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Case Report

Case Report: Secondary Hyperoxaluria Complicated with Systemic Oxalosis

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Abstract

Systemic oxalosis is the most severe complication of chronic hyperoxaluria resulting from either inherited disorder of glyoxylate metabolism (primary hyperoxaluria) or more rarely, increased intestinal oxalate absorption (secondary enteric hyperoxaluria). Significant hyperoxaluria may lead to calcium oxalate crystal formation, contributing to oxalate kidney stones and eventually to abundant crystal deposits within the renal parenchyma, a condition referred as oxalate nephropathy. We discuss and illustrate the case of a patient suffering from oxalate-induced nephropathy that evolves to end-stage renal disease (renal oxalosis) and progresses to systemic oxalosis while treated on hemodialysis.

Keywords: Systemic Oxalosis; Hyperoxaluria; Nephropathy; Hemodialysis; Calcium Oxalate Crystal

Case Report

A 72-year-old male patient from African origin presented at the emergency department for severe acute oliguric kidney failure on pre-existing mild chronic kidney disease (8.5 mg/dl, GFR 11 ml/min/1.73m^2 following MDRD equation) with a bland sediment and low-grade proteinuria, from unknown origin. His chronic medication included Medrol 16 mg/day, omeprazole 20 mg/day, native vitamin D and association of triamterene/hydrochlorothiazide 25-50 mg/day for recent diagnosis of hypertension. His past medical history was relevant for systemic sarcoidosis, chronic healed hepatitis B and antrectomy associated to truncal vagotomy and gastro-jejunal anastomosis in 2007 (Bilroth II surgery) after which he suffered from chronic diarrhoea and weight loss.

Renal work-up was negative for auto-immune, complement-mediated, or viral disease (low replicative hepatitis B) but renal sarcoidosis could not be excluded without biopsy. Interestingly, ultrasound imaging of kidneys showed slight bilateral hyper echogenicity of both kidneys with the presence of a single non-obstructive microlithiasis on the left kidney.

The renal biopsy realized at this time displayed 8 glomeruli (one of which was sclerotic) with mild interstitial fibrosis surrounding some atrophic tubules (IFTA grade I). Moderate lesions of acute tubular necrosis were observed, as well as several precipitations of crystals at the intratubular level, within the tubular cells and at the interstitial level associated with a discrete to moderate inflammatory infiltrate. These crystals appeared birefringent in polarized light in favor of calcium oxalate (CaOx) crystals (figure 1).

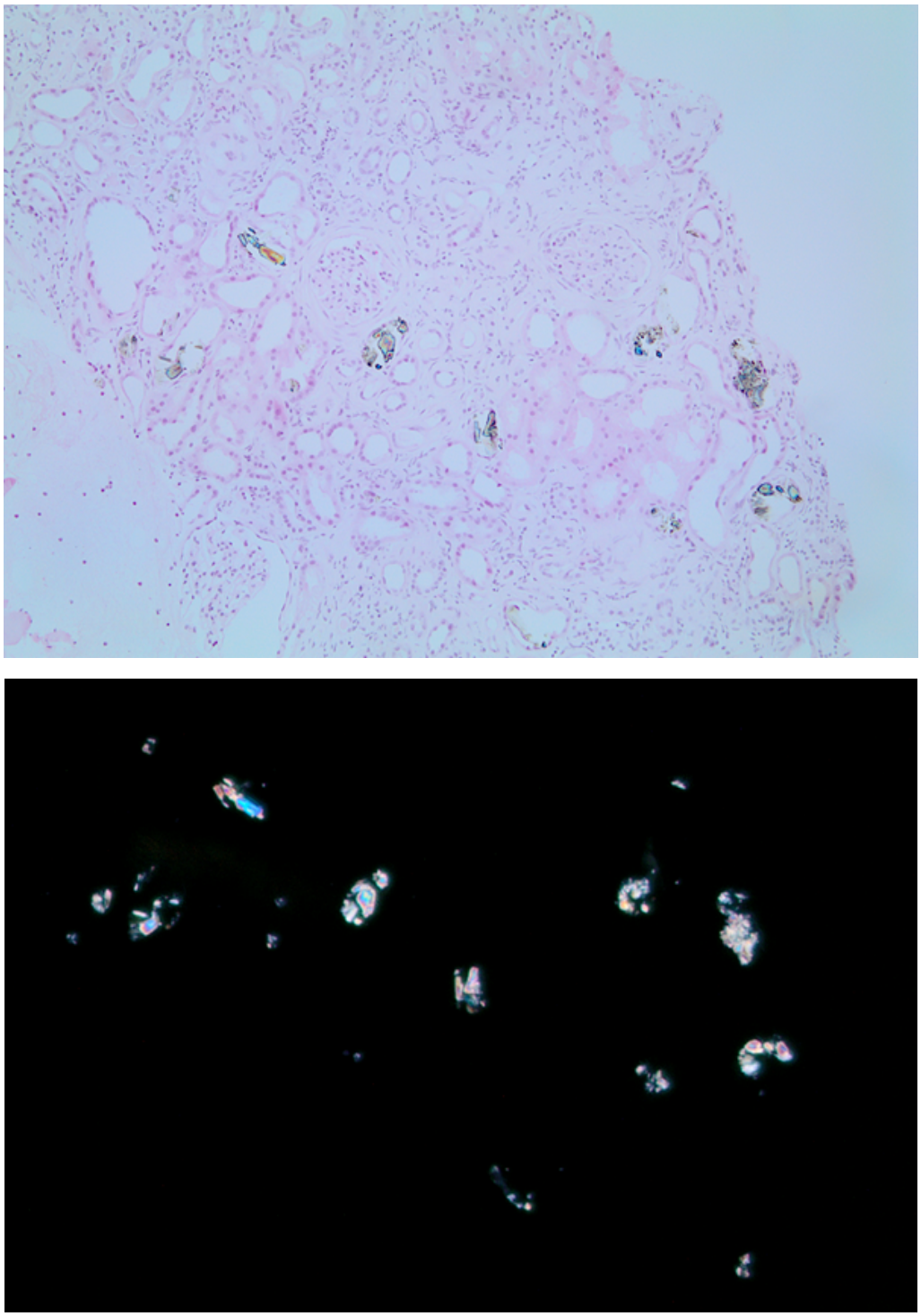

Figure 1: Polarized light microscopy renal biopsy sample (haematoxylin and eosin stain, original magnification x20) demonstrating birefringent intratubular, intracellular and interstitial polyhedral or rhomboid crystals of broken glass appearance with interstitial fibrosis surrounding atrophied tubules.

The ratio of CaOx crystals to glomeruli was 1.10 (9 crystals/8 glomeruli) defining acute oxalate nephropathy according to the threshold ratio ≥ 0.25 proposed by Buysschaert and al. There was also moderate chronic vascular involvement (nephrangiosclerosis).

Unfortunately, the patient didn't recover from his acute kidney failure (AKIN stage III) and evolved within the month to oliguric chronic kidney failure for which conventional thrice weekly haemodialysis through tunnelled CVC has to be started.

He died 4 years later from cardiac tamponade after an invasive complicated procedure of angioplasty to dilate a stenosis in his right brachiocephalic vein. An autopsy was performed as a part of the internal procedure for all iatrogenic death.

Materials and Methods

Autopsy: An external and internal macroscopic examination of the body was performed and samples of various organs (thyroid, trachea, oesophagus, aorta, lungs, hilar nodes, heart, coronary arteries, kidneys, adrenals, spleen, stomach, pancreas, liver, bladder, prostate, vena cava, small intestine and colon) were collected. All specimens were fixed in 4% buffered formalin (pH 7.2-7.4) and included in paraffin (31 blocks). Sections at 5 µm thickness were produced and stained with haematoxylin-eosin (HE). Histological slides were analysed by two pathologists (1 senior and 1 junior).

Immunohistochemestry: Sections (5 µm thick) were subjected to standard immunohistochemestry (IHC). Anti-CD68, CD163, CD3 and CD20 IHC were performed on a Dako Omnis. The slides incubated with the mouse anti-Human CD68 (1/2000 dilution, clone KP1, Dako; Agilent Technologies, Inc., Santa Clara, CA, USA), mouse anti-Human CD20 (1/500 dilution, clone L26, Dako; Agilent Technologies, Inc., Santa Clara, CA, USA) mouse anti-Human CD163 (1/200, clone 10D6, Leica Biosystems, Diegem, Belgium), and mouse anti-Human CD3 (1/200, clone LN10, Leica Biosystems, Diegem, Belgium) antibodies for 20 minutes each. The slides were washed and incubated thought the Flex Detection method for all antibodies, followed by the addition of complex avidin-horseradish peroxidase. Immunostainings were detected by incubation with diaminobenzidine and hydrogen peroxide. All IHC slides were counterstained with Gill's hematoxylin for 2 min at room temperature, dehydrated and mounted. For each staining, an external positive control was performed and verified according to clinical routine.

DNA extraction: We also performed DNA extraction from frozen renal tissue remaining from renal biopsy (rest of the sample dedicated to immunofluorescence). The tissues were embedded in Tissue-Tek O.C.T. (Sakura, California, USA) and stored at −80°C.

Total nucleic acids were extracted from frozen tissues using the QIAamp DNA mini-Kit (Qiagen, Germantown, MD, USA) following manufacturer's instructions and send to the genetics laboratory of the Erasme Hospital.

Pathological Findings

The major lesions found at autopsy were a hemopericardium, as well as a thrombosis stenosis of the superior vena cava and a thrombus of the right ventricle in the context of severe atheromatosis. Post-mortem samples revealed massive birefringent CaOx crystals deposits in the heart, the aorta walls, the kidneys, and the thyroid (figure 2).

In the renal parenchyma, the crystals were found in the intratubular level, within the tubular cells and in the interstitium with the presence of rare multinucleated giant cells. Interstitial fibrosis and tubular atrophy were strongly increased, representing more than 50% of the renal cortex (IFTA grade 3), associated with severe glomerulosclerosis (figure 2A).

For the aortic wall, the crystals were found in the intima which was thickened (atheromatosis) (figure 2B). In the heart, the crystals were found between the muscle fibres without inflammatory reactions or signs of acute infarction (figure 2C). However, there was a background of chronic ischemic cardiomyopathy with fibrous sequelae. Finally, in the thyroid, the crystals were present within the colloid and between the thyroid follicles (not shown).

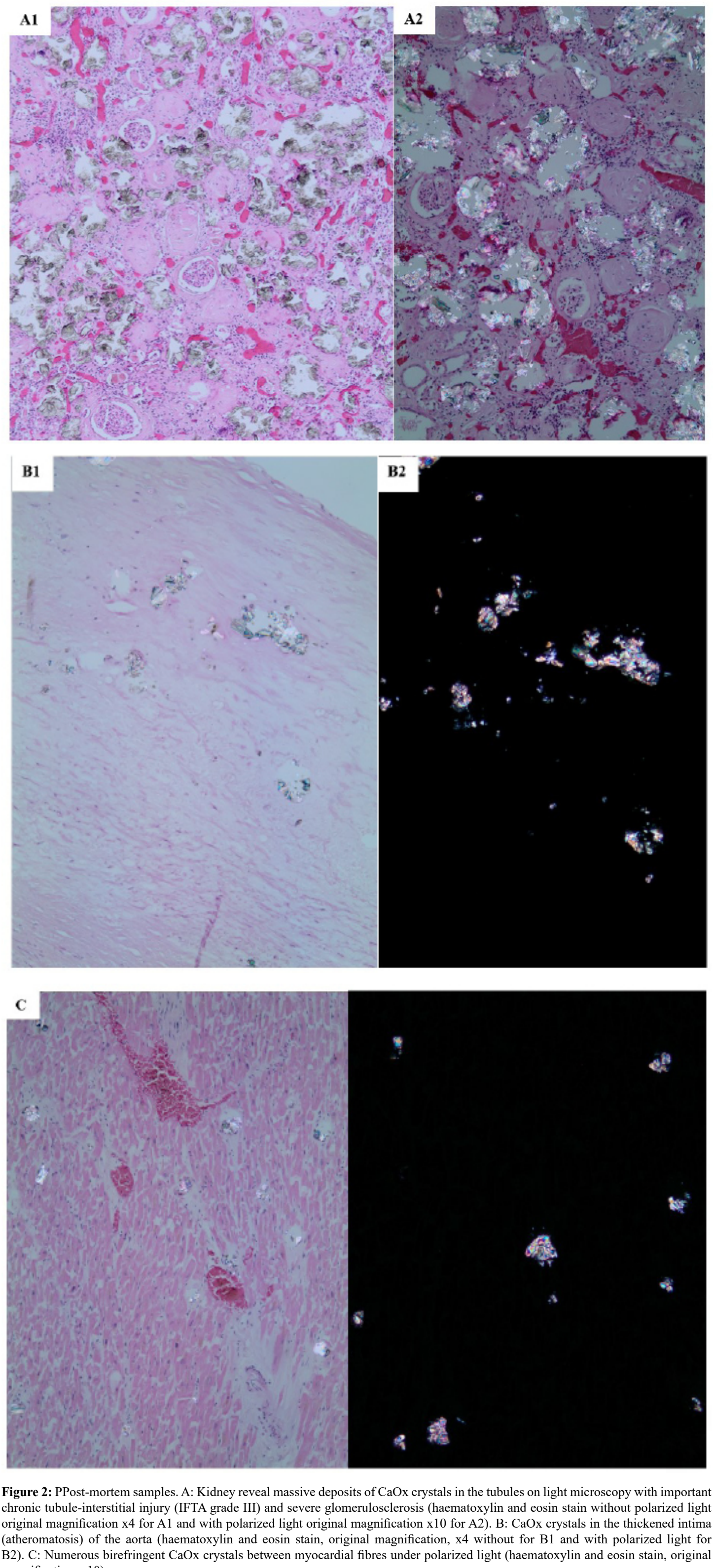

Figure 2: PPost-mortem samples. A: Kidney reveal massive deposits of CaOx crystals in the tubules on light microscopy with important chronic tubule-interstitial injury (IFTA grade III) and severe glomerulosclerosis (haematoxylin and eosin stain without polarized light original magnification x4 for A1 and with polarized light original magnification x10 for A2). B: CaOx crystals in the thickened intima (atheromatosis) of the aorta (haematoxylin and eosin stain, original magnification, x4 without for B1 and with polarized light for B2). C: Numerous birefringent CaOx crystals between myocardial fibres under polarized light (haematoxylin and eosin stain, original magnification, x10).

Bones were not collected at autopsy in that context due to the lack of clinical diagnosis provided before the autopsy.

Secondly, we characterised the inflammatory infiltrate present within the renal parenchyma on the autopsy blocks by immunohistochemistry and compared semi-quantitatively with that of the first renal biopsy (2016).

The renal parenchyma collected at autopsy revealed the same lymphocytic inflammatory profile (CD3+ T cells in the majority) as the first renal biopsy but in greater amount. The macrophagic infiltrate was also more important with a less marked difference between the number of CD68+ and CD163+ macrophages in the renal autopsy that in the first renal biopsy. However, the proportion of CD163+ macrophages in the cortex and renal medulla remains in always higher (figure 3).

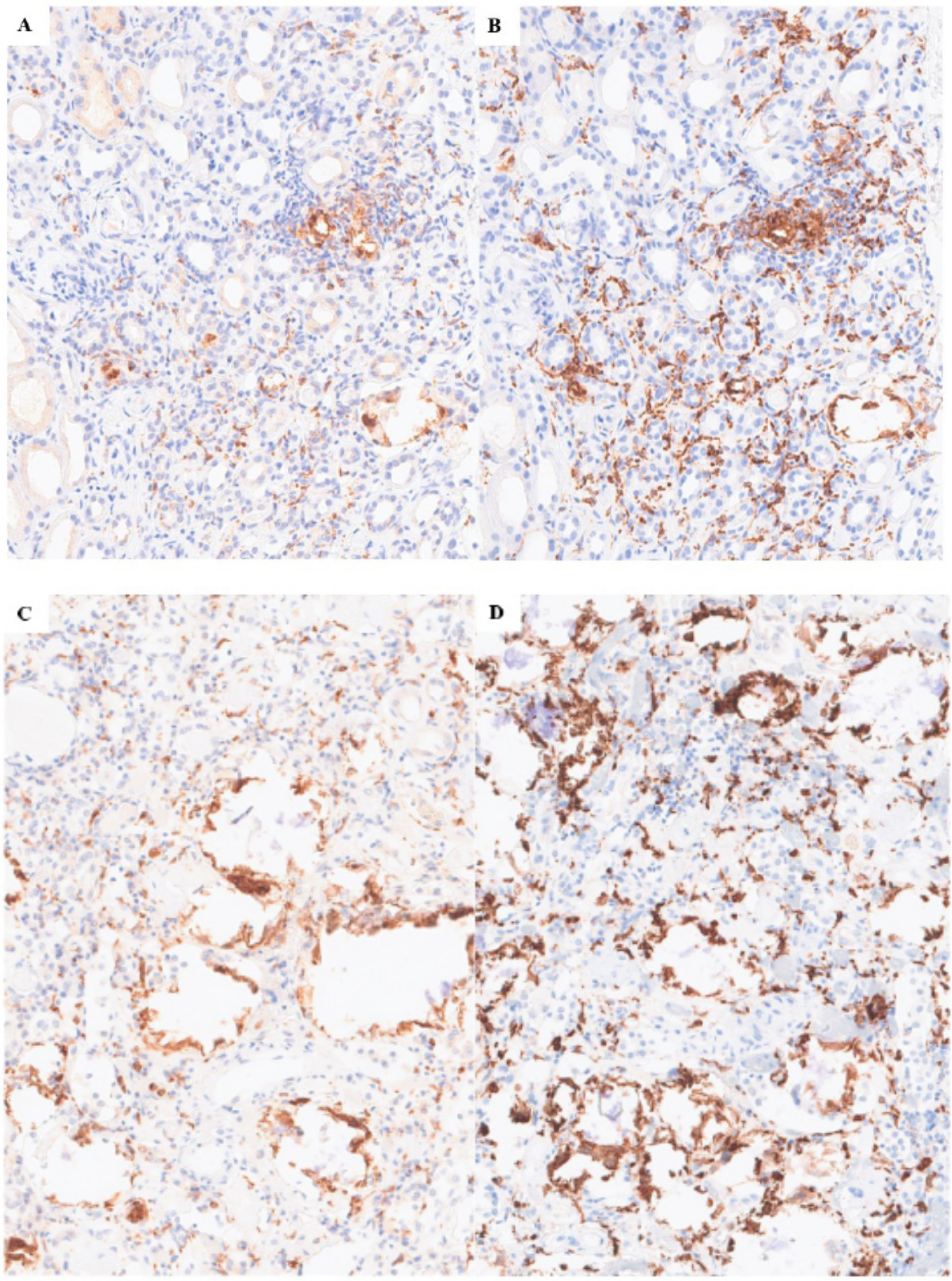

Figure 3: Characterisation of the inflammatory infiltrate by immunohistochemistry to compare the evolution over time. A : Illustration of the anti-CD68 immunostaining in the 2016 kidney biopsy (original magnification, x15). B : Illustration of the anti-CD163 immunostaining in the 2016 kidney biopsy (original magnification, x15). C : Illustration of the anti-CD68 immunostainingin the autopsy kidney sample (original magnification, x10). D : Illustration of the anti-CD163 immunostainingin the autopsy kidney sample (original magnification, x10).

Discussion

Acute oxalate nephropathy (AON) is a rare although under-recognized potentially irreversible cause of kidney failure characterized by interstitial nephritis with significant CaOx crystals deposits. Buysschaert et al. proposed a threshold of oxalate crystals-to-glomerulus ratio greater than or equal to 25% to distinguish oxalate nephropathy from other chronic nephropathies with fewer “by-standers” crystals.

In the most documented case series of oxalate nephropathy from Saint-Luc hospital (Brussels), the auteurs found that this diagnosis represents 1% of all kidney disease that deserved a biopsy (on more than 2000 biopsies) [1], with a mean age of 61 years and creatinine as high as 8 mcg/dl at the time of the renal biopsy. More than the two thirds (62%) of those patients had acute on chronic kidney injury (stage 3) as the main mode of presentation with a rapid (within the month) progression to renal failure for more than half of those patients (52%), which was quite similar to our observation.

In adults, oxalate nephropathy results most often from secondary hyperoxaluria than from primary hyperoxaluria, an inborn error of glyoxalate metabolism leading to hepatic overproduction of oxalate. However, rare cases of “late-onset” primary hyperoxaluria have been described in adults suffering from recurrent oxalate urotlithiasis as late as 60 years old [2]. In those rare cases, a diagnosis of primary hyperoxaluria were done after specific variants in AGXT, pyridoxine responsive, were found (Gly170Arg and Phe152Ile variants). For our patient, germline analysis return negative.

In physiological condition, less than 15% of dietary oxalate is normally absorbed because oxalate is eliminated in the stools after binding with calcium in the intestine and degraded by intestinal Oxalobacter formigenes [3]. Plasma oxalate from both endogenous hepatic production or dietary consumption does not have any biological function in the organism and is rapidly and fully excreted by the kidneys through glomerular filtration and tubular secretion [3].

Main causes of secondary hyperoxaluria include fat malabsorption from various malabsorptive conditions (gastric bypass, lipase inhibitor, lenalidomide, chronic pancreatitis, pancreatectomy, short-bowel syndrome, celiac disease, cystic fibrosis, bacterial pullulation or microbiota perturbations, and Crohn's disease), excessive oxalate or oxalate precursors intake (ethylene glycol intoxication or vitamin C supplementation > 1g/day, star fruits, cashew nuts, shaga mushrooms,…) along with possible concomitant reduced intestinal bacterial oxalate degradation due to gut microbiota perturbation (reduced oxalate-degrading bacteria taxa, Oxalobacter formigenes a.o, intestinal colonization). In the case series of Buysschaert et al., by-pass and chronic pancreatitis (exocrine insufficiency) account for most of the causes of enteric hyperoxaluria (48%) with delay between hyperoxaluria-enabling conditions and renal failure ranging from 1 to 22 years although lipase inhibitors use seems to cause a more rapid evolution to AON than bariatric surgery does [1].

In our observation, time between the gastro-jejunostomy and the diagnosis of oxalate nephropathy was 8.6 years, concording with the delay described in their case series (mean of 8 years after by-pass). Chronic volume depletion due to chronic steatorrhea and double diuretics treatment was suspected a posteriori to be the triggering factor that precipitate renal failure in our patient.

Compared to the first kidney biopsy samples obtained four years earlier, the autopsy kidney samples demonstrated much more crystals precipitation and chronic injuries, confirming the accumulation of oxalate calcium crystals within the kidneys over dialysis treatment time (4 years). Moreover, the computed CT-scan of the abdomen realized 6 months before his death revealed severe nephrocalcinosis/oxalosis of the kidneys.

Systemic oxalosis, defined by systemic oxalate deposition, usually accompanies patients suffering from primary hyperoxaluria when they reached advanced renal disease (GFR < 30 ml/min/1.73m^2) but is scarily documented in the setting of secondary hyperoxaluria [4]. Indeed, only individual observations have been reported so far by some authors, for instance in the setting of severe Crohn disease or high oral doses of vitamin C. Hueppelsaeuer et al. reported one 43 y.o. female patient suffering from short bowel syndrome from Crohn's disease who failed her first kidney transplantation after 8 years of dialysis because of recurrence of oxalate nephropathy due to systemic oxalate deposition during long dialysis period. However, after application of pre- and post-transplant measures identical to that of primary hyperoxaluria (increased HD regimen, vit B6, high fluid administration, alkaline citrate, decarboxylase enzyme), the second transplant was later successful [5].

The main sites of deposition well documented are the kidneys, blood vessel walls and bones. However, other locations may include the joints, retina, skin, bone marrow, heart and central nervous system [2]. The consequences are various organ dysfunctions depending on the organ affected, which can have serious consequences and even lead to death.

Under light microscopy, CaOx crystals have a clear broken glass appearance and are characterised by birefringence in polarised light. They precipitate in the renal tubules, with tubular damage as a direct consequence and interstitial fibrosis and tubular atrophy in the longer term. CaOx crystals are mainly found in the intratubular area, but also in the tubular cells and more rarely in the interstitium. In our case, we found all three locations.

Other types of crystals to exclude are 2,8 dihydroxyadenine, also birefringent but distinguishable by their brownish colour on haematoxylin-eosin [6], and non-birefringent calcium phosphate crystals stained black by Von Kossa staining. Calcium phosphate and CaOx crystals are the most common and together account for 80% of crystal induced-nephropathy kidney [7].

Histologically, primary forms of hyperoxaluria usually show a larger number of crystals along with a larger interstitial inflammatory infiltrate compared to the secondary form [7]. This chronic inflammatory context then leads to interstitial fibrosis and chronic renal failure. This theory was confirmed based on animal models, which showed that the inflammatory response was induced via the interleukin-1β (IL-1β) pathway by stimulation of the NLRP3 inflammasome [8,9].

In the literature, CD68+ pro-inflammatory macrophages (M1) are described as prominent in the renal tissue of lithiasis patients with a predominance in the medullary region. Furthermore, no significant difference was found between the number of CD163+ macrophages (M2) and T cells (CD3+) in lithiasis and non-lithiasis patients in a series of patients treated by nephrectomy for renal neoplasia [10].

When the number of pro-inflammatory M1 CD68+ macrophages was increased, a considerable increase in the expression of pro-inflammatory signals such as interleukin 6 (IL6), TNF and interleukin 10 (IL10) was observed in vitro [11]. While M1 macrophages facilitate the development of CaOx crystals in the kidney, with renal inflammation, fibrosis, and cell damage, M2 macrophages remove these crystals through a greater ability to phagocytose of CaOx crystals [12]. The identification of this signalling pathway of crystal induced renal injury makes it possible to determine future potential therapeutic targets [8], which would also be common to different crystals (calcium oxalate, uric acid and monoclonal light chains) according to animal models [3].

There are no specific therapies for enteric hyperoxaluria, and one should focus on treating the underlying disease to reduce fat malabsorption (bile acids or bile acid sequestrants, pancreatic

enzymes, by-pass reversal among others). Additional measures to reduce GI absorption of oxalate such as calcium supplements intake during the meals, probiotics, oxalate-degrading enzymes (oral oxalate decarboxylase, reloxaliase, currently in Phase III study) and low oxalate diet content should also be implemented as it has been shown that oxalate intestinal absorption is directly correlated to its excretion through kidneys, thus the severity of hyperoxaluria [5]. Finally, measures to reduce calcium oxalate crystallization in the urine such as increasing daily fluid intake and citrate alkalization are complementary [13,14].

It is well known that intensive haemodialysis regimen (5 to 6 times a week) is the common adopted strategy (among others) in patients suffering from primary hyperoxaluria to prevent further systemic oxalate accumulation and preparing them for kidney transplantation targeting plasma oxalate threshold of <30 µg/L at the end of dialysis session. It is far less documented if intensive haemodialysis strategies are required in patients with oxalate nephropathy from enteric causes. Based on this observation, we could reasonably assume that conventional thrice weekly haemodialysis may be insufficient to prevent further renal and systemic oxalate accumulation and further renal allograft deposition, especially in whom the underlying malabsorptive condition is not controlled, as illustrated in this present case. Expert consensus and therapeutic guidance to prevent evolution from enteric hyperoxaluria to systemic oxalosis in ESRD allowing them to be transplanted safely are needed in the future.

Conclusion

Malabsorptive hyperoxaluria-enabling conditions should be considered as potential "ticking bombs" for the kidneys, staying most of the time longstanding pauci-symptomatic before threatening the kidneys in a devastating manner when potential triggers are added. Most of the time, prognosis of oxalate nephropathy is severe with half of the patients requiring dialysis few times after diagnosis, mainly to delayed diagnosis and/or absence of preventive strategies against hyperoxaluria. Moreover, causal treatment should be maintained even after dialysis initiation to prevent further extra renal systemic oxalate crystals load and to allow successful kidney transplantation. Increased awareness of the nephrology community of the various causes, mechanisms, and potential treatment of secondary oxalate nephropathy would certainly prevent potential devastating consequences for these patients.

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