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Kidney stones, proteinuria, and renal tubular metabolic acidosis: Pathophysiology link, clinical manifestations, diagnosis, and management

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***Abstract*---Background:** Kidney stone disease is an increasingly recognized contributor to chronic kidney disease (CKD), particularly when associated with metabolic disorders such as distal renal tubular acidosis (dRTA). Primary Sjögren syndrome (pSS), an autoimmune disease primarily affecting exocrine glands, may present with renal

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involvement before the onset of classical sicca symptoms. Tubulointerstitial nephritis, dRTA, nephrolithiasis, and nephrocalcinosis are important but often underdiagnosed renal manifestations that may lead to progressive renal dysfunction. **Aim:** To describe the clinical presentation, diagnostic evaluation, pathophysiological mechanisms, and therapeutic management of primary Sjögren syndrome presenting with type 1 distal renal tubular acidosis, nephrolithiasis, nephrocalcinosis, and chronic kidney disease. **Methods:** A comprehensive review and synthesis of the presented clinical case and relevant literature were undertaken. Clinical findings, laboratory investigations, metabolic urine analysis, autoimmune serology, imaging studies, renal histopathology, genetic testing, differential diagnosis, and treatment outcomes were critically evaluated to establish the relationship between autoimmune renal injury and stone disease. **Results:** The patient presented with stage 3 CKD, complete type 1 dRTA, chronic tubulointerstitial nephritis, severe hypocitraturia, nephrocalcinosis, and recurrent nephrolithiasis. Autoimmune evaluation revealed positive antinuclear, anti-SSA, and anti-SSB antibodies, while renal biopsy demonstrated T-cell-predominant tubulointerstitial nephritis without glomerular involvement. Genetic testing excluded inherited dRTA. Combined treatment with potassium citrate and corticosteroids corrected metabolic abnormalities, stabilized renal function, and prevented recurrent stone episodes during follow-up. **Conclusion:** Primary Sjögren syndrome should be considered in patients presenting with unexplained dRTA, nephrolithiasis, nephrocalcinosis, and progressive CKD, even in the absence of sicca symptoms. Early recognition, renal biopsy, comprehensive metabolic evaluation, and prompt initiation of metabolic correction and immunosuppressive therapy are essential to preserve renal function and improve long-term outcomes.

***Keywords*---**Primary Sjögren syndrome, distal renal tubular acidosis, nephrolithiasis, nephrocalcinosis, chronic kidney disease, tubulointerstitial nephritis, autoimmune kidney disease, hypocitraturia.

Introduction

Chronic kidney disease (CKD) represents a major global public health challenge and is associated with substantial morbidity, mortality, and healthcare expenditure. Diabetes mellitus and systemic arterial hypertension remain the predominant causes of CKD worldwide, accounting for the majority of cases. Other important etiologies include primary and secondary glomerular diseases, nephropathies associated with herbal toxins or environmental exposures, and renal disorders secondary to chronic viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections [1]. Despite these well-recognized causes, nephrolithiasis and nephrocalcinosis remain relatively underappreciated contributors to progressive renal dysfunction, although growing evidence indicates that they play a

significant role in the development of CKD and end-stage renal disease (ESRD) [2,3]. Kidney stone disease is one of the most prevalent urological disorders worldwide, affecting individuals across different age groups and geographic regions. Epidemiological studies estimate that the prevalence of nephrolithiasis ranges between 1% and 13%, depending on dietary habits, environmental conditions, genetic susceptibility, and population characteristics [4,5]. Furthermore, the global burden of kidney stone disease has increased considerably over recent decades. In the United States, for example, its prevalence nearly tripled between 1976 and 2010, rising from 3.2% to approximately 8.8%, reflecting changes in lifestyle, obesity rates, dietary patterns, and metabolic disorders [4,5]. Although nephrolithiasis directly accounts for only 2–3% of CKD cases, patients with recurrent stone disease exhibit a significantly higher risk of renal functional deterioration and are approximately two to three times more likely to progress to ESRD compared with the general population, irrespective of associated cardiovascular risk factors [6–9].

The mechanisms through which kidney stone disease contributes to renal impairment are multifactorial and often progressive. Recurrent urinary tract obstruction caused by calculi may result in obstructive nephropathy, leading to elevated intrarenal pressure, ischemic injury, and irreversible nephron loss. In addition, recurrent urinary tract infections and secondary pyelonephritis frequently complicate nephrolithiasis, producing chronic inflammation and permanent renal parenchymal damage. Persistent crystal deposition, inflammatory responses induced by retained anions, repeated surgical interventions, and the presence of underlying metabolic or hereditary disorders further accelerate the decline in renal function [6,10]. Consequently, kidney stone disease should not be regarded solely as an episodic urological condition but rather as a chronic systemic disorder with important nephrological implications. The clinical evaluation of nephrolithiasis extends beyond the detection and removal of urinary calculi. Modern classification systems categorize kidney stones according to their morphologic and compositional characteristics because stone composition frequently reflects the underlying metabolic disturbance responsible for their formation. Detailed morpho-constitutional analysis provides valuable diagnostic information and guides individualized therapeutic strategies aimed at preventing recurrence. Equally important is a comprehensive metabolic evaluation, which identifies urinary abnormalities such as hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, cystinuria, or alterations in urinary pH. Correction of these metabolic abnormalities remains the cornerstone of long-term stone prevention and preservation of renal function [5,11].

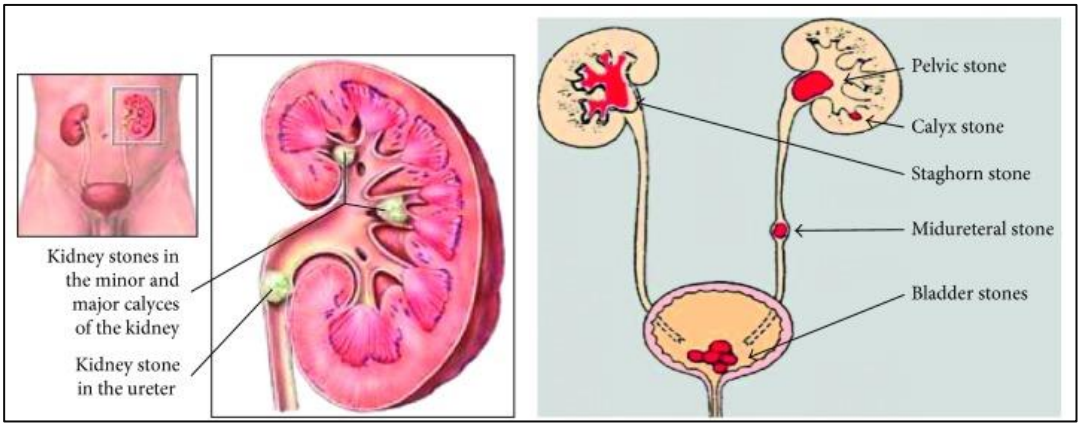

Figure 1. Kidney Stones

Among the metabolic disorders associated with nephrolithiasis, type 1 renal tubular acidosis (distal renal tubular acidosis, dRTA) represents one of the most lithogenic conditions encountered in clinical practice [5,11]. This disorder is characterized by impaired urinary acidification despite preserved glomerular filtration during its early stages. Patients typically develop calcium phosphate nephrolithiasis, nephrocalcinosis, persistent alkaline urine, hypocitraturia, and hypercalciuria, all of which substantially increase the risk of recurrent stone formation. Stone analysis often reveals the characteristic type IVa2 stone morphology, considered highly suggestive of distal renal tubular acidosis [5,11]. Inherited forms of distal renal tubular acidosis are relatively uncommon and arise from pathogenic variants affecting proteins responsible for renal acid-base regulation. These include mutations in the genes encoding the vacuolar proton pump H+(V)-ATPase subunits ATP6V1B1 and ATP6V0A4, as well as mutations involving the anion exchanger AE1 encoded by the **SLC4A1** gene. These genetic defects impair hydrogen ion secretion or bicarbonate transport within the distal nephron, resulting in defective urinary acidification and chronic metabolic acidosis [12]. In contrast, acquired forms of distal renal tubular acidosis are encountered more frequently in clinical practice and develop secondary to structural or functional injury of the renal tubules. Autoimmune disorders, including Sjögren syndrome and systemic lupus erythematosus, metabolic diseases, chronic interstitial nephritis, nephrotoxic medications, and various pharmacological agents have all been implicated in the development of acquired distal renal tubular acidosis [12]. The underlying pathophysiological defect in distal renal tubular acidosis involves impaired acid secretion by α-intercalated cells of the collecting duct. Dysfunction of the apical H+(V)-ATPase reduces hydrogen ion secretion into the tubular lumen, thereby limiting ammonium formation and urinary acid excretion. Alternatively, defects involving the basolateral AE1 anion exchanger impair bicarbonate reabsorption in exchange for chloride ions, resulting in reduced buffering capacity and persistent metabolic acidemia [12]. Initially, excess hydrogen ions are neutralized by circulating bicarbonate; however, chronic acid retention eventually overwhelms this buffering system. As compensation, skeletal mineral serves as the principal buffer, leading to progressive bone demineralization, osteopenia, and osteoporosis through enhanced calcium and phosphate mobilization [12].

Bone mineral dissolution further contributes to urinary abnormalities that promote stone formation. The released phosphate is filtered by the kidneys and binds urinary hydrogen ions, thereby increasing urinary pH. Simultaneously, chronic metabolic acidosis enhances proximal tubular citrate reabsorption, producing hypocitraturia. Because citrate normally binds urinary calcium and inhibits crystal formation, reduced citrate excretion markedly increases lithogenic potential. In addition, bone resorption contributes to hypercalciuria, while persistently alkaline urine favors calcium phosphate supersaturation. The combination of alkaline urine, hypocitraturia, hypercalciuria, and phosphate excess creates an optimal environment for calcium phosphate crystal nucleation, growth, and aggregation, thereby substantially increasing the likelihood of recurrent nephrolithiasis and nephrocalcinosis [12]. Histopathological examination provides further insight into the renal consequences of distal renal tubular acidosis. Calcium phosphate crystal deposits commonly form intratubular plugs within the inner medullary collecting ducts and the ducts of Bellini. These crystalline deposits initiate chronic tubulointerstitial inflammation characterized by inflammatory cell infiltration, progressive interstitial fibrosis, tubular atrophy, and localized ischemic injury. Over time, these pathological alterations contribute to irreversible nephron loss and gradual deterioration of renal function, ultimately increasing the risk of CKD and ESRD in affected individuals [6]. Recognition of nephrolithiasis as both a consequence and manifestation of systemic metabolic disorders has substantially altered contemporary approaches to diagnosis and management. Rather than focusing exclusively on stone removal, current clinical practice emphasizes comprehensive metabolic investigation, identification of underlying inherited or acquired disorders, correction of urinary biochemical abnormalities, and implementation of individualized preventive strategies. Early diagnosis and targeted management of disorders such as distal renal tubular acidosis are therefore essential not only for reducing stone recurrence but also for preserving renal function, minimizing chronic kidney damage, and improving long-term patient outcomes [5,6,11,12].

Case Description

A 35-year-old woman of Indian origin, who had been residing in Belgium for six years, was referred for specialized nephrological evaluation because of recurrent nephrolithiasis accompanied by chronic kidney disease (CKD). She reported a 15-year history of kidney stone disease characterized by a relatively low recurrence rate, with approximately one symptomatic episode every five years. Chronic kidney disease had been diagnosed in 2017. Her medical history was also significant for hypothyroidism and hypertriglyceridemia, while there was no family history of nephrolithiasis, chronic kidney disease, or inherited renal disorders. She denied alcohol consumption, illicit drug use, and exposure to nephrotoxic substances. Her regular medication consisted solely of L-thyroxine at a daily dose of 100 μg. At presentation, the patient was asymptomatic and denied flank pain, urinary complaints, xerostomia, xerophthalmia, hearing impairment, or other manifestations suggestive of sicca syndrome. Physical examination revealed no abnormalities. Her weight was 55.6 kg, corresponding to a body mass index (BMI) of 23.4 kg/m². Vital signs were stable, including a blood pressure of 113/70 mmHg, heart rate of 73 beats per minute, and body temperature of 35.9 °C. No peripheral edema, skin lesions, lymphadenopathy, or signs of systemic

autoimmune disease were identified. Initial laboratory investigations demonstrated preserved hematological parameters with a hemoglobin concentration of 13.8 g/dL. Mild eosinophilia was present (0.54 × 10^3/µL), while renal function tests revealed elevated serum creatinine of 1.48 mg/dL and blood urea of 34 mg/dL, corresponding to an estimated glomerular filtration rate (CKD-EPI) of 46 mL/min/1.73 m^2, consistent with stage 3 chronic kidney disease. Biochemical evaluation demonstrated a normal anion gap metabolic acidosis characterized by markedly reduced serum bicarbonate (16 mmol/L), borderline elevated serum chloride (107 mmol/L), and significant hypokalemia (3.0 mmol/L). Serum calcium, ionized calcium, phosphorus, and alkaline phosphatase levels remained within normal reference ranges. Vitamin D deficiency was evident with a calcidiol concentration of 19.2 µg/L, whereas bioactive parathyroid hormone was suppressed (<10 ng/L). Thyroid function tests confirmed adequate hormonal replacement therapy, with normal thyrotropin and free thyroxine concentrations despite markedly elevated anti-thyroid peroxidase antibodies (270 kUI/L), consistent with autoimmune thyroiditis. Liver function tests and bilirubin values remained within normal limits.

Inflammatory markers revealed a normal C-reactive protein concentration despite a markedly elevated erythrocyte sedimentation rate of 64 mm/hour, suggesting chronic immune activation rather than acute inflammation. Serum protein electrophoresis demonstrated significant polyclonal hypergammaglobulinemia (24.2 g/L), further supporting an underlying autoimmune process. Extensive immunological investigations revealed positive rheumatoid factor (52.6 IU/mL) together with strongly positive antinuclear antibodies at a titer exceeding 1:1280 displaying a fine granular nuclear staining pattern. Autoantibody profiling demonstrated high titers of anti-SSA and anti-SSA Ro52 antibodies, mild positivity for anti-SSB antibodies, and moderate titers of anti-histone antibodies. Conversely, anti-double stranded DNA, anti-Smith, and anti-nucleosome antibodies were absent, reducing the likelihood of systemic lupus erythematosus. Lupus anticoagulant testing using the dilute Russell's viper venom time assay was positive, whereas anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, cryoglobulins, and complement components C3 and C4 remained within normal limits. Serological testing excluded viral infections including hepatitis A, hepatitis B, hepatitis C, HIV, and Epstein-Barr virus. Urinalysis provided additional evidence supporting distal tubular dysfunction. Dipstick examination demonstrated an alkaline urinary pH of 7.0, microscopic hematuria without dysmorphic erythrocytes, mild leukocyturia, and trace proteinuria in the absence of urinary crystals. Urine culture was sterile, excluding urinary tract infection. Quantitative urinary assessment revealed tubular, non-selective proteinuria measuring approximately 1.0 g/g creatinine, accompanied by albuminuria of 150 mg/g creatinine without glycosuria. The urinary anion gap was markedly positive (29 mmol/L), supporting impaired urinary acidification consistent with distal renal tubular acidosis. Comprehensive metabolic urine evaluation demonstrated an adequate daily urine output of 2,150 mL with normal urinary excretion of uric acid, sodium, calcium, and oxalate. Weight-adjusted urinary calcium excretion remained within normal limits at 1.8 mg/kg/day, excluding significant hypercalciuria. However, profound hypocitraturia was identified, with urinary citrate excretion below 108 µmol/day, representing a major lithogenic risk factor. Fasting urine analysis demonstrated

persistently alkaline urine (pH 7.1) with low urine specific gravity (1.008) and normal fasting calciuria, findings highly suggestive of distal renal tubular acidosis.

Imaging studies further characterized the extent of renal involvement. Renal ultrasonography demonstrated bilateral renal calculi associated with calyceal and ureteral dilatation. Computed tomography confirmed numerous bilateral precalyceal calculi together with extensive medullary nephrocalcinosis while excluding ureterohydronephrosis. Diagnostic ureterorenoscopy revealed that many calculi were embedded beneath the urothelial mucosa, predominantly involving the calyceal system, indicating chronic intrarenal crystal deposition rather than freely mobile stones. Given the presence of significant proteinuria and chronic kidney disease, renal biopsy was performed to establish the underlying renal pathology. Histopathological examination demonstrated moderate acute and chronic tubulointerstitial nephritis without evidence of glomerular disease. Immunofluorescence studies were negative for IgA, IgM, IgG, C3, C1q, kappa, and lambda light chains, effectively excluding immune-complex glomerulonephritis. Furthermore, Von Kossa staining did not reveal intrarenal calcium phosphate deposition within the biopsy specimen. To exclude hereditary causes of distal renal tubular acidosis, comprehensive genetic testing targeting mutations involving ATP6V1B1, ATP6V0A4, and **SLC4A1**, as well as other tubulopathy-associated genes, was performed and yielded negative results. Collectively, the clinical presentation, biochemical abnormalities, autoimmune profile, urinary findings, imaging characteristics, histopathological results, and exclusion of inherited disease supported the diagnosis of primary Sjögren syndrome complicated by acquired type 1 distal renal tubular acidosis, chronic tubulointerstitial nephritis, nephrocalcinosis, and recurrent nephrolithiasis. Treatment was initiated with oral potassium citrate at a daily dose of 6 g to correct metabolic acidosis and severe hypocitraturia, resulting in partial normalization of electrolyte disturbances. Because of the biopsy-confirmed autoimmune tubulointerstitial nephritis, immunosuppressive therapy with prednisolone at 0.5 mg/kg/day (prednisolone equivalent) was subsequently introduced. Following 15 months of treatment, the patient demonstrated sustained clinical improvement, remained free from recurrent renal colic or acute stone episodes, and experienced stabilization of her overall clinical condition, supporting the effectiveness of combined metabolic correction and immunosuppressive therapy in managing autoimmune distal renal tubular acidosis associated with primary Sjögren syndrome.

Discussion

The present case illustrates an uncommon but clinically significant manifestation of primary Sjögren syndrome presenting with extensive renal involvement characterized by complete type 1 distal renal tubular acidosis (dRTA), chronic tubulointerstitial nephritis, nephrolithiasis, nephrocalcinosis, and stage 3 chronic kidney disease (CKD). Although primary Sjögren syndrome is primarily recognized as an autoimmune exocrinopathy affecting the salivary and lacrimal glands, renal involvement represents one of its most important extraglandular complications and may precede the development of classical sicca symptoms. This case highlights the diagnostic challenges associated with atypical presentations of

primary Sjögren syndrome and emphasizes the importance of considering autoimmune disorders in patients presenting with unexplained nephrolithiasis, nephrocalcinosis, metabolic acidosis, and progressive renal dysfunction. The patient's clinical presentation was remarkable for chronic kidney disease associated with normal blood pressure, mixed tubular proteinuria, persistent microscopic hematuria, sterile leukocyturia, profound hypocitraturia, alkaline urine, hypokalemia, and severe nephrocalcinosis. These findings strongly suggested chronic tubular dysfunction rather than primary glomerular disease. The immunological profile further supported an autoimmune etiology, demonstrating high-titer antinuclear antibodies together with strongly positive anti-SSA and anti-SSB antibodies while anti-double stranded DNA and anti-Smith antibodies remained negative. Although the patient did not fulfill the complete classification criteria for primary Sjögren syndrome because of the absence of sicca manifestations, the combination of serological findings and renal histopathology was highly consistent with this diagnosis [13,14]. Importantly, several studies have demonstrated that renal manifestations may precede exocrine gland involvement by several years, making early diagnosis particularly challenging [15,16].

Renal disease associated with primary Sjögren syndrome most frequently manifests as chronic tubulointerstitial nephritis, which accounts for nearly three-quarters of renal involvement in affected patients. Tubular dysfunction frequently leads to distal renal tubular acidosis, electrolyte disturbances, nephrolithiasis, nephrocalcinosis, and progressive impairment of renal function if left untreated. Tubulointerstitial nephritis and distal renal tubular acidosis are often underrecognized because clinical symptoms remain subtle until significant renal damage has occurred. Previous investigations have reported that these renal manifestations generally develop two to seven years after the onset of primary Sjögren syndrome but may also represent the initial clinical manifestation before sicca syndrome becomes evident [15,16]. The presence of an isolated lupus anticoagulant in this patient further supports the autoimmune nature of the disease, as similar findings have previously been described in patients with primary Sjögren syndrome [17]. The prevalence of renal involvement in primary Sjögren syndrome varies considerably among different populations. European and North American studies estimate renal involvement in approximately 0.5–15% of patients, whereas Asian cohorts have reported frequencies exceeding 30%, suggesting possible ethnic or genetic influences on disease expression [1]. The spectrum of renal abnormalities ranges from isolated electrolyte disturbances and distal renal tubular acidosis to chronic tubulointerstitial nephritis, nephrolithiasis, nephrocalcinosis, and ultimately chronic kidney disease. Tubulointerstitial nephritis represents the predominant pathological lesion, accounting for approximately 75% of renal manifestations, while nephrolithiasis and nephrocalcinosis occur less frequently, affecting approximately 9.5% and 5.3% of patients, respectively [2]. Previous studies have demonstrated that renal involvement is positively associated with anti-SSB antibodies and negatively associated with arthralgia, findings that are consistent with the immunological profile observed in the present patient [3]. One of the most striking features of this case was the disproportionate severity of nephrocalcinosis relative to the relatively modest clinical activity of recurrent nephrolithiasis. Extensive medullary nephrocalcinosis contributed substantially to the patient's decline in renal function despite only intermittent symptomatic stone episodes. Calcium

phosphate calculi are the most probable stone composition because the metabolic profile demonstrated persistent alkaline urine, profound hypocitraturia, and low urinary oxalate excretion, all of which strongly favor calcium phosphate crystallization. Although hypercalciuria was not documented, its absence does not exclude calcium phosphate stone disease. Patients with chronic kidney disease frequently exhibit reduced urinary calcium excretion secondary to declining glomerular filtration, and concurrent vitamin D deficiency may further reduce urinary calcium levels, thereby masking the underlying lithogenic process [18].

Hypocitraturia represents one of the principal metabolic abnormalities contributing to calcium phosphate stone formation in distal renal tubular acidosis. Citrate functions as an important endogenous inhibitor of urinary crystallization by forming soluble complexes with calcium, thereby reducing calcium supersaturation and preventing crystal nucleation. Chronic metabolic acidosis enhances proximal tubular citrate reabsorption, while hypokalemia further suppresses urinary citrate excretion. Consequently, severe hypocitraturia substantially increases the risk of recurrent nephrolithiasis and nephrocalcinosis. In addition, persistently alkaline urine promotes calcium phosphate supersaturation, creating an optimal physicochemical environment for crystal precipitation and intrarenal calcification. These metabolic abnormalities collectively explain the extensive nephrocalcinosis observed in this patient despite relatively modest urinary calcium excretion [18]. The diagnosis of acquired distal renal tubular acidosis required careful exclusion of hereditary forms of the disease. Autosomal recessive mutations involving the proton pump genes ATP6V1B1 and ATP6V0A4 typically present during infancy or childhood with growth retardation, severe metabolic acidosis, nephrocalcinosis, and sensorineural hearing loss. The absence of childhood manifestations, hearing impairment, and growth abnormalities made these inherited disorders unlikely in the present case. Autosomal dominant mutations involving the **SLC4A1** gene encoding the AE1 anion exchanger may present later in life without hearing loss and therefore represented a more plausible differential diagnosis [19]. However, comprehensive genetic analysis failed to identify pathogenic variants involving these genes, effectively excluding inherited distal renal tubular acidosis and supporting an acquired autoimmune etiology.

The differential diagnosis of acquired distal renal tubular acidosis encompasses numerous autoimmune, metabolic, infectious, and drug-induced disorders. In the present patient, the absence of hepatobiliary abnormalities, normal liver function tests, and lack of exposure to nephrotoxic medications argued against autoimmune hepatitis, primary biliary cholangitis, Wilson disease, or drug-induced nephropathy. Primary Sjögren syndrome is widely recognized as the most common cause of acquired hypokalemic distal renal tubular acidosis and therefore represented the most likely diagnosis in this clinical setting [20]. Although systemic lupus erythematosus may also produce tubular dysfunction, renal involvement in lupus more commonly results in type 4 renal tubular acidosis characterized by hyperkalemia rather than hypokalemia [21]. Likewise, sarcoidosis remained an alternative consideration but lacked supporting clinical, laboratory, and histopathological evidence. Medullary sponge kidney was also considered because of the extensive nephrocalcinosis, although the overall clinical and immunological findings strongly favored autoimmune tubulointerstitial

disease. Renal biopsy played a pivotal role in establishing the diagnosis and excluding competing etiologies. Histopathological examination demonstrated chronic tubulointerstitial nephritis without evidence of immune complex-mediated glomerular disease. Immunofluorescence studies were entirely negative, excluding glomerulonephritis and reinforcing the diagnosis of isolated tubulointerstitial injury. Furthermore, the inflammatory infiltrate consisted predominantly of T lymphocytes, a characteristic finding in primary Sjögren syndrome. Similar observations have been reported by Jasiek et al., who demonstrated T-cell predominance in approximately 65% of tubulointerstitial nephritis associated with primary Sjögren syndrome, whereas plasma cell-predominant and B-cell-predominant infiltrates account for approximately 25% and 10% of cases, respectively [22]. These findings provide further evidence that cell-mediated immunity plays a central role in the renal pathogenesis of primary Sjögren syndrome.

This case underscores the indispensable role of renal biopsy in patients with autoimmune-associated chronic kidney disease. Beyond excluding glomerular pathology, biopsy permits direct assessment of the extent of tubulointerstitial inflammation and fibrosis, both of which are important determinants of renal prognosis. Early identification of active inflammatory lesions is particularly important because timely immunosuppressive therapy may preserve renal function before irreversible interstitial fibrosis develops. Current evidence suggests that renal biopsy should be considered whenever unexplained deterioration of renal function occurs in patients with suspected primary Sjögren syndrome to facilitate accurate diagnosis and guide therapeutic decision-making [15]. Management of renal involvement in primary Sjögren syndrome remains incompletely standardized and is generally individualized according to disease severity, commonly assessed using the European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) [5]. Correction of distal renal tubular acidosis constitutes the cornerstone of treatment because normalization of systemic acid-base balance reduces nephrolithiasis recurrence, improves bone metabolism, corrects hypokalemia, and slows progression of chronic kidney disease. Potassium citrate remains the preferred therapeutic agent because it simultaneously replenishes potassium stores and restores urinary citrate excretion, thereby reducing calcium phosphate supersaturation and preventing further stone formation [20,23]. When tubulointerstitial nephritis accompanies autoimmune distal renal tubular acidosis, immunosuppressive therapy becomes essential to suppress ongoing inflammatory injury. Corticosteroids administered at doses exceeding 0.5 mg/kg/day prednisolone equivalent are generally recommended to stabilize renal function and preserve estimated glomerular filtration rate, particularly in patients with active inflammatory infiltrates. Treatment response depends largely on the degree of established interstitial fibrosis, emphasizing the importance of early diagnosis before irreversible structural damage develops [15,24]. In the present case, combined treatment with potassium citrate and corticosteroids resulted in clinical stabilization and prevention of recurrent stone episodes over a 15-month follow-up period.

Additional immunosuppressive agents have also demonstrated potential benefit. Mycophenolate mofetil has shown promising results in observational studies by

improving renal inflammation and stabilizing kidney function; however, robust randomized controlled trials remain lacking. Consequently, further clinical research is required to determine whether mycophenolate mofetil or other steroid-sparing agents offer superior long-term renal outcomes compared with corticosteroid monotherapy [25]. The coexistence of autoimmune hypothyroidism in this patient further illustrates the recognized association between primary Sjögren syndrome and autoimmune thyroid disease. Although the precise pathophysiological relationship remains incompletely understood, meta-analyses have demonstrated that thyroid disorders occur approximately three times more frequently in patients with primary Sjögren syndrome than in the general population, with autoimmune hypothyroidism representing the predominant endocrine manifestation [26]. Patients with concomitant autoimmune thyroid disease and primary Sjögren syndrome also exhibit an increased risk of developing additional autoimmune disorders and lymphoproliferative complications [26]. Moreover, thyroid hormone replacement therapy may indirectly contribute to calcium-based nephrolithiasis through enhanced osteoclastic bone resorption, potentially promoting hypercalcemia and hypercalciuria under certain clinical conditions [27]. Although this mechanism alone is unlikely to explain the severe nephrocalcinosis observed in the present patient, it may have contributed to the overall lithogenic environment in combination with distal renal tubular acidosis and profound hypocitraturia. Overall, this case emphasizes that primary Sjögren syndrome should be considered in patients presenting with unexplained distal renal tubular acidosis, recurrent calcium phosphate nephrolithiasis, nephrocalcinosis, and chronic tubulointerstitial nephritis, even in the absence of classical sicca manifestations. Early recognition, comprehensive metabolic evaluation, renal biopsy, and prompt initiation of targeted metabolic and immunosuppressive therapy are essential to prevent progressive renal impairment and improve long-term clinical outcomes.

Conclusion

Primary Sjögren syndrome is an important yet frequently overlooked cause of acquired type 1 distal renal tubular acidosis, chronic tubulointerstitial nephritis, nephrolithiasis, nephrocalcinosis, and progressive chronic kidney disease. Renal manifestations may precede the development of classical sicca symptoms, making diagnosis particularly challenging and often delaying appropriate treatment. Comprehensive clinical assessment, detailed metabolic evaluation, autoimmune serological testing, renal imaging, and renal biopsy are essential for establishing an accurate diagnosis and excluding alternative causes of renal dysfunction. Recognition of characteristic metabolic abnormalities, including hypokalemia, persistent alkaline urine, and severe hypocitraturia, facilitates early identification of distal renal tubular acidosis and its associated lithogenic risk. Potassium citrate remains the cornerstone of metabolic management, while corticosteroid therapy plays a crucial role in controlling autoimmune tubulointerstitial inflammation and preserving renal function. Early diagnosis and timely intervention are critical for preventing recurrent stone formation, limiting irreversible interstitial fibrosis, slowing CKD progression, and improving long-term renal and clinical outcomes in patients with autoimmune renal involvement secondary to primary Sjögren syndrome.

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