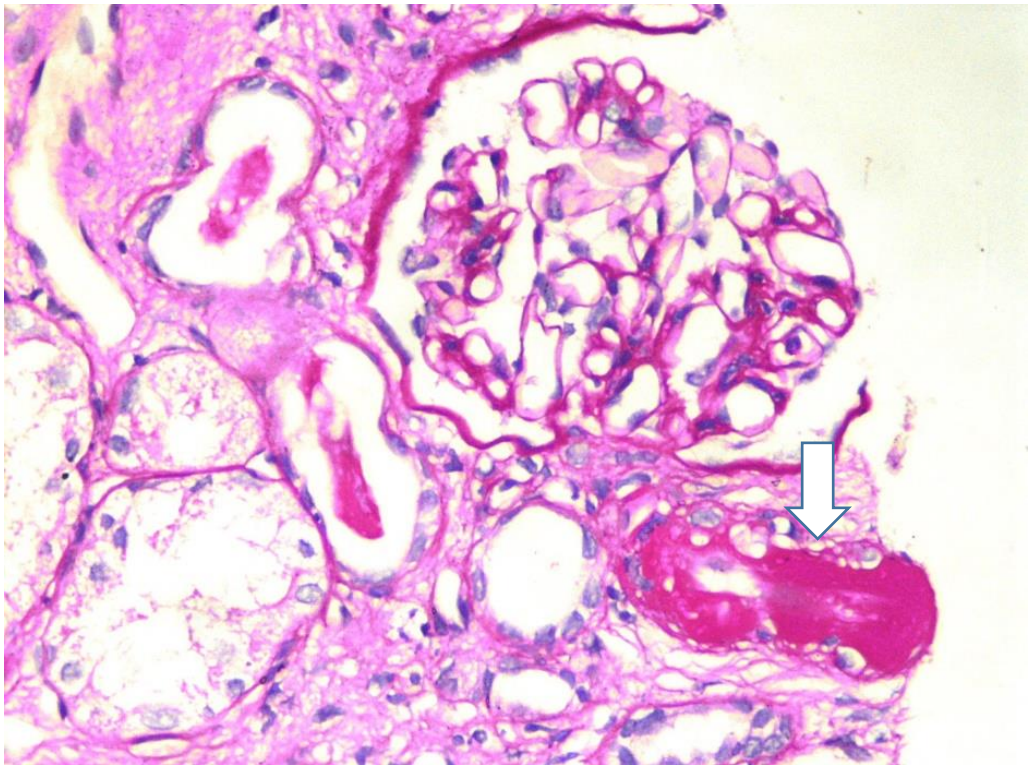

Figure 2. Morphological features suggestive of calcineurin inhibitor (CNI) toxicity. An extensive nodular arteriolar hyalinosis (arrow) is seen in this example of CNI toxicity with interstitial fibrosis in the background. (Periodic acid-Schiff (PAS) stain, ×400).

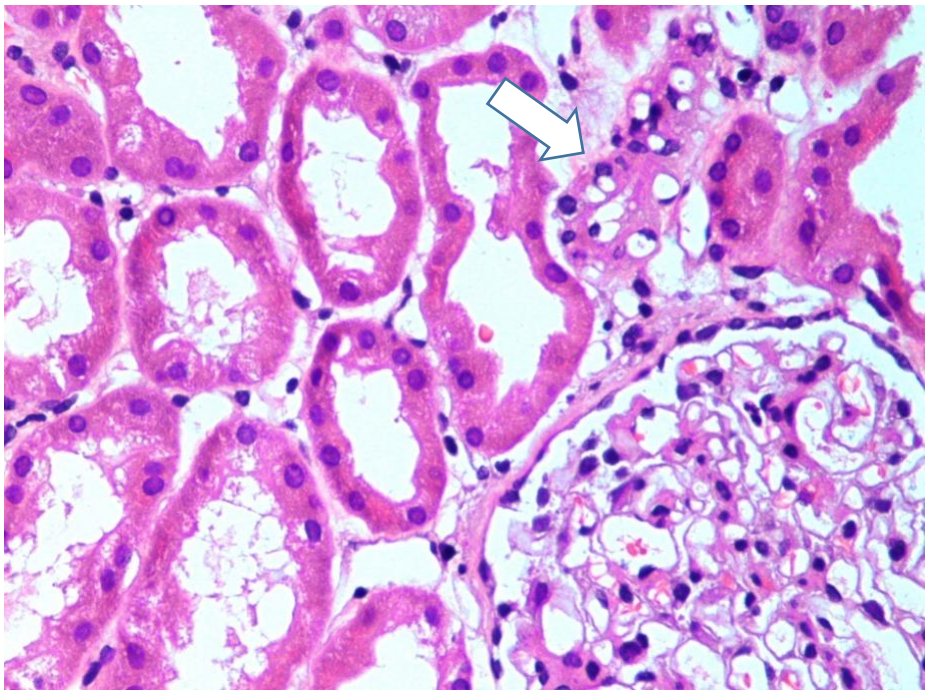

Figure 3. Morphological features suggestive of calcineurin inhibitor (CNI) toxicity. An arteriole is exhibiting vacuolization of medial smooth muscle cells (arrow). No nodular arteriolar hyalinosis is seen in this arteriole. (Hematoxylin and Eosin (H&E), ×400).

IFTA:

Although, IFTA is the end-stage result of chronic, repetitive forms of injury of whatever cause, IFTA with a "striped" ischemic distribution is the characteristic feature of chronic CNI toxicity. The patchy "striped"

pattern may be difficult to identify on core biopsies (Figures 4, 5, 6). The differential diagnosis includes preexisting donor injury, aging, fibrosis related to ischemia/reperfusion injury, previous tubulointerstitial rejection episodes, infections (e.g., polyoma virus), chronic ischemia, chronic obstruction/reflux, and diabetes mellitus. Staining for C4d is useful to exclude chronic antibody-mediated rejection (AMR). Co-incident thrombotic microangiopathy and/or isometric vacuolization of tubular cells (Figure 7) suggests ongoing toxic injury.

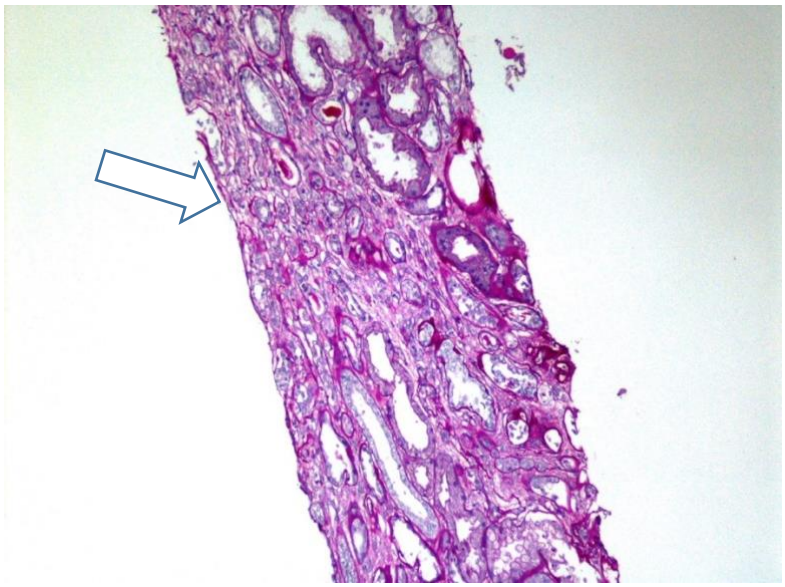

Figure 4. Morphological features suggestive of calcineurin inhibitor (CNI) toxicity. A strip of relatively bland fibrosis is seen interposed between relatively preserved nephrons. This stripped fibrosis is often difficult to identify on core biopsies. (Periodic acid-Schiff (PAS) stain, ×200).

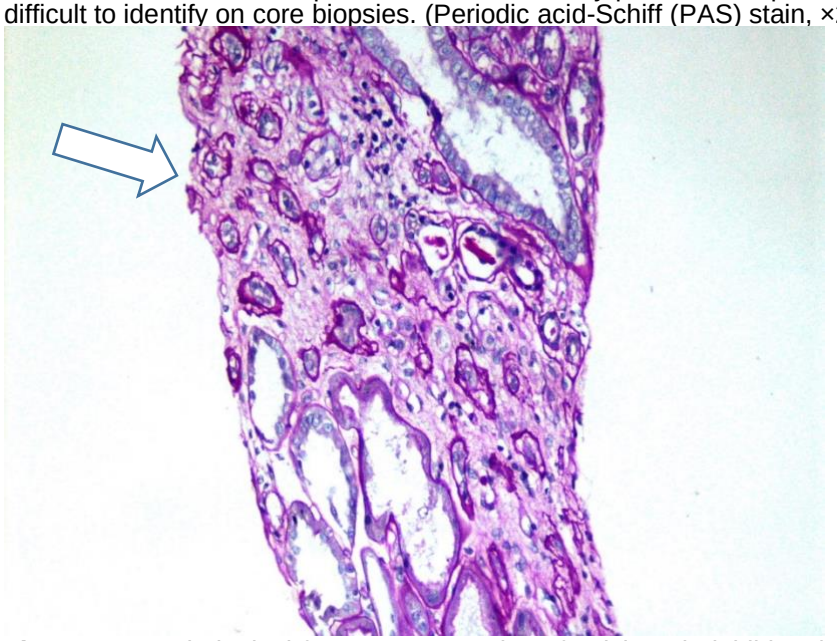

Figure 5. Morphological features suggestive of calcineurin inhibitor (CNI) toxicity. High magnification view of same example shown in Figure 3 with pauci-inflammatory stripped fibrosis interposed between relatively preserved tubules. (Periodic acid-Schiff (PAS) stain, ×400).

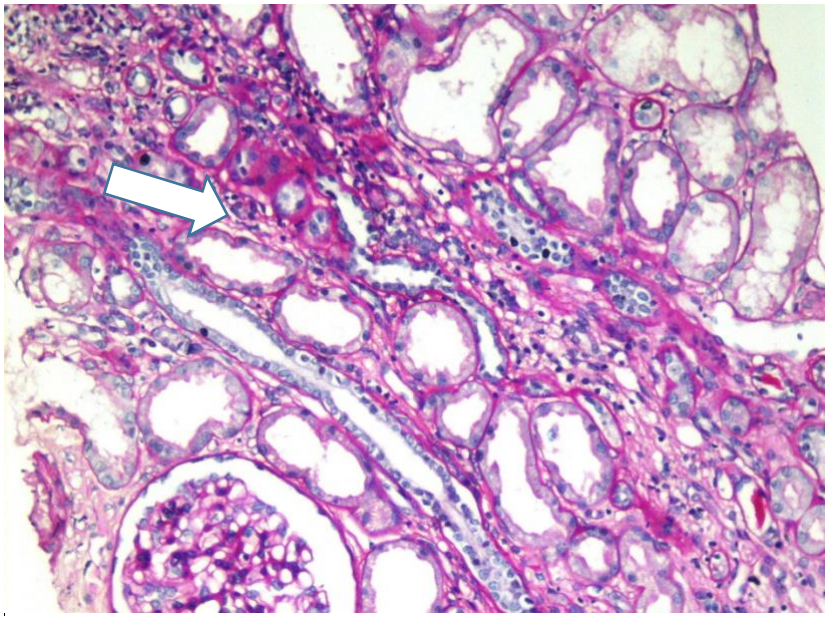

Figure 6. Morphological features suggestive of calcineurin inhibitor (CNI) toxicity. High magnification view of another example of a pauci-inflammatory stripped fibrosis interposed between relatively preserved tubules. (Periodic acid-Schiff (PAS) stain, ×400).

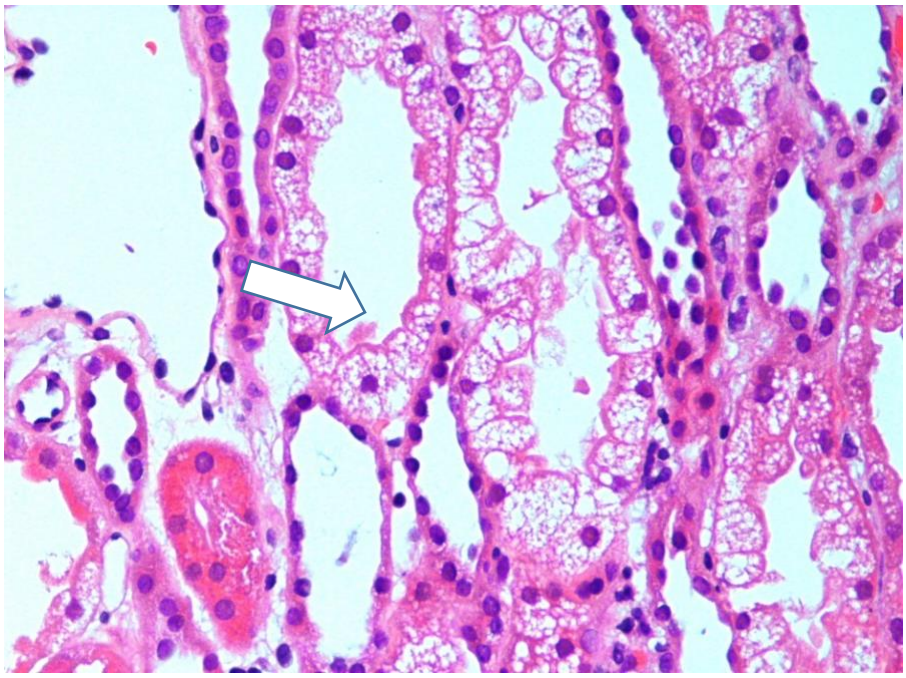

Figure 7. Isometric vacuolization of proximal tubular epithelial cells (arrow) suggest continuing CNI toxic injury. (Hematoxylin and Eosin (H&E), ×400).

Glomerular sclerosing lesions:

Glomerular sclerosing lesions, i.e., capsular fibrosis, global glomerulosclerosis (Figure 8), focal segmental glomerulosclerosis, are frequent but not specific. They most probably reflect ischemic injury resulting from CNI-induced arteriolopathy. Differential diagnosis includes recurrent primary disease, donor – recipient size discrepancy with hyperfiltration injury and FSGS secondary to other causes of glomerulosclerosis.

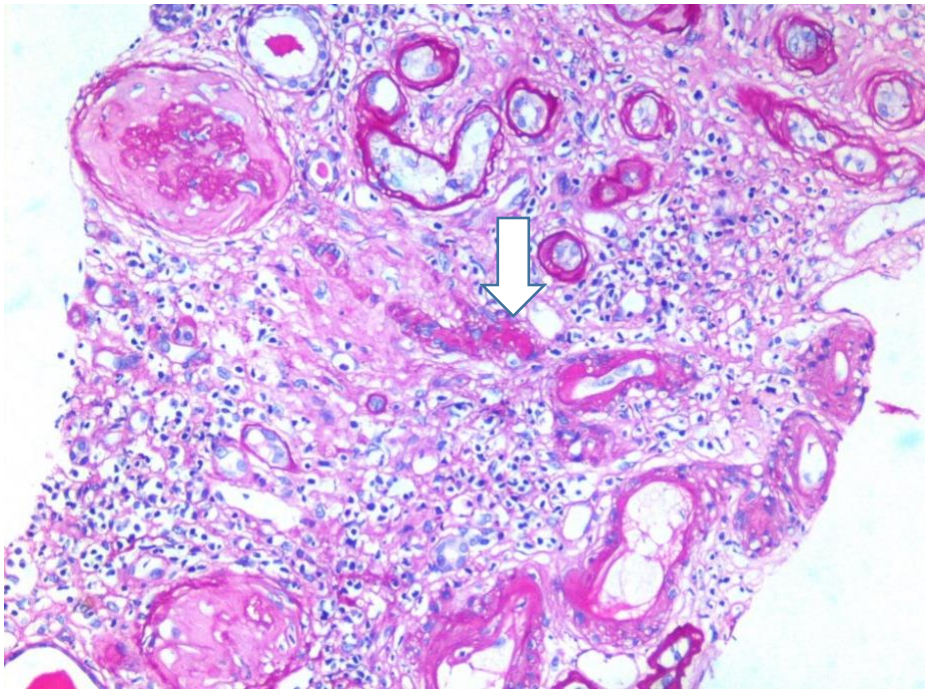

Figure 8. Ischemic global glomerulosclerosis involving both glomeruli in this field in a case of fairly advanced example of chronic calcineurin inhibitor (CNI) toxicity. Nodular arteriolar hyalinosis can be seen (arrow). In the background, interstitial fibrosis can be seen (Periodic acid-Schiff (PAS) stain, ×200).

Juxtaglomerular apparatus hyperplasia:

The juxtaglomerular apparatus is situated at the glomerular hilum, and effects tubule-glomerular feedback. This structure is indistinct in normal kidneys, but becomes prominent in some CNI treated allografts (Figure 9).

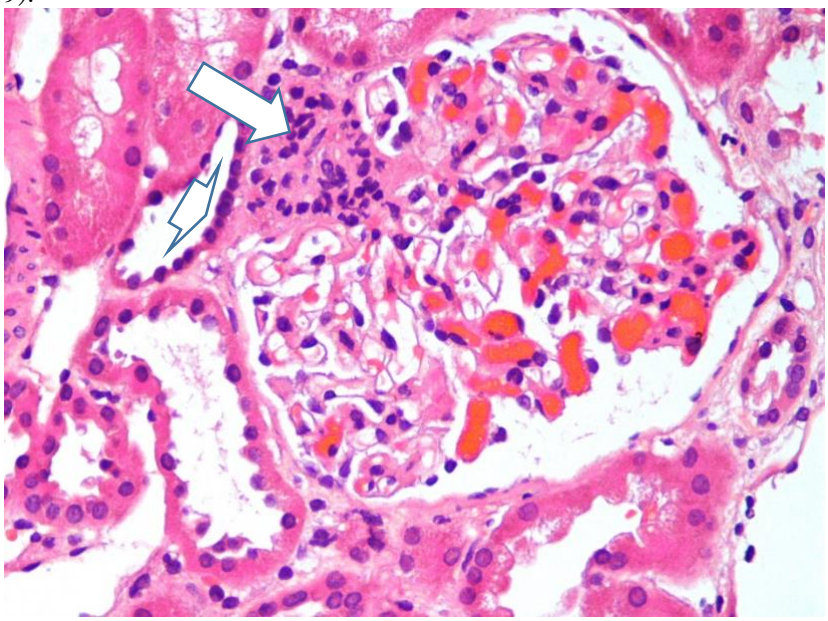

Figure 9. Juxtaglomerular apparatus hyperplasia (arrow) in a case of CNI toxicity. Arrowhead shows macula densa. Many glomerular capillaries are filled with sludged RBCs. (Hematoxylin and Eosin (H&E), ×400).

Tubulointerstitial microcalcifications:

Tubulointerstitial microcalcifications (Figure 10) are nonspecific and usually accompany ATI from acute CNI toxicity. Their presents indicates superimposed ATI on the background of chronic CNI toxicity. They are also commonly seen in preexisting donor injury, post-DGF/ATN, bone and calcium metabolic disorders, proteinuria, HUS, TTP (thrombotic thrombocytopenic purpura) and TMA.

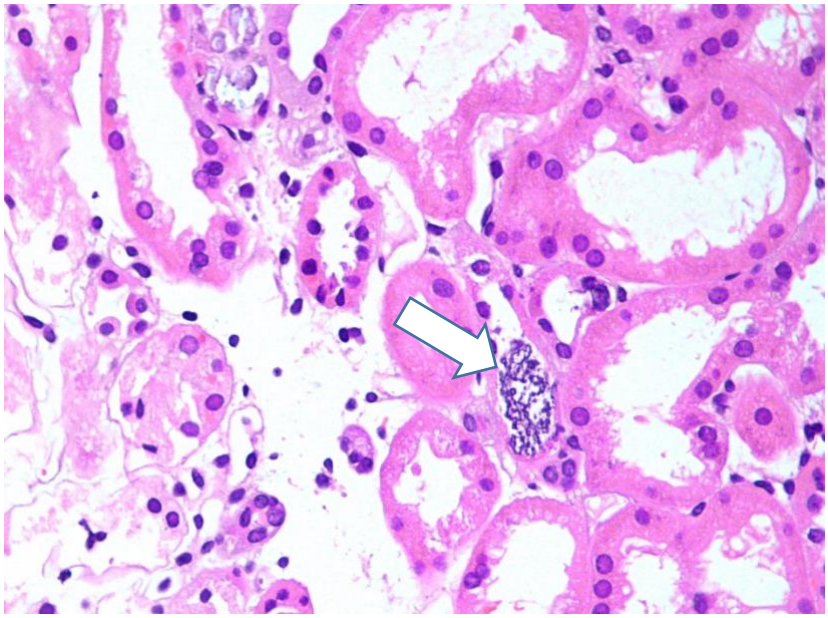

Figure 10. Dystrophic calcification (arrow) in the lumen of most probably a distal tubule in a case of CNI toxicity. It also indicates acute toxicity but can occur in the background of chronic toxicity (Hematoxylin and Eosin (H&E), ×400).

Further reading:

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