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Oxalate Nephropathy in Systemic Sclerosis: Case Series and Review of the Literature

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Abstract

Objective—To increase awareness of oxalate nephropathy as a cause of acute kidney injury (AKI) among systemic sclerosis patients with small intestinal dysmotility and malabsorption, and to prompt consideration of dietary modification and early treatment of predisposing causes of oxalate nephropathy in this population.

Methods—Two cases of biopsy-proven oxalate nephropathy were identified among systemic sclerosis patients in the course of direct clinical care. Subsequently, a retrospective search of the Johns Hopkins Pathology databases identified a third patient with systemic sclerosis who developed oxalate nephropathy.

Results—Among the three patients with qualifying biopsies, all three had systemic sclerosis with lower gastrointestinal involvement. All three presented with diarrhea, malabsorption, and AKI. In two of the three patients, diarrhea was present for at least two years before the development of AKI; in the third, incidental oxalate nephropathy was noted three years before she developed AKI and extensive oxalate nephropathy in the setting of a prolonged mycobacterium avium-intracellulare enteritis. In one case, oxalate crystals were present by urinalysis months before diagnosis by biopsy, in the second, hyperoxaluria was diagnosed by urine collection immediately after biopsy, and in the third, oxalate crystals had been noted incidentally on post-transplant renal biopsy three years before the development of fulminant oxalate nephropathy. All three patients died within a year of diagnosis.

Conclusions—Patients with systemic sclerosis and bowel dysmotility associated with chronic diarrhea and malabsorption may be at risk for an associated oxalate nephropathy. Regular screening of systemic sclerosis patients with small bowel malabsorption syndromes through routine urinalysis or 24 hour urine oxalate collection, should be considered. Further studies defining the prevalence of this complication in systemic sclerosis, the benefit of dietary modification on hyperoxaluria, the effect of treating small intestinal bowel overgrowth with antibiotics, and the effectiveness of probiotics, calcium supplements, or magnesium supplements to prevent hyperoxaluria-associated renal disease in these patients, are warranted.

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Keywords

scleroderma; systemic sclerosis; oxalate nephropathy; calcium oxalate; gastrointestinal disease; malabsorption; scleroderma renal crisis; small intestinal bacterial overgrowth; acute kidney injury; chronic kidney disease

Introduction

Systemic sclerosis is a systemic autoimmune disease characterized by a distinctive vasculopathy with intimal proliferation and dysregulated neoangiogenesis, systemic fibrosis, and the potential failure of visceral organs including the gastrointestinal tract and the kidneys. Gastrointestinal dysmotility affects over 80% of patients with systemic sclerosis; however, the region of the gastrointestinal tract that is affected is variable, and the severity of these manifestations varies widely among patients [1]. This clinical heterogeneity necessitates careful clinical phenotyping of patients: Approximately 50% of patients with systemic sclerosis have small bowel involvement, and for a subset, this is the dominant clinical manifestation [2]. Although the pathogenesis of gastrointestinal dysmotility is not well-understood, it is recognized that the disruption of intestinal pacing and smooth muscle atrophy can cause recurrent episodes of small bowel bacterial overgrowth, pseudoobstruction, malabsorption, and in severe cases, dependence on parenteral nutrition [1–4].

Renal crisis is another feared cause of morbidity and mortality in systemic sclerosis, and is associated with a five-year mortality of 40% and permanent dialysis dependence in up to 40% of cases, even with the use of ACE inhibitors [5]. Other contributors to kidney disease in systemic sclerosis, however, are present in up to 50% of patients, including hypertensive nephropathy, prerenal azotemia, drug reactions, and rarely, anti-neutrophil cytoplasmic antibody (ANCA)- associated glomerulonephritis [6–9]. Differentiating among these entities requires careful clinical contextualization and often a biopsy to evaluate for thrombotic microangiopathy, arteriolar fibrinoid necrosis, and fibrointimal thickening, which may also occur in association with systemic sclerosis. The diagnosis is complicated by the absence of hypertension in approximately 10% of cases of scleroderma renal crises, as well as the presence of similar pathologic changes even among systemic sclerosis patients without renal crisis [10, 11].

Oxalate nephropathy is a cause of acute renal tubular injury that is commonly associated with conditions affecting small bowel absorption. In the setting of chronic small intestinal malabsorption, enteric calcium is increasingly bound and sequestered from oxalate by unabsorbed luminal fatty acids, resulting in the increased absorption of the displaced unbound oxalate [12, 13]. Depending on factors such as urine chemistries, predisposing vascular endothelial injury, and the degree and chronicity of hyperoxaluria, calcium oxalate can subsequently precipitate, and induce further inflammation or necrosis of renal tubular epithelial cells [14–18]. The pathophysiology and epidemiology of oxalate nephropathy differ from the more common form of uncomplicated calcium oxalate nephrolithiasis. In the latter patient subset, high levels of urine calcium and low urine pH—but not high levels of urinary oxalate,—explain an increased risk of nephrolithiasis seen in Caucasians and men [19–21].

In contrast, enteric hyperoxaluria and oxalate nephropathy, are associated with a decreased average calcium excretion and the risk of oxalate nephropathy correlates with a urinary oxalate level that can more than double from a normal level of 30mg/day to more than 80mg/day [22–25]. As a result, the epidemiology of oxalate nephropathy is less well characterized, but is likely to parallel the population at risk for the predisposing enteric dysfunction.

Two case reports of acute kidney injury secondary to oxalate nephropathy have been reported in patients with systemic sclerosis and small intestinal involvement causing decreased motility and steatorrhea [26, 27]. We now report a case series of systemic sclerosis-related oxalate nephropathy among patients followed in the Johns Hopkins Scleroderma Center. Our goals are to highlight the importance of (1) identifying predisposed patients in the absence of a single highly predictive test, (2) modifying risk factors for hyperoxaluria when possible, and (3) considering oxalate nephropathy in the differential diagnosis when evaluating patients with systemic sclerosis, small bowel involvement, and acute kidney injury.

Methods

Two cases of systemic sclerosis and biopsy-proven oxalate nephropathy were identified at the Scleroderma Center of Johns Hopkins Hospital through the course of routine clinical care. A search was then undertaken of all renal pathology at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center using the search terms “scleroderma,” “systemic sclerosis,” and “kidney” to identify renal tissue from patients with systemic sclerosis. The pathology search returned 125 biopsies from 97 unique patients, from which one additional case (Case 3) was identified and evaluated in further detail through chart review. This study was approved by the Johns Hopkins Institutional Review Board.

Case 1

A 63 year old African American female with diffuse systemic sclerosis was admitted to the Johns Hopkins Hospital for acute kidney injury associated with progressive anasarca and diarrhea. She was diagnosed with systemic sclerosis seven years earlier, when she presented with a pericardial effusion in the setting of Raynaud’s, pulmonary arterial hypertension, and a positive ANA at a titer greater than 1:320, in a speckled pattern. Tests for RNA polymerase III antibodies and anti-Scl70 antibodies were negative. Over the following year, she developed esophageal dysmotility and diffuse skin thickening extending proximally through the arms, chest, and thighs. She had digital ulcers, telangiectasias, interstitial lung disease with an FVC of 62% predicted, right heart catheter-proven pulmonary arterial hypertension, and associated diastolic dysfunction. She was maintained on mycophenolate mofetil, sildenafil, ambrisentan, furosemide, and spironolactone. Three years prior to admission, she developed episodic abdominal bloating and pain, with radiographic evidence of diffuse small bowel dilatation, which was treated with rotating courses of metronidazole and rifaximin. The gastrointestinal symptoms gradually became more prominent, and she lost 30 pounds over the year prior to admission, during which time her creatinine increased from 0.9 mg/dL (30 months prior to admission) to 2.0 mg/dL (6 months prior to admission)

in the setting of intermittent diuresis for recurrent episodes of right heart failure. She was admitted with acute kidney injury, with an increase in her serum creatinine to 2.5 mg/dL, which climbed to 3.5 mg/dL while diuretics were held in the hospital. Her urinalysis did not demonstrate crystals or casts, and a 24-hour urine collection demonstrated normal levels of protein excretion. A barium study of the small bowel demonstrated diffuse moderate hypomotility throughout the small bowel, diffuse small intestinal dilatation, and a delayed transit time of 3 hours 25 minutes (normal: 30 minutes – 3 hours), with only minimal contrast reaching the proximal colon. Her median blood pressure was 100/50 mm Hg, and a biopsy was undertaken to rule out normotensive scleroderma renal crisis. The biopsy revealed no evidence of microangiopathy, but did demonstrate oxalate crystal deposits associated with focal moderate tubular injury and interstitial lymphocytic infiltration. After this diagnosis, a 24-hour urine oxalate collection demonstrated 98.9 mg of oxalate [lab reference range 3.6–38 mg/day]. On questioning, the patient admitted to taking 1000 mg of daily Vitamin C supplementation, and drinking approximately a quart of cranberry juice daily over the last 6 months. She was counseled to avoid oxalate-rich foods and was discharged home on intensified diuretics, but her creatinine remained above 3 over the subsequent months. She expired suddenly at home approximately 6 months after discharge from a presumed cardiac arrest, in the setting of severely low serum calcium and magnesium levels.

Case 2

A 76 year old African American woman was initially diagnosed with systemic sclerosis at the Johns Hopkins Scleroderma Center based on nine years of initially limited symptoms of puffy hands, sclerodactyly, gastroesophageal reflux disease, muscle weakness, and anti-centromere antibody positivity. Five years after her initial presentation, she underwent a knee replacement, after which her phenotype changed from limited to diffuse, with more widespread skin thickening and a peak Rodnan skin score of 22. Three years later, she had developed chronic constipation with episodic diarrhea and generalized weakness, with a creatinine kinase of 189 units/L (lab reference 24–170 U/L). Serologies were positive for ANA at 1:640, with a centromere pattern, and rheumatoid factor positivity, but no evidence of RNA-polymerase 3, Scl-70, and anti-citrullinated peptide antibodies. She was intolerant of a brief trial of mycophenolate mofetil due to diarrhea; further attempts at immunosuppression were not entertained. Four months after establishing care at the Johns Hopkins Scleroderma Center, she was admitted to an outside hospital with weakness, lethargy, and acute kidney injury, with a serum creatinine of 3.3 mg/dL (from a baseline value of 0.8 mg/dL), which improved to 1.6 mg/dL after hydration. A urinalysis performed shortly after this admission demonstrated new rare calcium oxalate crystals. She returned to the outside hospital just eight months later for another admission, with recurrent acute kidney injury and continued diarrhea and weight loss. In the setting of intermittent uncontrolled hypertension, there was concern for scleroderma renal crisis. A renal biopsy demonstrated acute tubulointerstitial changes with numerous intratubular calcium oxalate crystals, but no evidence of thrombotic microangiopathy or vasculitis. A CT performed during the hospitalization demonstrated colonic pseudoobstruction with dilated bowel loops to 10 cm, and upper and lower endoscopy demonstrated extensive, shallow erosions in the esophagus and stomach, as well as 4L of feculent material. She was briefly maintained on

hemodialysis but developed *Candida glabrata* fungemia, necessitating the removal of the hemodialysis catheter, and within six weeks of her admission, hemodialysis was stopped due to her poor overall prognosis and loss of vascular access. She was discharged to inpatient hospice where she expired shortly thereafter.

Case 3

A 60 year old Caucasian woman initially established outpatient care at Johns Hopkins Medical Institutions with complaints of Raynaud's phenomenon and puffy hands and feet. She subsequently had recurrent gastrointestinal bleeds in the setting of endoscopically-proven gastric antral vascular ectasias (GAVE) requiring multiple laser treatments. Initial antibody testing was positive only for ANA in a nucleolar pattern at a titer greater than 1:1280. She was diagnosed with systemic sclerosis six months later, when she developed biopsy-proven scleroderma renal crisis, requiring initiation of hemodialysis and irbesartan (due to an allergy to ACE-inhibitors). She underwent a sigmoidectomy for presumed colonic arteriovenous malformations and recurrent gastrointestinal bleeding. She was treated with mycophenolate mofetil for progressive skin disease until she received a related-donor positive cross-match renal transplant, 23 months after having started hemodialysis. A post-transplant biopsy was done per protocol after one month and demonstrated a single dilated tubule with a PAS-positive cast containing calcium oxalate. At the time her creatinine was 0.7 mg/dL. She continued on tacrolimus, mycophenolate mofetil, and prednisone with stable renal function until nearly three years later when she developed diarrhea due to mycobacterium avium-intracellulare, the treatment of which was complicated by worsening diarrhea. Her course was further complicated by sepsis, BK-virus nephropathy, and subsequent renal rejection caused by reduction of immunosuppression. A repeat renal biopsy demonstrated moderate chronic tubulointerstitial injury and arteriolar hyalinosis, with frequent calcium oxalate crystals, and moderate arteriolar hyalinosis with normal arteries, no significant peritubular capillary inflammatory cell margination or capillary endothelial abnormalities, and no evidence of microangiopathy. She continued to experience difficulty with malnutrition and recurrent infections, and developed pancytopenia secondary to myelodysplastic syndrome within six months of the second biopsy. This progressed to an acute blast crisis and she died one year later, while in hospice.

Discussion

In this report, we describe three patients with systemic sclerosis and clinically significant small bowel dysmotility or malabsorption, who developed acute kidney injury attributable to oxalate nephropathy. The association between oxalate nephropathy and small bowel disease in the systemic sclerosis patient is not well-defined. Each of our patients developed biopsy-proven oxalate nephropathy in the setting of chronic malabsorption, which was characterized by weight loss associated with chronic diarrhea, pseudoobstruction, and/or episodic small intestinal bacterial overgrowth. This illustrates the importance of considering oxalate nephropathy in the differential of systemic sclerosis-associated renal complications among patients with chronic gastrointestinal involvement.

Enteric hyperoxaluria is a well-described consequence of malabsorptive states, including Crohn's disease [25], Roux-en-Y gastric bypass [28], chronic pancreatitis [29, 30], and two cases of systemic sclerosis bowel disease [26, 27]. [19–24, 31–33][25][28][29, 30][26, 27] The common pathophysiology requires chronic malabsorption of dietary fats in the small intestine, with relatively preserved colonic absorption. The increased luminal fatty acids in the small intestine displace calcium from oxalate, which in turn is more readily absorbed in the colon in its unbound form [13]. The systemic oxalate is subsequently filtered at the glomerulus and further exchanged in the proximal tubules, without significant transtubular transport beyond the proximal tubule [16, 34]. Factors such as urine chemistry, endothelial injury, and the chronicity and severity of hyperoxaluria can affect the distribution and clinical evolution of renal oxalosis [16–18]. In secondary malabsorption-related hyperoxaluria, calcium oxalate crystals appear to precipitate in the cortical proximal tubules, possibly around debris arising from direct oxalate-induced tubular epithelial apoptosis and necrosis [14, 15, 35, 36].

While an elevated urine oxalate may be a sensitive marker of increased risk for oxalate nephropathy, its discriminatory power appears to be limited. In one study of patients post-gastric bypass, 43 of 58 (74%) of non-stone forming postsurgical patients demonstrated an increase in 24-hour urinary oxalate excretion above a “normal” cutoff of 45 mg/day on at least one of two collections. Further, substantial variability in the 24-hour collection was demonstrated with just 29 of 56 (52%) of individuals yielding concordantly elevated urine oxalate excretion on repeated tests [32]. Screening for oxalate crystals on urinalysis is similarly problematic. These crystals can be found in the urine of asymptomatic patients [37], while 0 of 12 pancreatitis patients and only 2 of 11 post-Roux en Y bypass patients demonstrated crystalluria on urinalyses around the time of their biopsy-proven diagnoses [22, 29]. Nevertheless, as the degree of oxalosis does appear to correlate with the extent of kidney injury in these studies, twenty-four hour urinary oxalate excretion may help identify patients at risk who could benefit from low-oxalate diets [38, 39].

Several other factors may also influence the risk of developing calcium oxalate crystals. It is well established that high-oxalate diets, such as those high in fruit juice, leafy greens, or tea, contribute to: (1) the risk of nephrolithiasis in a subset of recurrent stone formers, and (2) the risk of oxalate nephropathy in enteric hyperoxaluria [40–44]. More recently, the importance of *Oxalobacter formigenes* (*O. formigenes*) in preventing oxalate nephropathy has been increasingly reported. *O. formigenes* is a species of oxalate-metabolizing Gram negative anaerobic bacteria frequently found among normal intestinal flora. In one study, the odds ratio of colonization with *O. formigenes* among patients with recurrent oxalate nephrolithiasis was 0.3 (95% confidence interval, 0.1–0.5) [45]. Similarly, patients with Crohn's were less likely to be colonized with *O. formigenes* than controls (10.4% vs 56%). Colonized individuals had a trend toward lower daily oxalate excretion compared to uncolonized individuals, suggesting the lack of *O. formigenes* in patients with chronic bowel inflammation may result in increased oxalate absorption and an increased risk for stone formation [46]. [45, 46] Additionally, as oxalate is a metabolite of ascorbic acid, vitamin C supplementation on the order of 1–2g per day has been shown to significantly increase urinary oxalate levels [47, 48]. Dehydration with an associated drop in GFR may also

contribute to elevated plasma oxalate levels [49]. For example, in all 12 cases in a series of patients with chronic pancreatitis-related oxalate nephropathy, patients had acute alterations in glomerular filtration related to dehydration or diuretic use, at the time of presentation [29].

In the medical literature, enteric hyperoxaluria is relatively underrecognized in patients with systemic sclerosis relative to patients with inflammatory bowel disease or gastric bypass. While this may reflect a decreased recognition of this entity by rheumatologists compared to gastroenterologists managing post-gastric bypass and inflammatory bowel disease patients, it is also possible that various pathophysiologic mechanisms may be contributing. First, medications that are considered effective in limiting oxalate-associated renal tubular damage, namely ACE-inhibitors, angiotensin receptor blockers, and calcium channel blockers, are commonly used in systemic sclerosis to treat scleroderma renal crisis or to improve Raynaud's-related digital spasm [50–53]. Secondly, osteopontin is a proinflammatory and profibrotic extracellular matrix protein that is often upregulated in scleroderma, but also serves in the renal tubule to prevent crystal precipitation and adhesion to epithelium and could thereby provide these patients a degree of protection from oxalate nephropathy [35, 54–56]. Further characterization of serum and urine oxalate levels among patients with systemic sclerosis bowel disease is needed to better assess contributions to the risk of nephropathy in this population.

Consistent with the existing two case reports of systemic sclerosis-associated oxalate nephropathy in the literature, all three of our patients had episodes of malabsorption, recurrent small intestinal bowel bacterial overgrowth, or delayed small bowel motility for at least six months leading up to the development of kidney injury. In addition, all three presented with acute volume shifts and normal to decreased blood pressure. Though our third case did not have overt radiographic evidence of small bowel dilatation, she did have functional malabsorption secondary to MAI with severe diarrhea and associated dehydration. While the creatinine stabilized at a new elevated baseline in our patients, all three of our patients died within one year of diagnosis.

Despite the uniformly poor prognosis exhibited by the three patients described in this series, the degree to which acute renal oxalosis is directly responsible for the acute kidney injury in this population requires more systematic investigation. Chronic kidney disease has been linked to the development of renal oxalosis for decades, but in some cases calcium oxalate deposition may occur transiently with acute acidosis without demonstrating clear associated tubular injury [38, 39]. Nevertheless, even when some reversibility in renal injury is present and histology does not clearly demonstrate associated inflammation, renal oxalosis remains a predictor of poor transplant outcome, and it consistently denotes a poor prognosis in enteric oxaluria [22, 39, 57]. In a series of post-Roux-en-Y enteric nephropathy patients for example, 8 of 11 cases progressed to renal failure, similar to the poor recovery reported in the two systemic sclerosis cases to date [22, 26, 27]. Determination of whether oxalate nephropathy on renal biopsy remains a negative prognosticator even among the subset of patients with systemic sclerosis, kidney injury, and severe bowel disease, will require more cases and a more systematic identification of renal calcium oxalate deposition. [38, 39]

Dietary modification may play a role in reducing the risk of renal disease in patients with systemic sclerosis and associated bowel malabsorption syndromes. These individuals may benefit from formal nutritional assessment and should be counseled against vitamin C supplementation or diets high in oxalate-containing substances such as juice, spinach, tea, and coffee. Further interventions that demonstrate an ability to reduce oxalate absorption and subsequent urinary excretion in a non-systemic sclerosis population include increased dietary intake of calcium and magnesium [58, 59], and the use of probiotics [60, 61]. These modifications in diet do not carry substantial associated risks, are cost effective, and may benefit this patient subset. Early use of promotility agents to improve intestinal motility and reduce associated small intestinal bacterial overgrowth (SIBO) should be considered. Interestingly, antibiotics used to treat episodes of SIBO-associated malabsorption syndromes may decrease colonization rates with *O. formigenes* [62]. This may result in a decrease in intraluminal digestion of oxalate and a subsequent increase in plasma oxalate levels. The net effect of antibiotics on plasma oxalate levels and associated risk of oxalate nephropathy warrants further investigation.

Conclusions

Patients with systemic sclerosis-associated small bowel disease and chronic malabsorptive diarrhea are at risk for development of oxalate nephropathy. Oxalate nephropathy should be considered in the differential diagnosis when patients with chronic small bowel disease present with dehydration and acute kidney injury incompletely responsive to volume resuscitation. A 24-hour urine oxalate collection may be helpful in identifying patients at risk. The prognosis of those who develop oxalate nephropathy in systemic sclerosis is poor; however, the duration of renal injury, extent of bowel disease, and the patients' baseline functional and nutritional status must also be considered when defining clinical outcomes. Early recognition of patients at risk is critical as the institution of a low-oxalate diet may help to prevent this complication. The roles of early use of prokinetic agents, antibiotics for SIBO, calcium and magnesium supplementation, and probiotics all remain to be defined in prospective studies of at-risk patients with systemic sclerosis.

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Figure 1.

Case 1: (a) Translucent crystalline deposits (arrows) appreciable in thick ascending loops of Henle, with single sclerosed glomerulus and focal lymphocytic infiltrate (arrowheads). H&E, 200x. (b) Polarization of the same view emphasizes the presence of large calcium oxalate crystalline deposits.

Table 1

Patient Clinical Characteristics

Case	Sex and Race	Age at biopsy	Subset	Systemic sclerosis Duration at Biopsy	Organs Involved	Antibody Status	Forms of GI Systemic sclerosis	History of Renal Crisis	Oxalate Crystals on Urinalysis (Months before biopsy)	24-hour Urinary Oxalate (Ref: 3.6-38mg)	Creatinine at Time of Biopsy	Creatinine at Last Follow-up (Months after biopsy)	Died? (Months after biopsy)
1	AAF	63	Diffuse	7 years	Pulmonary (ILD), Cardiac (pericardial effusion, pulmonary hypertension), Skin (peak RSS 18, digital ulceration), GI	ANA >= 1:640, speckled pattern	GERD, small intestine dilatation, delayed transit time of 3 hours, recurrent SIBO	No	Never	98.9 mg	3.3 mg/dL	3.2 (7)	Yes (7)
2	AAF	~75yo	Diffuse	9 years	GI, Myopathy, Skin (peak mRSS 22)	ANA >= 1:640 centromere	GERD, recurrent SIBO, small intestine dilatation, delayed transit clinically	No	No	Not performed	4.0	Hemodialysis	Yes (0)
3	CF	63, 66	Diffuse	24mo, 66mo	GI, Skin, Renal (SRC)	ANA > 1:1280 nucleolar	GAVE, colonic AVMs s/p sigmoidectomy	Yes	Yes (1, 42)	Not performed	0.9, 2.8	3.0 (13)	Yes (13)

AVM: Arteriovenous malformation; GAVE: Gastric antral vascular ectasia; GERD: Gastroesophageal reflux disease; GI: Gastrointestinal; ILD: Interstitial lung disease; SIBO: Small intestinal bowel overgrowth; SRC: Scleroderma renal crisis