Enteric hyperoxaluria and renal failure associated with lymphangiectasia

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Introduction

Patients presenting with renal calculi are routinely screened for hyperoxaluria, defined as the excessive urinary excretion of oxalate anion. The aetiological diagnosis of hyperoxaluria is very important, since as well as causing renal disease, hyperoxaluria may reflect either potentially lethal genetic disorders of glyoxylate metabolism (the primary hyperoxalurias) or underlying gastrointestinal disease (secondary enteric hyperoxaluria). Other causes of secondary hyperoxaluria include overconsumption/production of oxalate or its precursors from exogenous sources. The primary hyperoxalurias are typically associated with nephrolithiasis, nephrocalcinosis, renal failure, and systemic deposits of calcium oxalate in young people, but the secondary hyperoxalurias can also cause nephrolithiasis and progressive renal disease. Thus the presence of hyperoxaluria demands effective investigation and therapy. We here describe a patient with primary intestinal lymphangiectasia who presented with hyperoxaluria and oxalate-induced interstitial nephritis. The diagnostic and therapeutic approaches are discussed.

Case report

A 46-year-old caucasian female was referred to Hammersmith Hospital in 1994 for investigation of renal impairment associated with calcium oxalate crystal deposition and interstitial fibrosis demonstrated on percutaneous renal biopsy at the referring hospital.

Her childhood was normal, with no urinary sepsis or nephrolithiasis, but on routine urinalysis in 1973 she was noted to have proteinuria. Investigation at that time demonstrated plasma creatinine 105 μmol/l with 0.8 g/24 h proteinuria, and an intravenous urogram was normal, with no evidence of calculi or nephrocalcinosis. In 1982 she developed non-insulin-dependent diabetes mellitus which was treated with a sulphonylurea. Plasma creatinine at this point was 131 μmol/l.

The patient moved abroad, and in April 1994 presented to hospital with pruritus and steatorrhoea. Her alkaline phosphatase and aspartate transaminase were elevated. Serological tests for hepatitis A, B and C were negative, as were antimitochondrial and antinuclear antibody assays. A liver ultrasound scan was normal, as was a liver biopsy, and she underwent endoscopic retrograde cholangiopancreatography (ERCP), which demonstrated pancreatic calcification and some beading of the intrahepatic ducts, raising the possibility of sclerosing cholangitis. Plasma creatinine was 172 μmol/l and there was no nephrocalcinosis. Her symptoms settled without therapy.

The patient returned to the UK in August 1994 and was seen at her local hospital, where she reported feeling well and denied gastrointestinal symptoms including diarrhoea, steatorrhoea, or abdominal pain. Examination was unremarkable, with normal blood pressure, normal fundi, and no evidence of neuropathy. Plasma creatinine was 271 μmol/l, creatinine clearance 19 ml/min with 0.78 g/24 h proteinuria; immunological screening for connective-tissue disease was negative. A renal ultrasound scan showed two small kidneys (7 cm bipolar diameter) which were hypechoic, with no evidence of calculi or obstruction. A percutaneous renal biopsy (Figure 1) showed severe interstitial nephritis with giant-cell reaction and the presence of calcium oxalate crystals within both tubules and interstitium. Glomeruli were normal. No specific treatment was initiated at this point.

Six weeks later the patient presented as an emergency with a 4-week history of anorexia, vomiting, lethargy, pruritus, and weight loss. She had evidence of volume depletion on examination, and urgent
laboratory investigations demonstrated plasma creatinine 843 μmol/l, urea 64.9 mmol/l and bicarbonate 7 mmol/l. She was admitted, received intravenous normal saline, and transferred to Hammersmith Hospital for further investigation and treatment. She had recently begun insulin therapy for her diabetes but took no other medication or traditional remedies. There was no family history of renal disease, nephrolithiasis, or diabetes mellitus.

On arrival she was febrile (37.7°C) and had an abscess on her forehead. She had evidence of persistent volume depletion with sinus tachycardia, low jugular venous pressure, and postural hypotension. Respiratory, abdominal and neurological examinations were unremarkable. Urinalysis revealed + proteinuria and + glycosuria with 4 white cells per high-power field and multiple organisms on microscopy. No crystals were seen in the sediment.

Immediate laboratory investigations showed haemoglobin 8.3 g/dl, white cell count 17.2 × 10^9/l (90% neutrophils) and normal platelet count and clotting studies. Serum sodium was 141 mmol/l, potassium 4.8 mmol/l, urea 36.8 mmol/l, and creatinine 509 μmol/l. Serum albumin was 28 g/l, aspartate transaminase 39 IU/l, alkaline phosphatase 175 IU/l, bilirubin 8 μmol/l, and amylase 15 Somogyi U/dl. The serum C-reactive protein level was 16 mg/l, glucose 8 mmol/l and glycosylated haemoglobin 8.6%. Arterial blood gases taken whilst breathing room air revealed pH 7.27, pCO₂ 1.88 kPa, pO₂ 22.65 kPa, HCO₃⁻ 6.2 mmol/l, base excess −19.9 mmol/l. An abdominal ultrasound scan showed normal liver and biliary tract and confirmed the presence of two small kidneys with no pelvicalyceal dilatation or calculi evident. Plasma oxalate was 31.2 μmol/l (normal 1–3 μmol/l). A provisional diagnosis of chronic renal failure due to hyperoxaluria with interstitial nephritis was made on the basis of the renal biopsy, with an acute deterioration in renal function related to volume depletion and sepsis. The patient received intravenous fluids and antibiotics and underwent surgical drainage of the facial abscess. She commenced a low-oxalate diet and remained on insulin therapy with the addition of oral sodium bicarbonate. Serum creatinine fell initially but subsequently rose, and plasma oxalate climbed to a peak of 93 μmol/l.

Intensive (daily) haemodialysis was begun in December 1994 in order to reduce plasma oxalate and treat uraemia. There was no evidence of systemic oxalosis on fundoscopy, nerve conduction studies, X-ray skeletal survey, ECG, or echocardiogram.

Further investigation to define the cause of the hyperoxaluria was undertaken. Twenty-four-hour urinary oxalate excretion prior to dialysis was 1.06, 1.17 and 0.75 mmol/24 h on three estimates (normal 0.1–0.46) and urinary glycolate was 0.4 and 0.35 mmol/24 h (normal 0.1–0.33). L-glycerate was not detected in the urine. Liver biopsy was performed and alanine: glyoxylate aminotransferase (AGT) activity was 13.8 μmol/h/mg protein (reference range 9.7–18.5). AGT immunoactivity was positive and immunocytochemical studies showed normal peroxisomal localization of AGT. Hyperoxaluria had thus been confirmed, but both type 1 and type 2 primary hyperoxaluria (PH1 and PH2 respectively) were excluded on the basis of AGT assay for PH1, and the absence of glycemic aciduria for PH2. A search for causes of secondary hyperoxaluria was undertaken.

The history was retaken but no new information emerged. The patient denied steatorrhea, weight loss, and abdominal pain and there were no extraintestinal features of inflammatory bowel disease. In view of the dysmorphic facies, karyotype analysis and a dysmorphicology database search were performed but were both normal/negative. Serum B₁₂, folate, iron and ferritin were normal as were serum immunoglobulins and electrophoresis. There was no Bence Jones proteinuria and autoimmune profile was negative. A pancreatealceal test and small-bowel follow through were both normal. CT scan of abdomen and pelvis disclosed pancreatic calcification and thickening of the duodenal/small bowel wall. A repeat ERCP showed chronic calcific pancreatitis and minor intrahepatic ductal changes, again suggesting possible sclerosing cholangitis. A 3-day faecal fat collection demonstrated steatorrhea with 36 g fat (normal 0–5), and a transferrin–indium scan suggested protein-losing enteropathy with only 72% of indium retained (normal >90%).

Duodenal biopsy (Figure 2) demonstrated the presence of dilated villous and mucosal lymphatic channels with no granulomas. Villi were focally shortened but brush borders preserved, and there was no excess of intraepithelial lymphocytes. There was a moderate increase in acute and chronic inflammatory cells in the lamina propria and focal gastric metaplasia, but no microorganisms were seen.

A diagnosis of primary intestinal lymphangiectasia with secondary (enteric) hyperoxaluria and oxalate-induced chronic interstitial nephritis was made. The patient remained on relatively high-intensity haemodialysis (Kt/V = 2.0) with typical predialysis plasma oxalate 21.8 μmol/l and postdialysis 13.2 μmol/l. She received a low-oxalate, low-fat and high-calcium diet and was treated with insulin and magnesium glyco-
the gut or increased oxalate synthesis from exogenous sources (secondary hyperoxaluria).

There are two well-defined types of primary hyperoxaluria (Figure 3). In type 1 primary hyperoxaluria (PH1), there is deficient activity of the hepatic peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT, EC2.6.1.44), which catalyses the conversion of glyoxylate to glycine, using pyridoxine as a cofactor [3]. Accumulating glyoxylate is oxidized to oxalate by lactate dehydrogenase (LDH, EC 1.1.1.27) and also reduced to glycolate under the catalytic influence of glyoxylate reductase—hyperglycolic aciduria is noted in around 75% of patients with PH1. The calcium salt of glycolate is soluble and causes no tissue damage, unlike calcium oxalate, which has a very low solubility and can precipitate widely. In PH1, calcium oxalate nephrolithiasis and nephrocalcinosis develop initially, progressively impairing renal function. The combination of oxalate overproduction and reduced excretion accentuates the hyperoxalaemia, resulting in supersaturation of tissue fluids and systemic deposition of calcium oxalate (oxalosis). This usually occurs within the first two decades of life and is associated with peripheral neuropathy, retinopathy, subcutaneous calcinosis, synovitis, livedo reticularis, ischaemic vasculitis of the digits, osteodystrophy, and cardiomyopathy.

Primary hyperoxaluria type 2 (PH2) is less common than PH1. It is an autosomal recessive condition caused by mutation in the gene for glyoxylate reductase (GR) which usually reduces glyoxylate to glycolate [5]. Glyoxylate, accumulating behind the metabolic block, is converted to oxalate by LDH, resulting in hyperoxaluria. The enzyme GR is identical to D-glycerate dehydrogenase (DGDH) which catalyses reduction of hydroxyacetone to D-glycerate. In PH2, hydroxyacetone therefore accumulates, and is converted to both L-glycerate (by LDH) and serine (by alanine:hydroxyacetone aminotransferase). Urinary L-glycerate (absent in normal subjects) and hyperoxaluria are the diagnostic features of PH2. GR assays are possible on systemic leukocyte lysates, but are not widely available. A novel HPLC assay for L-glycerate in body fluids has been proposed by Marangella and colleagues, and it may become possible to demonstrate that many patients labelled as PH1 without enzymological confirmation of the diagnosis do, in fact, have PH2 [6].

Discussion

This case is the first description of secondary hyperoxaluria associated with intestinal lymphangiectasia and illustrates the diagnostic approach to a patient with hyperoxaluria. The renal biopsy provided the clue to the presence of hyperoxaluria in our patient, but it is more often discovered during investigation of nephrothiasis. Oxalate is an inert anion derived mainly from endogenous glyoxylate and ascorbic acid metabolism (Figure 3). In normal subjects, less than 10% of dietary oxalate is absorbed and contributes little to the systemic oxalate load [1,2]. Hyperoxaluria represents excessive urinary oxalate excretion and can be caused either by genetic mutations resulting in overproduction of oxalate (primary hyperoxaluria), or acquired conditions associated with increased oxalate absorption from phosphate. She was judged to be a suitable candidate for renal allotransplantation, but moved abroad in late 1995.
PH2 causes nephrolithiasis and end-stage renal disease, usually within the first two decades of life, and can also be associated with systemic oxalosis. The absence of urinary L-glycerate from our patient excluded the diagnosis of PH2.

A third form of primary hyperoxaluria has been proposed by Yendt and Cohenim [7]. They described a 13-year-old girl with hyperoxaluria and calcium oxalate nephrolithiasis, whose hyperoxaluria appeared to respond to thiazides, but insufficient data was given to confidently exclude PH1, PH2 and all causes of secondary hyperoxaluria.

The secondary hyperoxalurias are a more heterogeneous group—the commonest form being due to excessive absorption of oxalate from the gut (enteric hyperoxaluria). In normal subjects, less than 10% of dietary oxalate is absorbed, but in enteric hyperoxaluria this is significantly increased, and up to 60% of intestinal oxalate may be absorbed, as determined by radioisotope studies [1,2]. Dietary calcium usually binds to luminal oxalate, forming insoluble calcium oxalate, which passes through the gut unabsorbed. In malabsorptive states, an elevated concentration of luminal free long-chain fatty acids saponifies the calcium, making less calcium available for oxalate binding. Consequently, oxalate hyperabsorption across the colonic mucosa occurs, with a rise in plasma oxalate and associated hyperoxaluria [1,8,9]. Enteric hyperoxaluria occurs in any condition associated with fat malabsorption, e.g. jejuno-ileal bypass (JIB) surgery for obesity, ileal resection, and chronic inflammatory bowel disease. The degree of hyperoxaluria has been found to parallel the magnitude of steatorrhoea in several studies [2,8,10], but not all [9]. Secondary hyperoxaluria is also seen in severe dietary pyridoxine (AGT cofactor) deficiency, and where oxalate precursors are in excess, e.g. consumption of ascorbic acid or ethylene glycol, methoxyfluorane use, glycine irrigation of the bladder, and aspergillosis.

Calcium oxalate crystals are seen in the urine almost universally after jejuno-ileal bypass (JIB) performed for obesity, and hyperoxaluria was documented in 60% of these patients in one study [11]. Calcium oxalate nephrolithiasis is also common in such patients, occurring in up to 32% [11]. The first description of oxalate-induced interstitial nephritis in association with enteric hyperoxaluria was by Cryer et al. [12]. In 1975 they described a 41-year-old morbidly obese male who underwent JIB, and 3 years later was found to have hyperoxaluria and significant renal impairment (creatinine clearance 21 ml/min). He underwent renal biopsy, which demonstrated calcium oxalate deposition and an associated interstitial nephritis. The JIB was reversed and the hyperoxaluria swiftly returned to normal, with stabilization of his renal function. There have been several similar reports [13–17], most frequently describing JIB patients, with renal biopsies typically showing intratubular oxalate crystal deposition with associated giant-cell reaction, tubular destruction, interstitial inflammation and fibrosis. End-stage renal disease occurred in several of these cases [14,16]. It has been proposed that the formation of intratubular crystals is the initiating event, crystal growth resulting in tubular rupture and exciting a peritubular inflammatory response leading to interstitial nephritis and subsequent fibrosis [14]. It is interesting that some patients develop nephrolithiasis after JIB, whilst others, with similar degrees of hyperoxaluria, develop interstitial nephritis. This difference may reflect variation in excretion of urinary inhibitors of stone formation, urine pH, or habitual fluid intake.

An acute renal failure syndrome has been described in enteric hyperoxaluria by Mandell et al. [18]. A woman with short-bowel syndrome developed acute renal failure in association with volume depletion and renal biopsy demonstrated typical oxalate interstitial nephritis. It was proposed that hypovolaemia resulted in tubular obstruction by calcium oxalate crystals, with subsequent dissolution of the crystals, resulting in recovery of renal function. Clearly, acute tubular necrosis may have also played a major part in the pathophysiology of renal failure in this patient. Our patient had an acute exacerbation of renal impairment following volume depletion and sepsis, and similar mechanisms may have been operative. Her subsequent recovery was limited, however, and continuing oxalate deposition and/or interstitial inflammation resulted in end-stage renal disease.

It is of interest that uric acid calculi have been reported in several patients with enteric hyperoxaluria, as well as the expected calcium oxalate calculi [15,16]. Urinary urate excretion was not recorded in these reports, but would not be expected to increase with steatorrhoea. It is possible that urinary calcium oxalate may act as a nidus for uric acid calculus formation. Uric acid calculus formation is increased in urine of low pH, but this would also not be expected in the presence of tubulointerstitial disease, which often causes renal tubular acidosis.

Apart from general supportive measures, there are several specific therapies for enteric hyperoxaluria, aimed at reducing both oxalate absorption from the gut and calcium oxalate crystallization in the urine [19]. A low oxalate diet should be instituted [20], limiting the enteric oxalate load. To maximize the concentration of calcium in the gut lumen, promoting calcium oxalate salt formation, a diet low in fat and high in calcium should also be provided [21]. All attempts should be made to treat the malabsorptive bowel disorder, JIB reversal being the commonest example, since resolution of steatorrhoea will abolish oxalate hyperabsorption. A seaweed-derived polymer, organic marine hydrocolloid, has been used by one group to adsorb intraluminal calcium, trapping bound oxalate and preventing systemic absorption, although the effect was limited and hyperoxaluria was not fully corrected [22]. To minimise urinary precipitation of calcium oxalate, high urinary volumes should be maintained and inhibitors of crystal formation and aggregation used, such as magnesium, orthophosphate and citrate [23].

When renal replacement is necessary in enteric hyperoxaluria, haemodialysis is usual, since inherent
abdominal pathology precludes peritoneal dialysis. Peritoneal dialysis may also afford inadequate oxalate clearance, permitting systemic oxalosis, although the oxalate load in secondary hyperoxaluria is less than that in PH1/PH2. Renal transplantation is not contra-indicated in enteric hyperoxaluria, although reduction/reversal of hyperoxaluria would minimize risk of recurrent disease in the allograft. There is a case report of a female patient with short-bowel syndrome from multiple bowel resections who underwent cadaveric renal transplantation and had good graft function 7 years post-transplant despite persistent hyperoxaluria [24]. Of note, the patient received calcium and magnesium supplements, with double immunosuppression using prednisolone and azathioprine. Cyclosporin A was not used because of poor absorption in association with steatorrhoea. Successful renal allotransplantation in the setting of persistent hyperoxaluria has also been demonstrated in primary hyperoxaluria, providing adequate measures are taken to inhibit calcium oxalate nephrolithiasis [25].

Hyperoxaluria and renal failure have not previously been described in association with intestinal lymphangiectasia, a condition in which gut lacteals and other lymphatics, such as those of serosa and mesentery, are dilated. This is associated with impaired chylomicron absorption and a ‘lymph leak’ into the intestinal lumen, resulting in steatorrhoea. Lymphangiectasia can be a primary, idiopathic condition or secondary to other disorders which obstruct intestinal lymphatic drainage, such as retroperitoneal fibrosis, lymphoma, Crohn’s disease, or systemic sclerosis. The condition presents with varying degrees of steatorrhoea and malabsorption, gastrointestinal symptoms seldom being prominent, as in our patient. Management comprises a low fat diet, with short- and medium-chain fatty acids sometimes being provided, since their absorption is thought to be superior to that of long-chain fatty acids in this disorder.

Hyperoxaluria is a complex disorder, which may signal a life-threatening genetic condition, or reflect gastrointestinal disease. Consequently, determining the aetiology of a patient’s hyperoxaluria is vital to their successful management. In this report we have described the diagnostic approach to a patient found to have hyperoxaluria and renal impairment. This is the first recorded case of primary lymphangiectasia associated with enteric hyperoxaluria and oxalate-induced interstitial nephritis resulting in end-stage renal failure. Unfortunately for our patient, her interstitial nephritis was sufficiently advanced to progress to dialysis dependence, despite appropriate therapy.

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