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Crystals in renal allograft biopsies; a 5-year study with review of literature

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ABSTRACT

Introduction: The kidney is exposed to a variety of crystalline substances which can cause tissue damage. There are limited studies on the frequency of crystal deposits in renal allograft biopsies especially from our part of the world.

Objectives: The objective of this study was to find out the prevalence of crystal deposits among the allograft biopsies received at our centre over five years, and to identify its clinicopathological implications.

Patients and Methods: We have retrospectively searched the records of renal biopsies reported during the period from 2014 to 2018, to identify allograft biopsies with crystal deposits. The histopathological findings including the density of deposits were noted and correlated with demographic and clinical profile in the light of available literature.

Results: Of 1225 transplant biopsies received during the study period, 1.5% had crystal deposits reported on morphology. These biopsies were from 13 patients evaluated for graft dysfunction; 10 had oxalate crystals while three had the rare 2,8-dihydroxyadenine (DHA) crystals. Crystal density varied from 1 to 26/mm² and all showed acute tubular injury. Around 39% of the biopsies with crystals, included in this study, were taken within a month of transplant and those cases with subsequent biopsies showed progressive interstitial fibrosis/tubular atrophy (IF/TA). All three cases of DHA nephropathy were first diagnosed only on allograft biopsies.

Conclusion: In the process of graft dysfunction, interpretation of allograft biopsy should include a careful search for crystals including polarised microscopy as this might not only explain deterioration of renal function, but also clinch the diagnosis of native kidney disease. Though our study has limitations, it addresses a less discussed issue and further studies are required to reinforce the significance of crystal induced allograft injury.

Implication for health policy/practice/research/medical education:

Awareness about crystal induced renal damage should prompt practicing clinicians and pathologists to consider various crystal nephropathies in their differentials for worsening renal function in appropriate context, in allografts as well as native kidneys.

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Introduction

The kidney is a filtering organ that receives nearly 25% of cardiac output and concentrates various substances in our body making it a favoured site for deposition of crystals. These cause tissue damage from direct tubular toxicity and obstruction, inflammation, epithelial-to-mesenchymal transition and subsequent fibrosis (1). Although a variety of crystals have been described, there are only a few studies and case reports on crystal deposition in renal allografts, most of which have looked into calcium oxalate (CaOx).

Their results vary widely, though various studies have recognised the role of crystals in poor graft function and outcome.

Objectives

The purpose of this study was to find out the prevalence and morphological features associated with crystal deposits in renal allograft biopsies received at our centre and to correlate with their clinical profiles.

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Patients and Methods

Study design

This retrospective descriptive study was conducted at our institution, a tertiary health care centre in Kerala, south India, wherein our nephropathology section receives native and allograft renal biopsies for interpretation from several centres throughout the state along with in-house cases.

For this study, the records of in-house and referred native kidney and transplant renal biopsies received from 2014 to 2018 in the department of pathology were searched to identify allograft biopsies where crystal deposits were reported. The slides of those biopsies were retrieved and examined to assess the abundance of crystal deposits. The available demographic information, clinical details and investigation results were systematically recorded which included; age at biopsy, gender, nature of transplant- live donor/ deceased, native kidney disease, timing of biopsy after transplant, serum creatinine as well as details of previous/subsequent biopsies.

The tissue of kidney biopsies was fixed in 10% neutral buffered formalin, processed and embedded in paraffin wax. Tissue sections were obtained at 3 microns thickness and stained with hematoxylin-eosin (H&E), periodic acid-Schiff (PAS), Jones methenamine silver, and Masson's trichrome for light microscopic examination. Immunohistochemistry for C4d was conducted in cases of suspected rejection. Biopsies were evaluated using the Banff classification and all significant pathological findings were recorded. Tissue for immunofluorescence was received in Michel's transport medium or normal saline and antibodies against IgG, IgA, IgM, C3, C1q, kappa and lambda light chains were used.

Crystals in biopsies were identified by their tinctorial properties (clear/ pale yellow/ greenish/ golden brown/ bluish colour), refractility and fractured/fragmented appearance on routine stains (colourless crystals with fractured glass appearance suggestive of oxalate and radially arranged/ finely fragmented brownish green crystals suggestive of 2,8-dihydroxyadenine) combined with findings on polarised microscopy. For further assessment of these deposits in the transplant biopsies, the tissue dimensions were measured on the slide (expressed as mm²), morphology noted and the number of crystal deposits in the tissue section counted under polarized light and recorded.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Amrita Institute of Medical Sciences, Kochi approved the study. Additionally, written informed consent was taken from all participants before any intervention.

Data analysis

This is an observational study of descriptive nature. The data collected including the biopsy findings and clinico-demographic parameters were systematically recorded and manually analysed to draw relevant inferences.

Results

During the 5 year period from 2014 to 2018, we received a total of 9059 renal biopsies including 1225 transplant biopsies. Crystal deposits were reported in 18 transplant biopsies from 13 patients, amounting to 1.5%. These patients' age ranged from 11 to 60 years and there were eight males and five females. While two of these were deceased donor transplants (15.4%), one of them had undergone a simultaneous liver kidney transplant for primary hyperoxaluria, all others were live donor transplants (84.6%). The native kidney disease was not known in 5 cases, crystal nephropathy in 3, recurrent renal calculi in one, diabetic nephropathy in 2, IgA nephropathy (IgAN) and reflux nephropathy in one case each. Graft dysfunction was the indication for biopsy in all these cases and serum creatinine values at the time of biopsy ranged from 1.53 to 7.63 mg/dL. Drugs used for immunosuppression were mainly prednisolone, mycophenolate mofetil, tacrolimus and azathioprine. The histological diagnoses of these cases are summarised in Table 1.

The biopsy tissue surface area as measured on slide ranged from 2.8 mm² to 15.4 mm². Morphologically, we identified two polarisable crystal types on these biopsies – colourless crystals with fractured glass appearance consistent with oxalate in 10 cases (77%) and radially arranged and finely fragmented brownish green crystals consistent with a much rarer substance - 2,8 DHA seen in the rare genetic disease – 2,8 DHA nephropathy due to adenosine phosphoribosyl transferase deficiency in three cases (23%). The density of crystal deposits counted under polarised light ranged from 1/mm² to as high as 26/mm² which did not vary significantly between crystal types. We observed oxalate crystals mostly in renal tubular lumina and within the tubular epithelial cells while DHA crystals were also noted frequently in the interstitium (Figure 1).

Seven of these 13 patients had crystals on biopsies we received within a month of transplant and the maximum time lapse post-transplant in this group was 33 months. Two of the seven cases with crystals on allograft biopsy within a month of transplant showed DHA while the other five cases had oxalate and included the case of proven primary hyperoxaluria. Six of our cases had more than one allograft biopsy on record—three of these were known crystal nephropathies – 2 oxalate and one DHA nephropathy while the other three were a case each of IgAN, diabetic nephropathy and unknown native kidney

Table 1. Histopathological diagnoses of allograft biopsies of 13 patients included in the study

Sl no.	Age	Gender	Native kidney disease	Biopsy report
1	55	M	Unknown	Acute cell mediated rejection with antibody mediated component and crystal induced nephropathy morphology favouring 2,8-DHA (Banff 2013 g1,t2,i2,v0,ptc2,C4d3).
2*	36	M	IgA nephropathy	Acute tubular injury with oxalate crystals in tubules. (Banff 2015 g0, t0, i1, v0, ptc0, C4d0)
3	18	M	Unknown	Suggestive of acute oxalate nephropathy. (Banff 2015 g0, t0, i1, v0, ptc0, C4d0).
4	11	F	Reflux nephropathy	Acute tubular injury with oxalate crystals (Banff 2009 g0,t0, i1, v0, ptc0, c4d0).
5*	39	M	Primary hyperoxaluria	Acute tubular injury with crystal induced nephropathy (in a known case of primary hyperoxaluria, post SLKT).
6	39	M	Diabetic nephropathy	Acute tubular injury with crystals (morphology favouring oxalate), mild global glomerulosclerosis, IF/TA grade I and arteriosclerosis (Banff 2013 g0, t0, ct1, i1, ci1, v0, ptc0, ah2, mm1)
7*	50	M	Diabetic nephropathy	Suspicious for acute antibody mediated rejection with moderate acute tubular injury and oxalate crystals (Banff 2009 g1, t0, i0, v0, ptc3, C4d0)
8	55	M	Unknown	Mild acute tubular injury with crystals, morphology favouring calcium oxalate (Banff 2009 g0, t0, i1, v0, ptc0, C4d0).
9	49	F	Suspected oxalate nephropathy	Crystal induced nephropathy with IF/TA grade I and hypertensive vascular changes. Note: Morphology of crystals favour 2-8 DHA. (Banff 2015 g0, t0, v0, i0, ct1, ci1, i IFTA1, ptc0, C4d0)
10*	28	F	Oxalate nephropathy/nephrocalcinosis	Acute cell mediated rejection grade IA in a background of oxalate nephropathy (Banff 2015 g0, t2, i3, ct1, ci1 i IFTA1, v0, ptc0, C4d0).
11	60	F	Unknown	Acute tubular injury with oxalate crystals in a background of mild global glomerulosclerosis, IF/TA grade I and hypertensive vascular changes (Banff 2013 g0, t0, i1, ct1, ci1, v0, ptc0, ah2).
12*	47	F	Recurrent calculi	Acute tubular injury with intraluminal crystals morphology favouring 2,8-DHA (Banff 2009 g0,t0, i1,v0,ptc0, C4d0).
13*	34	M	Unknown? HTN	Acute tubular injury with polarising crystals (likely oxalate)in a background of borderline changes suspicious for acute rejection and interstitial fibrosis/tubular atrophy grade I.(Banff 2015 g1, t1, i2, ct1, ci1, v0, ptc1, C4d0)

*More than one renal biopsy on record.

disease. Among these, the three crystal nephropathy cases showed crystals on their first biopsy taken within a month of transplant and subsequent biopsies too which were performed at different points in time for graft dysfunction. The other three cases had inconsistent presence of crystals, the diabetic nephropathy and IgAN cases had crystals on biopsy taken within a month of transplant but not in subsequent biopsies. The last case had no crystals on the first biopsy taken within a month but showed oxalate crystals on subsequent biopsy. Five out of these six cases showed progressive interstitial fibrosis/tubular atrophy (IF/TA) on later biopsies.

Discussion

Different types of endogenous and exogenous crystals may deposit within the kidney due to its filtration and concentration functions. Various factors like the patient's volume status, urine pH and flow rate and solubility of the crystal influence precipitation within the kidney (2). Many kidney diseases involve crystalline micro-particles which contribute to mechanical obstruction, local inflammation and tissue injury. While acute super-

saturation causes acute kidney injury due to sudden onset crystal formation inducing tubular cell injury and interstitial inflammation, long-standing moderate super-saturation causes slow crystal formation, tubule obstruction, and tissue remodelling leading to chronic kidney disease (3). Clinical manifestations may range from no symptoms to pain with hematuria, crystalluria or sterile pyuria and impaired renal function.

In their review, Herlitz et al categorised crystalline nephropathies as calcium-containing, drug-induced, dysproteinemia associated and metabolic or genetic (4). Mulay et al divided them into three subgroups: ischemic due to vascular calcifications or crystal embolism (type 1), tubular injury caused by intra- and extra-tubular crystalline precipitates (type 2), and obstructive nephropathy due to nephrolithiasis (type 3) (3).

Though well documented in native kidneys, many aspects of crystal-induced renal disease in allografts are less recognised (1). Of these, oxalate deposition is the most commonly described with a highly variable prevalence in previous studies - from just 4% in the study by Troung et al (5) to a much higher 52.6% in that by Pinheiro et al

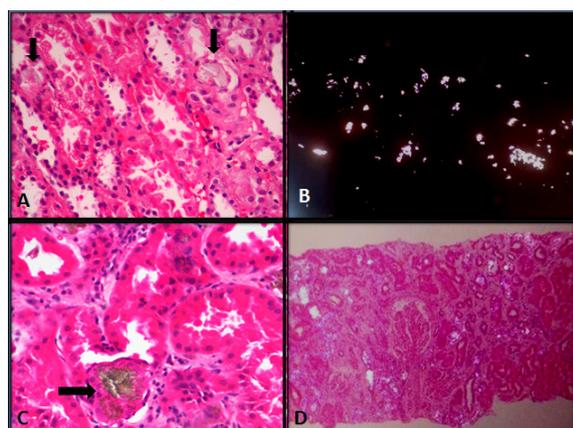


Figure 1. (A) Renal biopsy showing tubules with calcium oxalate crystals having 'fractured glass' appearance; H&E 400 \times . (B) Strongly birefringent oxalate crystals on polarised microscopy. (C) Renal biopsy showing radially arranged brownish green 2,8-DHA crystals; H&E 400 \times . (D) Birefringence of DHA crystals on polarised microscopy (half polarised).

(6). In our study, the overall frequency of crystal deposits in allograft biopsies was 1.5% with oxalate in 1%. Palsson et al attributed this variation to differences in patient characteristics in these studies and timing of biopsy after transplant (1). Surprisingly, our cohort showed much rarer DHA crystals in 3/13 cases.

Oxalic acid is an end-product of many metabolic pathways. Its plasma levels are determined by the balance between dietary intake, intestinal absorption, endogenous production and renal excretion through free glomerular filtration and secretion by the proximal tubule (7). Hyperoxaluria can be primary due to inborn errors of metabolism or more commonly, secondary resulting from enteric hyperoxaluria as in pancreatic insufficiency, gastric by-pass and small bowel resection, toxic exposure or excessive dietary intake (4). Lefaucheur et al have mentioned oxalate nephropathy as a potential side effect of prolonged treatment with antibiotics in transplant recipients (8). When the GFR drops below 30–40 mL/min/1.73 m², oxalic acid excretion by the kidneys is impaired and the plasma concentration rises with little improvement by hemo- or peritoneal dialysis. Plasma oxalic acid concentrations may normalize within weeks after a successful kidney transplant, but a large amount of oxalate is excreted in the first few days which might result in CaOx deposits in renal tubules (7).

Accordingly, Troung et al classified their allograft biopsies with CaOx into three groups. In the first group, the deposition could be explained by the increased tubular oxalate load routinely expected in the immediate post-transplant period resulting in its precipitation. In the second group, the timing of biopsies was usually months or years post-transplant and they revealed chronic allograft nephropathy with tubular atrophy, interstitial

fibrosis and inflammation associated with irreversible loss of renal function. The third group included recurrences in primary hyperoxaluria cases developing shortly after transplant with massive CaOx deposition, severe acute and chronic renal tissue injury possibly due to heavy pre-transplant burden and high plasma level of oxalate (5).

Of 10 cases in our study with CaOx deposits, one was a genetically proven case of primary hyperoxaluria and the patient had undergone simultaneous liver kidney transplant. In others, an inborn error of oxalate metabolism could not be confirmed although there was strong suspicion in one of these patients with a history of recurrent bilateral renal calculi since childhood, and oxalate nephropathy on her graft biopsies within the first month of transplant and later on. Pinheiro et al found a significantly higher incidence of delayed graft function (DGF) in patients with CaOx in their allograft biopsy compared to those without (6). Five of our 10 patients with oxalate had undergone biopsy within the first month of transplant for slow/ worsening graft function with their serum creatinine values ranging from 1.53 to 7.63 mg/L, supporting this very point, though we could not find a direct correlation between density of deposits and serum creatinine levels.

The sequence in the relationship between CaOx deposition and DGF is challenging. In the first study of its kind, Bagnasco et al, found no CaOx deposition in any of the 26 donor kidney biopsies suggesting that it is recipient derived (9). While CaOx can cause direct tubular damage promoting DGF, tubular injury and low tubular flow in DGF can also facilitate CaOx deposition. We have observed acute tubular injury in all our cases with CaOx deposits with concurrent features suggestive or suspicious of acute rejection in three cases.

As mentioned earlier, five cases in the oxalate group (50%) had more than one biopsy on our records, at least one of which was taken within a month of transplant. These included the confirmed and the suspected primary hyperoxaluria cases both of who had crystals on initial and subsequent biopsies beyond 6 months, next two cases who had oxalate only on initial biopsies explainable by high oxalate load in immediate post transplant period and the last case with crystals only on later biopsies. In primary hyperoxaluria, severe hyperoxaluria may persist for months or even years after transplant as oxalate is mobilized from the tissue stores (10). All these cases had features suggestive or suspicious of acute rejection on at least one of their biopsies. Four of them had progressive tubular atrophy and interstitial fibrosis. Although, Bagnasco et al noted no association with occurrence of acute rejection, analysis of repeat biopsies from allografts with oxalate showed a significant increase in IF/TA over a shorter time (9). Snijders et al also noted that CaOx

deposition in biopsies taken within three months post-transplant was associated with inferior renal function at the time of biopsy and subsequent worse graft survival (7).

Of the rest of our oxalate cases, two were biopsied within a month and lacked any IF/TA. Two others with biopsy performed more than a year later, had changes of IF/TA. One was a case of end-stage renal disease (ESRD) due to diabetes and the other, with unknown native kidney disease and retinopathy, had morphological features of early diabetic nephropathy on allograft biopsy. Unfortunately, we do not have previous/subsequent biopsies for these cases. Palsson et al noted that diabetes as an underlying cause of ESRD was independently associated with CaOx deposition in transplants as their urinary oxalate excretion rate is higher (1,11). We could not rule out excessive oxalate intake or possible effects of drugs on oxalate metabolism in our patients.

Most studies on crystals in allografts have dealt with oxalate and only a few cases of recurrent DHA nephropathy are described in literature. Surprisingly, we have encountered 3 allografts with these rare crystals during our study period. It is a rare autosomal recessive disorder characterized by deficiency of adenine phosphoribosyltransferase (APRT) enzyme leading to formation and renal excretion of 2,8-DHA. This entity is probably under-recognized as the crystals are readily mistaken for oxalate due to their strong birefringence under polarized light though these are brownish-green tinted (4). All three of our patients were in fifth and sixth decades of life, but had their disease rightly diagnosed only on their graft biopsies. Two of them had biopsies within a month of transplant showing crystals, of whom one had serial biopsies at our centre which showed progressive worsening with grade 3 IF/TA in a year. The third case diagnosed elsewhere, pre-transplant, as oxalate nephropathy, was biopsied after a year and had grade 1 IF/TA. Kaartinen et al emphasized that patients with previously undiagnosed APRT deficiency undergoing renal transplantation are at a high risk (>25%) of losing their transplant (12). Hence in suspected cases, diagnostic tests including urine examination for DHA crystals, stone examination in cases with urolithiasis, APRT enzyme assay and genetic studies should be readily done though the biopsy appearance is quite characteristic (13). We could demonstrate DHA crystals in the urine of one of our patients and sibling of another with family history of chronic kidney disease. Early and accurate diagnosis enables initiation of treatment with allopurinol which can help improve renal function and prevent further deposition (14).

In their review, Mulay et al have described the complex mechanisms involved in crystal induced renal injury encompassing direct and indirect cytotoxic phenomena

including necrosis, autophagy, necroptosis and an auto-amplification loop of necroinflammation (3). Increase in transcription of activating factors (c-myc, EGR-1, Nur-77, c-jun), extracellular matrix regulators, MAP kinases and growth factors also suggest role of oxalate in renal interstitial fibrosis (15-17).

Conclusion

In conclusion, ours is a descriptive study trying to estimate the frequency of crystal deposits in kidney allograft biopsies and to understand their clinicopathological implications. Crystals in allograft biopsies are often misinterpreted as non-specific, especially when they are fewer in number despite significant tubulointerstitial changes, leading to erroneous diagnoses such as rejection, interstitial nephritis or acute tubular necrosis (12,18,19). Our observations suggest that a diligent search for crystals in renal allograft biopsies including polarised microscopy might help explain graft dysfunction in quite a few cases. Awareness of the wide range of its etiologic factors enables prevention or early treatment. It rarely helps identify native kidney diseases like DHA nephropathy and primary hyperoxaluria especially when there is a history of urolithiasis or previous biopsy with crystals, thereby prompting family screening too. As hypothesized in previous studies, our findings also support crystal deposition as a non-immunologic factor in the pathogenesis of IF/TA. However, more elaborate studies are required to understand the intricacies of crystal induced tissue injury and the role of interventional methods to tackle crystal deposition.

Limitations of the study

We understand that our study has limitations due to the small case cohort, study design which is retrospective and observational as well as lack of information on certain variables known to be significant in this context. Ours is a referral centre for renal biopsies from multiple centres across the state, hence our access to clinical details is often limited. We do not have serial protocol allograft biopsies for any of our patients as almost all our clinicians resort to for-cause biopsies. In the event of any pathology, follow up is also mostly based on clinical parameters unless biopsy is absolutely necessary.

Authors' contribution

JY is the principal investigator of the study and prepared the concept and design. SNV revised the manuscript and critically evaluated the intellectual contents. Both authors participated in preparing the final draft of the manuscript. Both authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism) have been completely observed by the authors. There has been no data fabrication or double publication.

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