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Urolithiasis After Kidney Transplantation - Clinical and Mineralogical Aspects

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Summary. Urolithiasis is a rare complication following kidney transplantation. Experience with this complication in 6 of 426 transplantations performed from 1968 to 1979 is reviewed. The clinical symptoms are different from the disease in non-transplant patients. Three major predisposing causes for the development of calculi after kidney transplantation were found in our patients - urodynamic disorders following complications of the ureterovesical anastomosis, persistent bacteriuria and renal tubular acidosis and, less importantly, the presence of hypercalcemia and hypercalciuria as a result of secondary hyperparathyroidism. Crystal-optical and x-ray-diffraction studies contributed to the interpretation of the constituents and texture of the calculi and of the aetiological factors concerned.

Key words: Urolithiasis, Kidney transplantation, Hyperparathyroidism, Crystallography, X-ray diffraction studies.

INTRODUCTION

Of the numerous complications which recipients of kidney transplants are subject to, urolithiasis is one of the most uncommon. Altogether, 43 patients with urolithiasis after kidney transplantation were reported up until 1979 (4-8, 10-18, 20, 21, 23-26, 29-34). However, a detailed analysis of the cases was made in only a few reports (13, 16, 26, 30, 34). Opinions on the aetiology of urolithiasis after transplantation differ considerably, especially on the problems of secondary hyperparathyroidism and subtotal parathyroidectomy (13, 16, 21, 26, 30, 34).

Exact analyses of the calculi are reported only in a few cases (16, 21, 26, 30) and detailed investigations of the structure of calculi have not been published.

These facts stimulated us to review our experience in a series of kidney transplant patients suffering from this complication. The aim of the present study was to make a contribution to the understanding of the aetiology of urolithiasis after kidney transplantation by reporting our clinical and mineralogical findings.

MATERIALS AND METHODS

Among 426 human cadaver kidney transplantations performed from March 1968 to December 1979, 6 patients developed urolithiasis (1,4%). There were 4 male patients, 1 female patient and a 14-year-old boy. Ages of the patients ranged from 14 to 39 years. Data of these patients are summarized in Table 1 (see also (27)). Suitable recipients were selected on the basis of HLA typing and final cross matching for cytotoxic antibodies. Kidney preservation consisted of simple hypothermic storage with Collins solution in all 6 cases and an additional continuous hypothermic perfusion with the Gambro machine in one case. We employed standard surgical procedures. The method of donor ureteric implantation into the recipient's bladder was modified. In the first 60 patients the ureteroneocystostomy was performed according to the methods of Stevens and Marshall or Paquin. Since May 1972 we have employed the method of Braun (3) with extravesical anastomosis and submucosal tunnel. Immunosuppressive therapy consisted primarily of azathioprine and prednisolone as previously described (22). Rejection episodes were diagnosed by the usual clinical and laboratory criteria and treated with bolus doses of prednisolone. The

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Table 1. Data of transplant patients with urolithiasis

Patient	Sex/age (years)	Date of transplantation	Original disease	Ischaemia time Warm (min)	Ischaemia time Cold (h)	Delay in onset of normal graft function (days)
CD 11	m/33	4/70	GN/PN	65	4.15 C	58
CD 26	f/31	4/71	PN	45	7.40 C	23
CD 62	m/30	6/72	GN	60	11.00 C	13
CD 218	m/27	7/76	PN	5	9.00 C	1
CD 229	m/39	8/76	GN	30	8.40 C 7.35 G	8
CD 240	m/14	10/76	PN	4	8.00 C	9

C = preservation with Collins solution, G = perfusion with the Gambro machine, GN = glomerulonephritis, PN = pyelonephritis

analysis of stone composition was performed with a highly differentiating combined crystal-optical-x-ray-diffraction method as described by Bick and Brien (2). In addition, the texture of the calculi was investigated on thin sections by polarization microscopy.

RESULTS

A. Clinical Findings

The 6 patients developed urolithiasis 3 to 32 months after kidney transplantation. 4 patients had one episode and 2 patients had three episodes of urinary stone formation. 9 of the 10 episodes occurred within the first 24 months after transplantation.

The clinical pattern at the time of calculus demonstration was painless hematuria in 2 patients, anuria in 3 cases, from ureteric and urethral obstruction each in 1 patient and c/ot retention of the urinary bladder in 1 patient. Only 1 patient had a ureteric colicky pain; the origin of this patient's (CD 218) calculus was suspected to have been in his own kidneys. In 4 patients a temporary deterioration of graft function was observed, in one of them a rise of the serum creatinine level from 1,4 to 6,4 mg% occurred due to ureteric obstruction by the calculus.

3 patients passed 5 calculi spontaneously. In the other 3 patients 5 calculi had to be removed by operative procedures. Compared with the transplant patients without urolithiasis a striking fact in the 6 patients was the simultaneous occurrence of 5 factors which are possibly responsible for or predispose towards the development of urinary calculi after transplantation.

1. Long warm ischemia time ($\geq$ 30 min, 4 patients) and a marked delay in onset of normal graft function (5 patients).

2. High incidence of complications at the site of the transplant ureter and the urinary bladder (4 patients).

3. Persistent bacteriuria (6 patients).

4. Alkaline urinary pH (5 patients).

5. Occurrence of postoperative hypercalcemia and hypercalciuria as a consequence of secondary hyperparathyroidism (3 patients).

B. Mineralogical Findings

Table 2 shows the results of the semiquantitative analyses of 8 calculi. The composition of the calculi was uniform in 5 of 6 patients. They were found to be exclusively composed of struvite and carbonate apatite which are typical of urinary tract infection with urea-splitting bacteria. Only one calculus was composed of whewellite and uric acid. This patient's calculus, as mentioned above, was suspected to have originated in his own kidneys.

From the other 7 calculi microscopical analyses of thin sections of calculi by polarization microscope were performed. In all of the 7 stones investigated we found the 3 texture types of struvite/carbonate apatite calculi as observed by Schubert and Brien (28).

Type 1: Irregular mosaic texture of isometric struvite grains; basic mass is carbonate apatite and/or organic material.

Type 2: Concentric ring texture; isometric struvite grains are pearl-string-like deposits in layers of carbonate apatite and/or organic material.

Type 3: Radiating arrangement of mostly large struvite crystals.

In spite of the similarities in the texture types the transplant calculi showed various specific features when compared with other stones of infective origin. The central part of the transplant calculi always consisted of an irregular mosaic

Table 2. Analysis of stone composition

Calculus	Patient	Stone locality	Composition (%)			
			Struvite	Carbonate apatite	Whewellite	Uric acid
1	CD 11	transplant	100	trace	-	-
2	CD 11	bladder	80	20	-	-
3	CD 26	transplant	100	trace	-	-
4	CD 62	bladder	50	50	-	-
5	CD 218	own kidney	-	-	90	10
6	CD 229	transplant	70	30	-	-
7	CD 229	transplant	60	40	-	-
8	CD 240	transplant	80	20	-	-

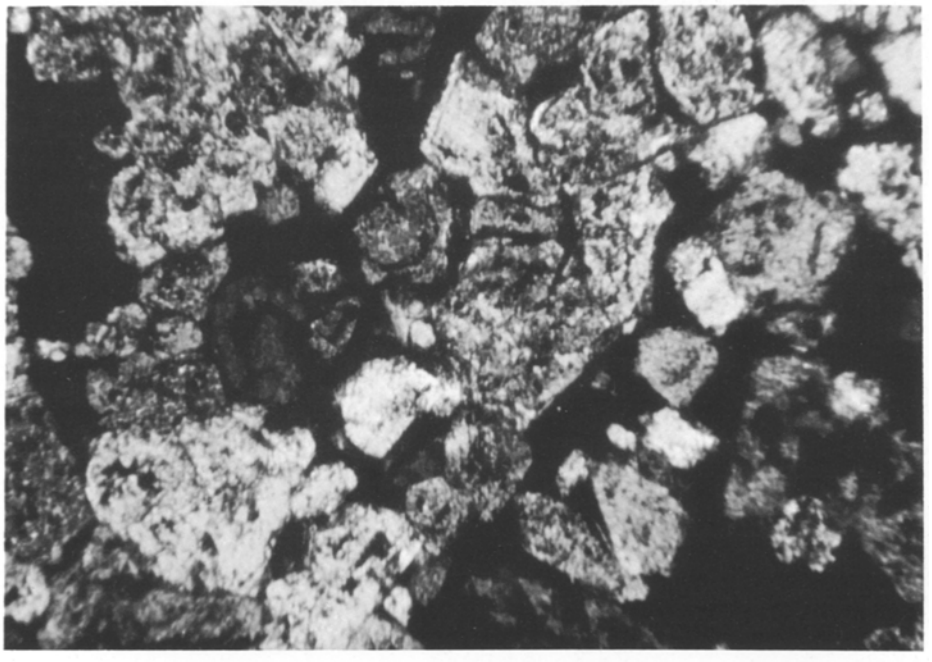

Fig. 1. Patient CD 26; central part of the calculus, mosaic-like texture of greater, compact struvite grains, within the struvite crystals irregular structure of organic substance. (x 60, crossed polarizers)

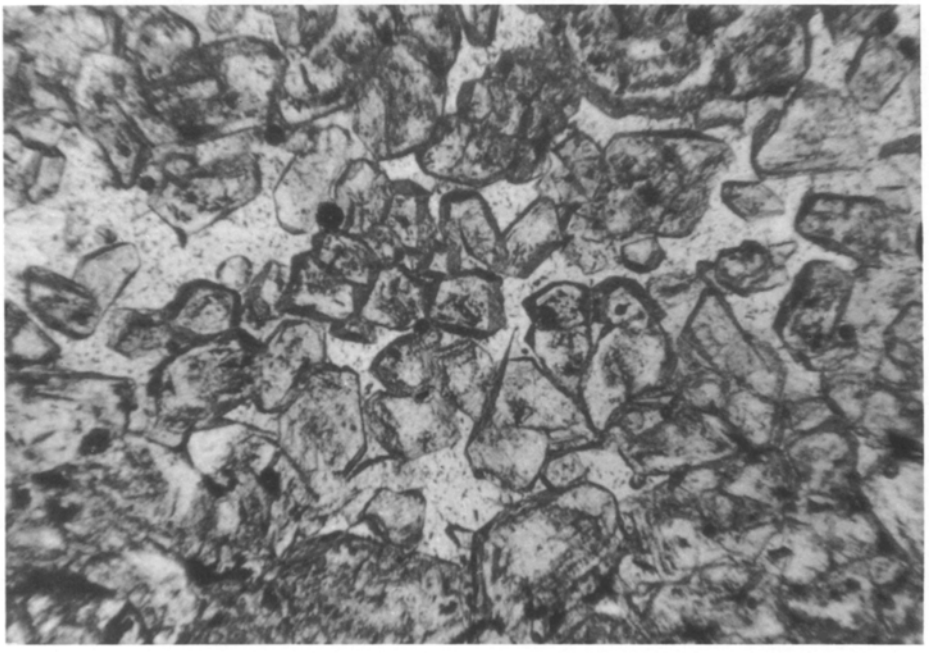

Fig. 2. Patient CD 26; peripheral part (layer 1) of the calculus, following the central part, smaller struvite crystals in a basic mass of carbonate apatite and organic substance. (x 75, light-field microscopy)

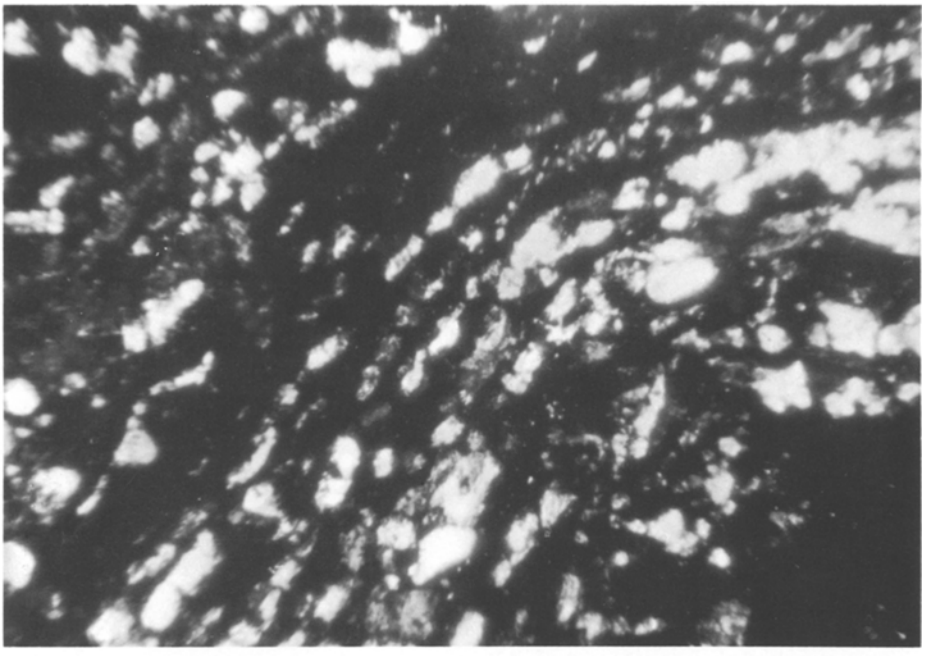

Fig. 3. Patient CD 62; peripheral part of the calculus, deposition of pearl-string-like struvite grains in layers of organic substance and carbonate apatite. (x 75, crossed polarizers)

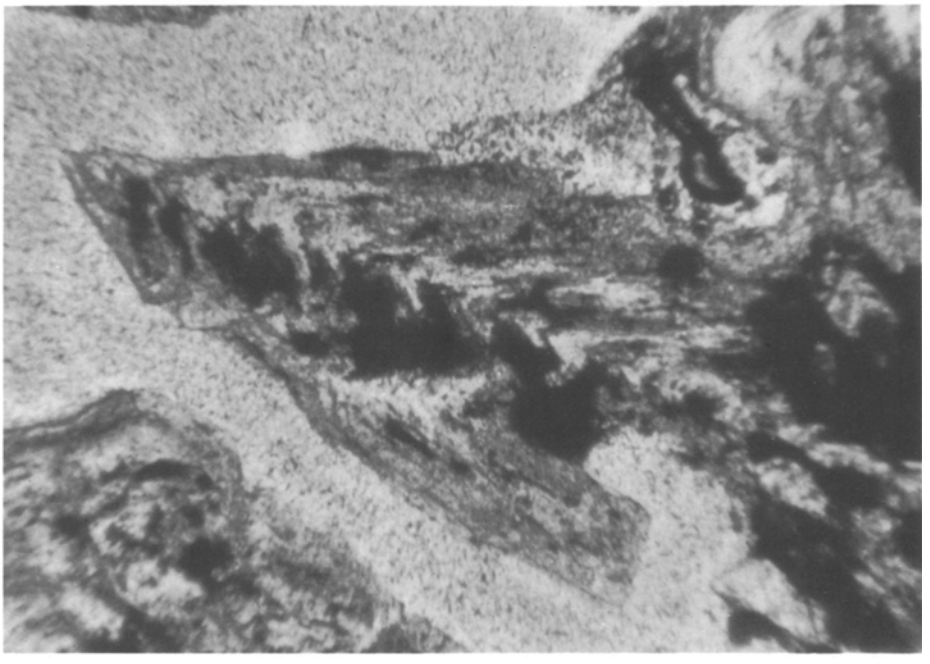

Fig. 4. Patient CD 11; peripheral part of the calculus, great idiomorphic struvite crystal with striped deposition of organic substance. (x 75, light-field microscopy)

structure (Type 1, Fig. 1). Furthermore, a massive deposition of isotropic, non-transparent, probably organic substance was observed. This isotropic substance can be seen in various parts of the struvite texture, for example on the edges of grains of the struvite crystals (Fig. 1) and together with carbonate apatite forming the basic mass in the struvite mosaic texture (Fig. 2). In type 2 the organic substance is taken up in layers in the calculus (Fig. 3).

It is striking that this substance can be observed also as inclusions in the struvite crystal (Fig. 4). The deposition of the organic substance occurs during the calculus growth and is partially manifested as striation (Fig. 4).

These phenomena in the texture of the transplant calculi can be explained by the particular pathogenetic conditions. The permanent composition of the central part of the calculi as an irregular mosaic structure points to a rapid growth at the beginning of calculus formation and a high oversaturation of the urine with stone-forming ions. Also the massive deposition of an isotropic substance is made possible by a high concentration of organic material in the urinary tract. This isotropic substance can be observed in all parts

Table 3. Details of calculi after kidney transplantation reported in the literature

Authors	Number of patients (frequency)	Stone composition	Suspected cause of stone formation
Brynger et al., 1976	1	-	-
Caralps et al., 1977	7	-	HPT, donor kidney, infection
Christensen and Nielsen, 1977	1	-	HPT
Dominguez et al., 1970	1	calcium phosphate	HPT
Dreikorn et al., 1975	2 (1, 6%)	uric acid	-
Hume et al., 1966	1 (1, 1%)	-	HPT
Küss et al., 1973	3 (2, 5%)	-	-
Lattimer et al., 1970	1	calcium phosphate	HPT
Leary et al., 1975	1 (0, 4%)	-	-
Lucas and Castro, 1978	3 (1, 1%)	calcium phosphate	HPT, stenosis and infection
Mac Kinnon et al., 1968	4 (6, 7%)	-	-
McLaughlin, 1977	1	-	proline suture nidus
Narayana et al., 1978	1	carbonate apatite, brushite	idiopathic ?
Previte et al., 1978	1	calcium oxalate	HPT
Rambar and MacKenzie, 1978	3	-	-
Rattazzi et al., 1975	2 (0, 3%)	struvite ?	stenosis (ileum conduit)
Rosenberg et al., 1975	1	whewellite, struvite	HPT; RTA ?
Schweizer et al., 1977	1	-	-
Shackford et al., 1976	1	calcium oxalate, apatite	idiopathic ?
Starzl et al., 1970	2 (0, 9%)	-	stenosis, obstruction
Stubenbord et al., 1978	1	-	-
Thiel et al., 1976	3 (2, 5%)	weddellite, calcium oxalate, apatite, organized blood clot	urinary flow disorders, infection, hematuria
Present series	6 (1, 4%)	struvite, carbonate apatite	urinary flow disorders, infection, RTA

HPT = hyperparathyroidism, RTA = renal tubular acidosis

of the calculus texture. Therefore, it must be assumed that the organic material is available in abundance during the whole growth process. The long warm ischemic time and the delayed onset of normal graft function (see Table 1) lead to an optimal milieu for calculus formation consisting of a massive occurrence of cell degradation products and organic material in the presence of an infection with urea-splitting bacteria.

DISCUSSION

The development of urolithiasis after kidney transplantation is a late complication occurring between 2 months and 6 years following transplantation (4, 13, 16, 20, 25, 29). Details of the 43 cases reported in the literature are described in Table 3. The clinical pattern and the symptoms are different from the disease in non-transplant

patients. Hematuria and transplant ureteric obstruction may occur without pain because of the division and absence of regeneration of pain fibres (23, 29, 30). If hematuria occurs in a transplant patient, particularly in the presence of some deterioration of graft function, as observed in our series, the possibility of urolithiasis should be considered. Failure to appreciate that a rise in the serum creatinine level might be caused by ureteric obstruction rather than rejection might lead to the unnecessary and potentially dangerous use of high dose immunosuppressive therapy (30).

The management of urolithiasis after kidney transplantation should include the treatment of the underlying causes of stone formation (1). Patients with stones in the transplanted kidney or ureter should be investigated thoroughly for all possible aetiological factors (21). Secondary hyperparathyroidism as a possible cause of urolithiasis has been given most attention (6, 12, 13, 26, 32). Leapman et al. (13) advocate early surgery when secondary hyperparathyroidism and recurrent transplant calculi occur. We disagree with this point of view. Indeed, parathyroid exploration and subtotal parathyroidectomy should be reserved for resistant cases and those with evidence of metastatic calcification or secondary bone disease (16). In none of our patients was parathyroidectomy performed. We observed hypercalcemia and hypercalciuria only in the first months after transplantation at the time of restoration of normal graft and parathyroid function and mobilization and resolution of metastatic calcifications developed during chronic hemodialysis as described by Hornum (9).

It is remarkable that no calculus formation has occurred in our last 186 transplant patients. By the introduction and technical perfection of the extravesical ureterneocystostomy (3) and technical improvements in donor nephrectomy in recent years a significant reduction of ureteric and urinary bladder complications from 33,3% to 12, 6% has been obtained (19). The delayed onset of normal graft function and urodynamic disorders as a result of posttransplant ureteric and bladder complications (fistula, stenosis, insufficient, anastomosis) accompanied with persistent bacteriuria and occurrence of renal tubular acidosis possibly caused by ischemic damage resulting from long warm ischemic time (35) constitute the common predisposing causes of urolithiasis in our patients. These aetiological factors are also demonstrated and discussed in the literature (16, 29, 34). A typical case of stone formation which seemed to follow urinary infection and stagnation caused by stenosis of the ureterovesical anastomosis was described by Lucas and Castro (16). Following restoration of patency and normal urinary drainage, no further infection or stasis calculi were observed. A similar aetiology accounts for the formation of calculi in the allograft in patients with supravesical urinary diversion into ileal conduits (25, 33).

An exact mineralogical investigation of transplant calculi seems important to us especially with regard to the relevance of secondary hyperparathyroidism in calculogenesis and the resulting therapeutic procedures. Our crystal-optical and x-ray-diffraction studies of the transplant calculi clearly show the importance of urinary tract infection and ischaemic damage of the transplant kidney as causes of stone formation after renal transplantation.

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ADDENDUM

Since the preparation of the manuscript 15 further patients with urolithiasis after kidney transplantation were reported in the literature (1, 2, 3). However, detailed investigations of the structure of calculi likewise have not been published.

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