

*Images in Nephrology*  
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## Calcineurin inhibitor toxicity in a renal transplant recipient

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A 40-year-old Caucasian male who suffered end-stage renal disease due to unknown cause received a living-related renal allograft on 28 July 2008. Rabbit anti-thymocyte globulin was utilized for immediate post-transplant immunosuppressive induction, followed by maintenance immunosuppression with tacrolimus, mycophenolate mofetil and prednisone. Metoprolol was also administered for hypertension. Nadir serum creatinine occurred on post-transplant day number 7 (serum creatinine 2.2 mg/dL). At that time, the blood tacrolimus level was 14.8 ng/mL (reference range 5.0–20.0 ng/mL). The patient's serum creatinine abruptly rose to 2.6 mg/dL 3 days later, at which time his blood tacrolimus level was 46.8 ng/mL. A renal allograft biopsy (Figures 1 and 2—see Online Supplementary Material for colour illustrations) was performed a few days later, which revealed isometrically vacuolated proximal tubular epithelial cells and focal nodular arteriolar hyaline. The tubular epithelial cell isometric vacuolization seen was very focal, affecting only a few tubules in the biopsy sample. Isometric vacuolization describes the finding of numerous equally sized tiny clear cytoplasmic vacuoles. A diagnosis of acute calcineurin inhibitor toxicity (toxic tubulopathy) was made. These small, uniformly sized tubular epithelial cell cytoplasmic vacuoles are caused by toxic levels of the calcineurin inhibitors cyclosporine and tacrolimus and are due to dilatations of smooth endoplasmic reticulum by aqueous fluid [1,2,3]. This type of cytoplasmic hydropic change is light microscopically indistinguishable from that seen in osmotic nephrosis caused by hypertonic sucrose solutions, mannitol, high molecular weight dextrans, radiocontrast material or intravenous immunoglobulin. However, in contrast to those seen in cal-

calcineurin inhibitor toxicity, isometric vacuoles induced by the latter agents represent distended lysosomes rather than dilated smooth endoplasmic reticulum [4]. Ethylene glycol poisoning and hypokalaemia cause very large, coarse cytoplasmic vacuoles, easily distinguished by light microscopy from the numerous tiny vacuoles seen in calcineurin inhibitor toxicity and osmotic nephrosis [4]. In the case of calcineurin inhibitor toxicity, the typical cytoplasmic hydropic change may be so focal as to affect only a few tubules within a given biopsy [3]. Another, more serious acute toxic effect of calcineurin inhibitors is thrombotic microangiopathy, which was not seen in this biopsy. The patient's tacrolimus dose was lowered, followed by a reduction in his blood tacrolimus level and serum creatinine (2.1 mg/dL, 2 weeks post-biopsy).

### Supplementary data

Supplementary data is available online at <http://ndtplus.oxfordjournals.org>.

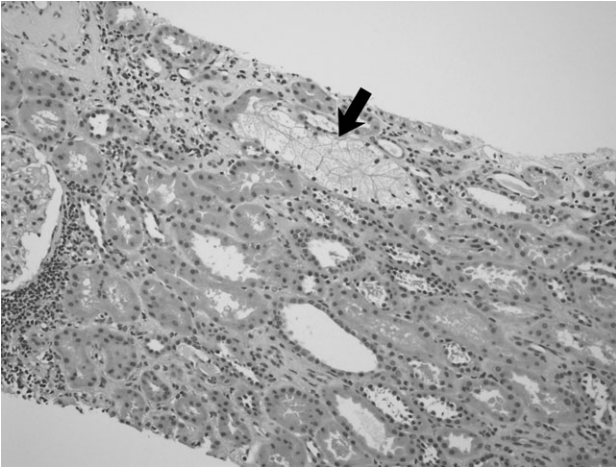
*Conflict of interest statement.* None declared.

### References

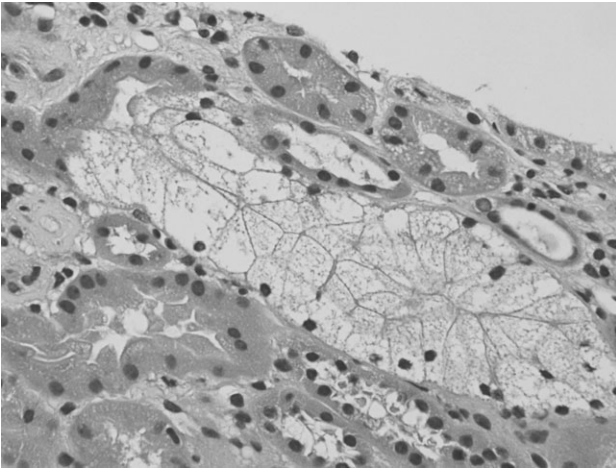
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**Fig. 1.** Renal biopsy, stained with haematoxylin and eosin, reveals isometric vacuolization of proximal tubular epithelial cells. Tubular epithelial cell vacuolization is only focal (arrow), as seen by surrounding normal appearing tubules (original magnification  $\times 200$ ). For colour illustration, please see online supplementary materials.



**Fig. 2.** High-power view of involved renal tubule reveals marked epithelial cell swelling due to numerous tiny clear cytoplasmic vacuoles (original magnification  $\times 600$ ). For colour illustration, please see online supplementary materials.