Tissues, Pathology, and Diagnostic Microscopy

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Preservation and Electron Microscopic Presentation of Crystals in Iatrogenic Foscarent - Induced Crystalline Nephropathy

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Drugs can induce kidney injury by various mechanisms. A number of poorly soluble drugs, including foscarnet, can crystallize within renal tubules and cause tubular injury and inflammation [1,2]. Because of its very common adverse effect on kidney function, foscarnet (trisodium phosphonoformate hexahydrate) is a second-line agent for treatment of ganciclovir resistant viral infections. Very few histopathologic data have so far been reported about the unique foscarnet-associated not only tubular but also glomerular crystalline nephropathy [3].

We present a 73-year-old male patient with a past history of autosomal dominant polycystic kidney disease and cadaveric kidney transplantation. After two intravenous foscarnet applications of 21 and 33 days, one week apart, because of ganciclovir – resistant Cytomegalovirus infection, needle allograft biopsy showed a severe glomerular and tubular crystalline nephropathy. An autopsy was performed when he died 17 months after transplantation and 6 weeks after the second foscarnet application.

Irregular empty clefts of various sizes remained after total or subtotal washing out and/or mechanical removal of water-soluble foscarnet crystals in standard paraffin sections (Figure 1), as well thick and ultrathin Epon-embedded sections after routine formalin fixation of kidney biopsy and autopsy specimens. Presentation of birefringent crystals in fairly thick fresh-frozen air-dried sections, visualized best in a polarization microscope, lacked detail. Light microscopy revealed pale yellow rectangular crystals, preserved after 100% alcohol fixation of autopsy tissue but to some extent damaged and removed during cutting of the paraffin sections. Massive crystalline precipitates were observed in 80% of transplanted kidney glomeruli, associated with capillary destruction, fibrin release, extracapillary crescents and focal segmental glomerulosclerosis, as well as in 20 % of proximal tubuli, causing macrophage tubulitis, tubular ruptures and foreign body granulomatous inflammation (Figure 1). Crystals were found in smaller amounts scattered in the bone marrow, heart and skeletal muscles.

We succeeded in preserving the foscarnet crystals for electron microscopy studies after 100% alcohol fixation and O_SO_4 postfixation. However, the crystals were mostly mechanically removed by cutting ultrathin sections but remained in significantly thicker sections of around 1000nm. The numerous rectangular flat plate-like foscarnet crystals measured from 100nm x 80nm to 970nm x 830nm in stacks. To the best of our knowledge, this was the first time that they had been visualized by electron microscopy (Figure 2).

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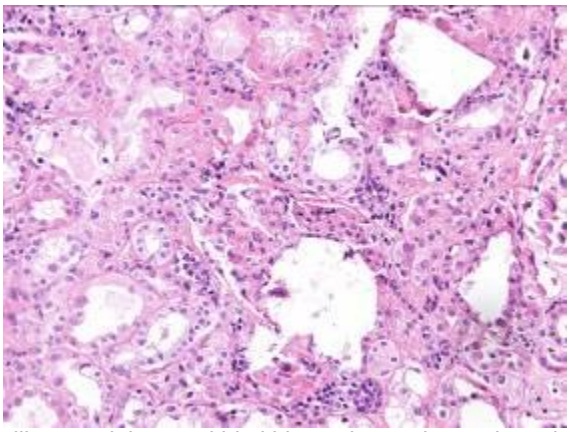

Figure 1. Destructive crystalline precipitates within kidney glomerulus and proximal tubuli. 100% alcohol fixation, paraffin embedding, HE, X20.

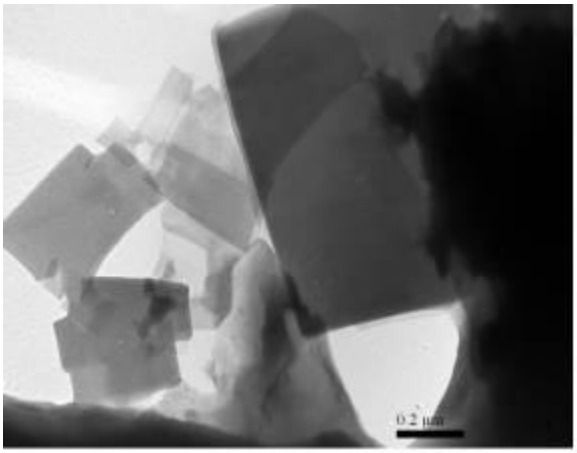

Figure 2. Electron micrograph showing numerous rectangular crystals in the kidney glomerulus. 100% alcohol fixation, O_SO_4 postfixation, Epon embedding, 1000nm section, X80.000.