Furosemide Overuse-related Acute and Chronic Tubulointerstitial Nephritis: A Case Report

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Abstract

Furosemide is a diuretic agent widely used to treat edema or hypertension. We present a 45-year-old woman with interstitial nephritis resulting from chronic furosemide dependence. Impaired renal function was initially found at a clinic. A renal biopsy showed mixed acute and chronic interstitial nephritis. After cessation of furosemide, the patient's renal function completely recovered. Although furosemide is generally considered safe, serious adverse effects may occur, such as dehydration, hyperuricemia, electrolyte imbalance, ototoxicity, allergic reactions and interstitial nephritis. Most cases of acute interstitial nephritis are caused by drug allergy or infections. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most common offending drugs. Treatment is aimed at early cessation of the offending agents and steroid administration if necessary. After treatment, most patients have partial or complete recovery of renal function. A prolonged course of acute tubulointerstitial nephritis can progress to chronic tubulointerstitial nephritis, in which renal function impairment may be permanent. Since there are few reports of furosemide-related tubulointerstitial nephritis in the literature, we presented this case to remind all physicians of the possible renal toxicity of furosemide. (J Intern Med Taiwan 2015; 26: 217-226)

Key Words: Diuretic, Furosemide, Tubulointerstitial nephritis

Introduction

Furosemide, a sulfonamide-based medication widely used for edema or hypertension, is generally considered safe. To our knowledge, there are few case reports of furosemide-related kidney injury in the literature. We report a case in which long-term furosemide overuse resulted in mixed acute and chronic tubulointerstitial nephritis.

Case Presentation

A 45-year-old woman was admitted for a renal biopsy due to worsening renal function. Her medical history included chronic furosemide overuse, bilateral renal stones, and stage 3 chronic kidney disease.

This 157- centimeter tall woman had self-medicated with furosemide (120 to 400 mg per day) to keep her body weight around 42 kilograms (kg) since she was 23 years old. Impaired renal function,

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with a serum creatinine concentration of 1.6 mg/dl and estimated glomerular filtration rate (eGFR) of 33.78 ml/min, was first noted when she was 31 years old. Her renal function fluctuated and had progressed to stage 3 kidney disease (eGFR: 26.1 ml/min) at this presentation. Drug- related renal injury was suspected and cessation of furosemide was suggested. However, every time she tried to discontinue furosemide, her body weight increased with swelling over the face and bilateral lower limbs which prevented her from discontinuing the diuretic.

She also had recurrent gout attacks about once to twice per year. Colchicine, benzbromarone, allopurinol, and prednisolone had all been prescribed but drug compliance was poor. Mostly she took NSAIDs during acute gout attacks. When she was 40 years old, a renal sonogram revealed bilateral renal stones. After she was 42 years old, she had been hospitalized several times for acute pyelonephritis. The patient refused to increase her water intake since drinking would increase her body weight. In addition, episodic hypokalemia (as low as 2.5 mEq/L) with general malaise were also noted, which could be improved by discontinuation of furosemide.

On admission, her blood pressure was 110/53 mm Hg and pulse rate 86/min. Physical examination showed no other abnormalities except for poor skin turgor.

Blood examinations revealed a serum white blood cell count, of $7.99\times10^3/\mu L$ with 0.5% eosinophils; hemoglobin 10.8 g/dL, blood urea nitrogen 57 mg/dl, creatinine 1.8 mg/dL; uric acid 8.8 mg/dL; sodium 139 mEq/L, and potassium 4.3 mEq/L. Immunological examinations including IgM, IgG, IgA, C3, and C4 were all within normal limits. Urinalysis showed leukocyturia but was negative for bacteria, occult blood, protein and glucose. A plain radiograph of the kidney-ureter-bladder showed scattered radiopaque lesions in the bilateral kidneys. A renal sonogram showed increased echogenicity of the renal cortex bilaterally and nephrocalcinosis. The right and left kidneys were 9.1cm and 9.2 cm in length, respectively.

After admission, all diuretics were discontinued and she was administered 0.5 liters of normal saline daily, followed by a renal biopsy.

Pathologic Findings

Light microscopic examination under hematoxylin and eosin stain revealed 7 glomeruli, one of which was obsolete. The non-obsolete glomeruli were unremarkable on morphology. The most prominent finding on renal biopsy was the presence of both acute and chronic tubulointerstitial nephritis. Multifocal inflammatory cells infiltrating the tubular epithelium and interstitium were seen (Figure 1, Figure 2a, Figure 3c). The majority of infiltration cells were lymphocytes, a few eosinophils (Figure 2b), and plasma cells (Figure 2a). Features of acute tubulointerstitial nephritis (ATIN), such as interstitial edema (Figure 2a), acute tubular necrosis (Figure 2c) and tubulitis (Figure 3c) were prominent. In addition, features of chronic tubulointerstitial nephritis (CTIN), such as tubular atrophy (Figure 3a-c) and interstitial fibrosis (Figure 3d) were also observed. Immunofluorescence studies for IgG, IgA, IgM, C3, C1q, kappa light chains and

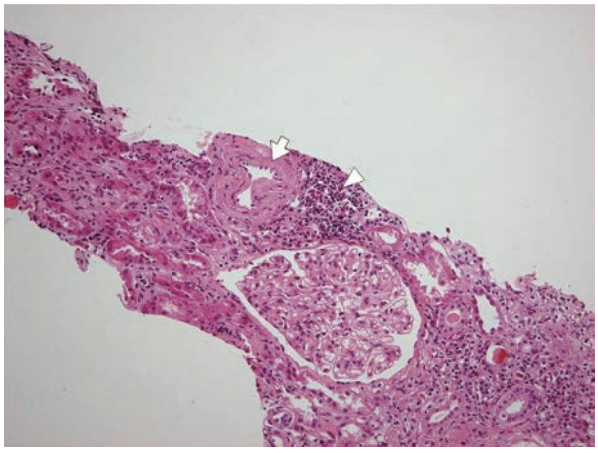

Figure 1. Light microscopy reveals a normal appearing glomerulus and normal vascular structure (arrow) with diffuse mononuclear cells infiltrating the interstitium (arrowhead). (hematoxylin and eosin stain).

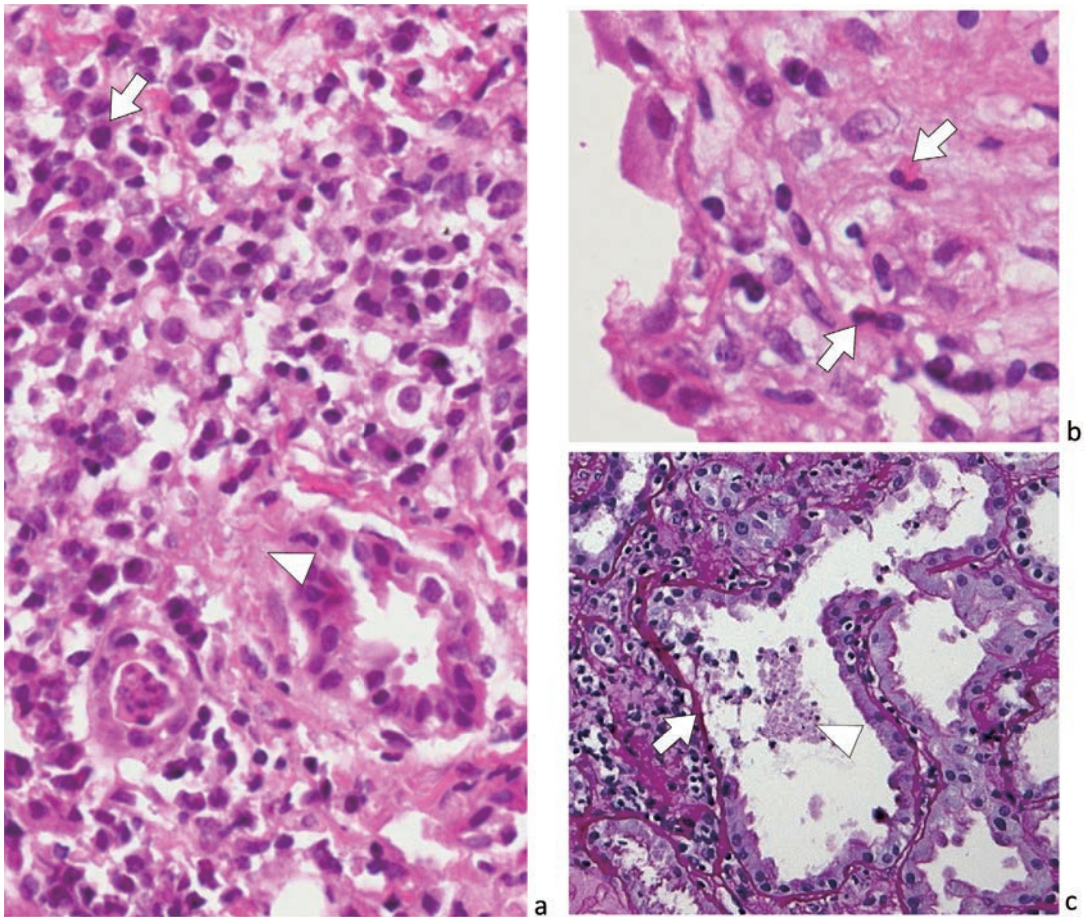

Figure 2. (a) Hematoxylin and eosin stain reveals interstitial edema (arrowhead) and plasma cell infiltration (arrow). (b) Eosinophils are also noted with hematoxylin and eosin stain (arrows). (c) Acute tubule necrosis with periodic acid-Schiff (PAS) stain. Note the tubular epithelium (arrowhead) detached from the tubular basement membrane (arrow).

lambda light chains were all negative. Granulomas were also absent.

Final Diagnosis

Mixed acute and chronic tubulointerstitial nephritis was diagnosed.

Clinical Follow-up

Six days after admission, the patient was discharged with a serum creatinine concentration of 1.4 mg/dL (eGFR 34.4 ml/min). The importance of abstinence from furosemide and adequate hydration were emphasized. However, it took her 5 years to completely quit furosemide. During this period, her renal function finally became stable at a serum creatinine concentration of 1.2 mg/dL (eGFR 38 ml/min). There were no more episodes of hypokalemia.

Discussion

We presented a case of chronic kidney disease caused by long-term furosemide overuse. The possible causes of renal injury included: A. furosemide-related ATIN and CTIN; B. fluid depletion and hyperuricemia and C. hypokalemic nephropathy.

Furosemide-related ATIN and CTIN

ATIN

The adverse effects of furosemide include fluid depletion, electrolyte disorders (e.g., hypokalemia), hyperuricemia, allergic reactions, ototoxicity

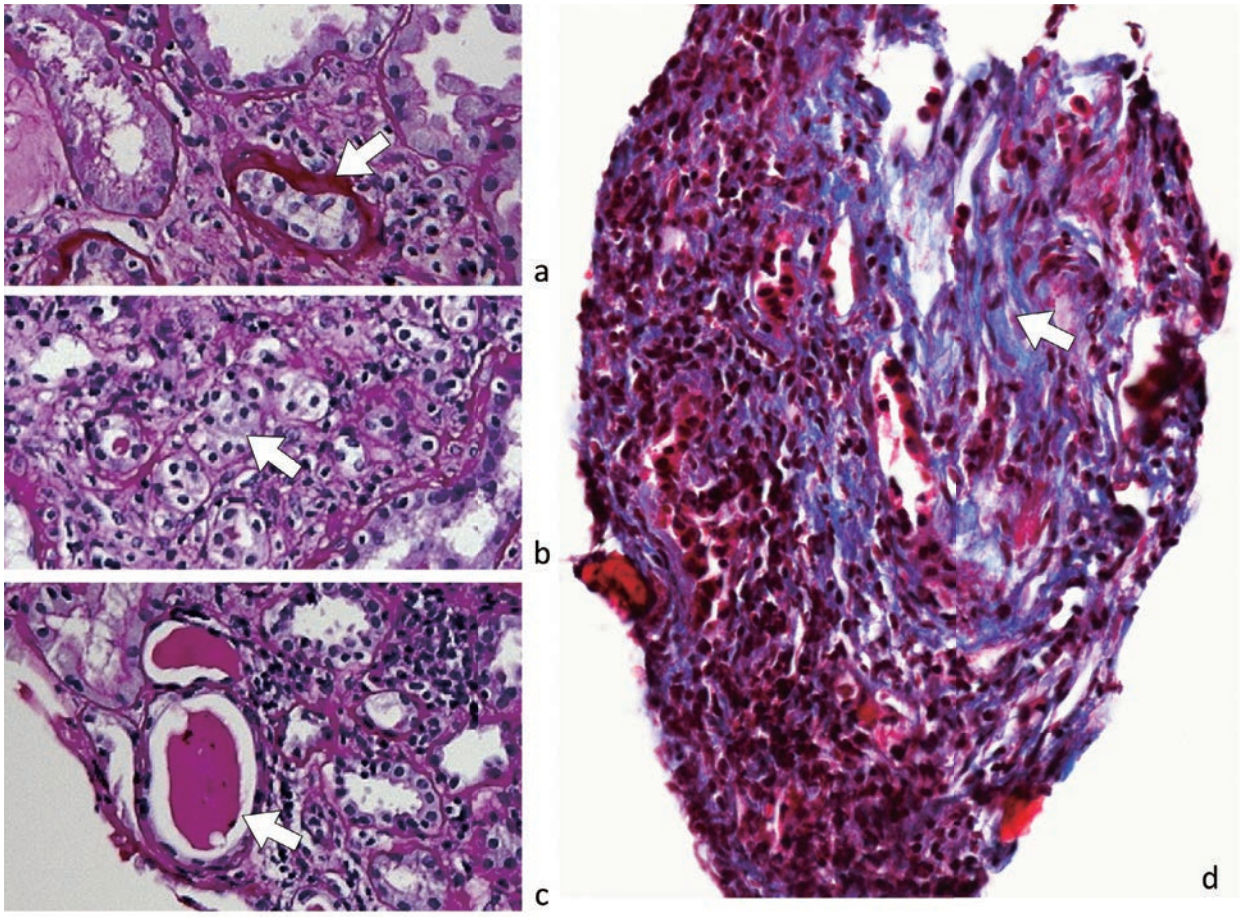

Figure 3. (a) “Classic type” atrophic tubules with PAS stain (arrow). (b) “Endocrine type” atrophic tubules with PAS stain (arrow). (c) “Thyroidization type” atrophic tubules with PAS stain (arrow). Mononuclear cells infiltrating tubules are also noted. (d) Masson’s trichrome stain reveals interstitial fibrosis (arrow).

and tubulointerstitial nephritis. While acute allergic reactions to furosemide may cause ATIN, a prolonged duration of ATIN may progress to CTIN.[1,2]

ATIN is diagnosed in 15-27% of renal biopsies in patients with acute kidney injury.[3,4] An immunoallergic reaction to certain drugs remains the most common cause, accounting for more than 75% of cases of ATIN. Other etiologies of ATIN include infections (5~10%, such as scarlet fever, hantavirus infection), systemic diseases (10~15%, for example, sarcoidosis, systemic lupus erythematous) and idiopathic causes (5~10%).[4,5] Theoretically all drugs can cause ATIN. NSAIDs and antibiotics cause the majority of cases of drug -related ATIN.[4] Furosemide, on the other hand, remains an infrequent cause of ATIN and is often overlooked.[1,2,6-9] The presentation includes insidious onset of renal function impairment, which occurs weeks to months after initiation of furosemide.[10] The clinical manifestations and pathologic findings are similar to other drug-related ATIN.

Pathogenesis of Drug-related-ATIN

Most cases of ATIN are allergic reactions which cause damage to the renal tubules and interstitium. This hypersensitivity is induced by expression of endogenous nephritogenic or exogenous antigens on tubular cells.[4]

It is widely believed that T cells play the major pathologic role in the development of ATIN. The major infiltration cells are lymphocytes.[11] These lym-

phocytes demonstrate activation against drug haptens, which causes interstitial infiltration of T cells or immune complex deposition and an inflammatory reaction.[12-14] The expression of these antigens is counterbalanced by complex protective mechanisms mainly involving suppressor T cells. When these protective mechanisms are surpassed, these antigens elicit cell-mediated immunity and cause ATIN. Immunofluorescence studies are mostly negative in these patients, which indicates antibody-mediated immunity plays little role in the pathogenesis.[4]

Pathology of ATIN

Histologic findings of ATIN include inflammatory cell infiltration within the renal interstitium, interstitial edema, and acute tubular injury. Glomeruli and blood vessels are mostly spared (Figure 1).[4,5,15] The majority of inflammatory cells are T-lymphocytes. Infiltration by macrophages, eosinophils and plasma cells may also be present (Fig 2a-b). Interstitial edema is defined as interstitial expansion with fluid leakage from damaged blood vessels or tubules without collagen deposition (Figure 2a).[16] Tubular injury is characterized by tubulitis, breaks in the tubular basement membrane, necrosis of tubular cells, and loss of tubules. Tubulitis is defined as the presence of inflammatory cells infiltrating the tubular epithelium (Figure 3c). Major pathologic features of tubular necrosis include swelling of the tubular epithelium, detachment of the tubular epithelium from the underlying tubular basement membrane, loss of the periodic acid-Schiff (PAS)-positive brush border of the proximal tubular epithelium, thinning (simplification) of the tubular epithelium, dilated tubular lumen and sloughed epithelial cells in the tubular lumen (Figure 2c). Granulomas can be observed in some cases of drug-related ATIN. Immunofluorescence stains are mostly negative, but sometimes granular or linear deposits of IgG can be observed.[4]

Clinical Manifestation of Drug-induced ATIN

In one study, all patients with ATIN presented with acute kidney injury a few days to a few weeks after exposure to the offending drug.[10] The classic triad of drug-induced ATIN includes three allergic-type reactions, fever, rash and eosinophilia. However, clinical presentations varied between individuals and the classic triad may be absent in up to 86% of cases. Aside from acute kidney injury, non-nephrotic proteinuria (93%) and leukocyturia (82%) are the most common clinical manifestations. Drugs other than NSAIDs rarely induce nephrotic-range proteinuria.

Diagnosis of ATIN

Given the fact that the classic triad is often absent and other findings are nonspecific in patients with ATIN, renal biopsy remains the gold standard for diagnosis.[17] Eosinophiluria was once considered to be suggestive of ATIN. However, pooled data revealed eosinophiluria has poor sensitivity (67%) and a low positive predictive value.[18] Eosinophiluria may also occur in a variety of other conditions, such as acute tubular necrosis, glomerulonephritis, atheroembolic renal disease, urinary tract infection and even prerenal acute kidney injury. Thus eosinophiluria should not be used as a screening test. Renal gallium 67 scanning provides suggestive evidence but is unable to reliably confirm or exclude the diagnosis of ATIN.[15]

Treatment and Prognosis of ATIN

To date, the mainstay of therapy for ATIN is early discontinuation of the offending agents or treatment of the underlying disease. Whether corticosteroids are beneficial is still under debate. Many studies have shown negative results.[5,19-22] However, others showed positive effects, especially with early initiation after exposure to the offending drug. Galpin et al evaluated 14 patients with methicillin-induced ATIN who had a peak serum creatinine of

8 mg/dL. The eight patients treated with glucocorticoids recovered more quickly (9 versus 54 days) with a lower final serum creatinine concentration (1.4 versus 1.9 mg/dL) than the other six patients who received no therapy.[23] Buysen et al studied 27 patients with biopsy- proven ATIN. Among them, 10 patients who did not improve following discontinuation of the offending drugs or treatment of the infection were given corticosteroids within 5 to 20 days of biopsy. The serum creatinine normalized within one month in 6 patients. The other 4 patients had partial improvement of renal function.[17] Another multicenter retrospective study by Gonzalez et al involved 61 patients with biopsy- proven drug-induced ATIN. Corticosteroids were given to 52 patients for 8 to 12 weeks. After 18 months, the steroid-treated group had a lower chronic dialysis rate (4% versus 44%) and a lower mean final serum creatinine (2.1 mg/dL versus 3.7 mg/dL). In the steroid-treated group, those who started treatment with corticosteroids longer than 7 days after drug withdrawal had a higher risk of incomplete renal function recovery (odds ratio, 6.6, 95% confidence interval, 1.3-33.6).[24]

In general, the prognosis of ATIN is good. At least partial recovery of renal function occurs in most patients after withdrawing the offending agent or treating the underlying disease.[24,25] NSAIDs are the most common causes of permanent renal insufficiency after ATIN.[5] Given the potential benefit and relative safety of short -term corticosteroid use, it is reasonable to initiate corticosteroids if the patient's renal function doesn't improve significantly within 7 days after cessation of the offending drug. The initial approach may include prednisone 1mg/kg/day for a minimum of 1 to 2 weeks, followed by gradual tapering after the serum creatinine has returned to near baseline.[17] Intravenous methylprednisolone 250 to 500mg/day for 3 days may be used in more severe cases.[17]

CTIN

Pathogenesis of CTIN

While most cases of ATIN are associated with allergic drug reactions, cases of CTIN are mostly secondary to other systemic disorders involving the kidney or chronic primary glomerular diseases. The tubulointerstitium can be injured by various mechanisms, including toxins (lead, cadmium), drugs (lithium, aristolochic acid), infections (vesicoureteral reflux, chronic pyelonephritis), immunologic reactions (lupus, Sjögren syndrome), ischemia and massive proteinuria.[18,26] The tubulointerstitial responses to these different mechanisms are similar. Injured tubular cells release chemotactic substances, complement components, and vasoactive mediators and express human leukocyte antigens. These tubular cells also act as antigen-presenting cells and attract inflammatory cells (macrophages and T cells) into the interstitium. Several kinds of growth factors, including transforming growth factor β and platelet-derived growth factor, are secreted by these tubular cells and macrophages.[18] These growth factors cause matrix expansion by stimulating fibroblast proliferation and inhibiting matrix degradation.[27] Tubulointerstitial injury also causes loss of the peritubular capillaries.[28] The expanded matrix and loss of peritubular capillaries cause decreased oxygen diffusion, which makes the kidney hypoxic.[26,28] Hypoxia of the tubular cells leads to local apoptosis and fibrosis which lead to permanent renal function impairment.[28]

Pathology of Drug-related CTIN

In drug-related CTIN, histologic features include tubular atrophy (Figure 3a-c) and interstitial fibrosis (Figure 3d). Tubular atrophy has three morphologic subtypes, the "classic type", "endocrine type", and "thyroidization type".[16,29] The "classic type" includes a thick, wrinkled tubular basement membrane and simplified or lamellated epithelium. The "endocrine type" includes small tubules, a

narrow lumen or no lumen, clear cells and a thin basement membrane. These tubules usually occur in clusters. The "thyroidization type" has round tubules with simplified epithelium, a mildly thickened basement membrane and a lumen filled with eosinophilic PAS-positive homogenous proteinaceous material. These tubules also occur in clusters and resemble thyroid follicles. These three subtypes were all observed in our patient (Figure 3). Interstitial inflammatory infiltrates often persist, but are usually milder than in ATIN. These cells are often nodular and present in fibrotic areas.[16] The infiltration cells are composed largely of nonactivated lymphocytes, plasma cells and macrophages. Granulomas may be seen in tubulointerstitial nephritis caused by drugs, infections with mycobacteria, fungi or parasites, sarcoidosis, and vasculitis.[16]

Clinical Manifestations of CTIN

The most common manifestation of CTIN is insidious onset of renal function impairment. Patients with proximal tubular dysfunction may have aminoaciduria, phosphaturia, proximal tubular acidosis or Faconi syndrome. Patients with distal tubular dysfunction may have type IV renal tubular acidosis. Patients with medullary tubule dysfunction may have concentrating defects, which may be severe enough to result in nephrogenic diabetes insipidus. Other patients with microvascular disease may be unable to excrete salt, resulting in salt-sensitive hypertension. Anemia may occur early due to loss of erythropoietin-producing interstitial cells.[18]

Treatment of CTIN

Treatment focuses on elimination of factors causing the chronic tubulointerstitial injury.[18] General supportive measures, such as blood pressure and serum glucose control and use of renin-angiotensin-aldosterone system blockers, are widely accepted. Specific treatments are reserved for each clinical entity, such as corticosteroids for sarcoidosis.

Fluid depletion and Hyperuricemia

Furosemide blocks the sodium-potassium-chloride co-transporter (NKCC2) in the ascending loop of Henle, causing the excretion of water, sodium, potassium, magnesium, calcium and chloride. Fluid depletion could cause prerenal azotemia, hyperuricemia and possibly, gout attacks. Diuretic therapy may increase the serum urate concentration by as much as 35%.[30] The increment of serum urate concentration is due to decreased urate clearance, which is associated with extracellular fluid depletion. There is a trend toward a higher risk of acute gouty arthritis in patients on loop and thiazide diuretics.[31] However, whether diuretics can cause gout attacks is still controversial.[32-35] NSAIDs, which are frequently prescribed for gouty arthritis and renal colic, could further cause afferent arteriole vasoconstriction-related renal damage, ATIN, and CTIN with chronic use.

Hypokalemic Nephropathy

Hypokalemia could induce renal vasoconstriction and local ammonia production, which may contribute to renal damage in hypokalemic nephropathy. The associated intracellular acidosis can stimulate cell proliferation, which may account for the development of renal cysts. The pathologic findings include vacuolation of the proximal renal tubules, tubular atrophy, interstitial fibrosis, and cyst formation.[36-39] Clinically, chronic hypokalemia causes progressive loss of renal function and formation of renal cysts. The renal concentrating ability may be impaired, which leads to polyuria, nocturia and polydipsia, especially when the serum potassium concentration is consistently below 3 mEq/L for months or years. Proteinuria may also be noted. Hypokalemic nephropathy generally requires at least one month to develop and is reversible with potassium repletion at initial presentation. Hypokalemia can usually be treated with oral potassium supplements. Correction of hypokalemia can lead to

a decrease in the number and size of cysts, although the tubulointerstitial lesions and associated renal insufficiency may be irreversible.[36]

Conclusion

Our patient developed chronic kidney disease after 22 years of furosemide dependence. She had tried to quit furosemide but failed due to rebound sodium and water retention. The pathologic report revealed mixed acute and chronic tubulointerstitial nephritis. A review of her medical history showed that furosemide was the most likely offending drug. Other furosemide-related side effects such as volume depletion, hypokalemia, hyperuricemia, gouty arthritis with subsequent NSAID exposure (though not frequent), bilateral renal stones and recurrent acute pyelonephritis may also have contributed to her kidney injury. Her kidney injury resolved after cessation of furosemide.

In conclusion, furosemide is a widely used sulfonamide-based diuretic agent. It influences renal function in several ways. Drug -related ATIN and CTIN caused by furosemide are often neglected. Since there are few reports of furosemide-related kidney injury in the literature,[1,2,40-43] we present this case to remind physicians that the use of furosemide is not risk-free and the drug may impair renal function permanently. The importance of close monitoring of renal function and electrolyte balance should also be emphasized.

Acknowledgements

The authors thank Dr. Tung-Ying Chen for identification of the pathologic features. There are no conflicts of interest to disclose.

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濫用服樂洩麥 (Furosemide) 導致之急性與慢性腎小管間質腎炎

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摘 要

服樂洩麥 (Furosemide) 是一種被廣泛使用的利尿劑，常用來治療水腫或是高血壓。本文報導一位因服用服樂洩麥而導致腎小管間質腎炎的案例。病人為45歲女性，長期大量服用服樂洩麥來控制體重，門診追蹤時發現腎功能不全，腎臟切片顯示急性及慢性腎小管間質腎炎。在停止使用服樂洩麥後，病人的腎功能順利恢復至正常範圍。根據一般經驗，服樂洩麥的耐受性良好，但此藥仍可能造成一些嚴重的副作用，例如：脫水、高尿酸血症、電解質失衡、耳毒性、藥物過敏及腎小管間質腎炎。大部分的急性腎小管間質腎炎由藥物過敏或感染症所造成，常見引起的藥物為抗生素及非類固醇消炎藥。治療方式為盡早停止引發過敏的藥物，必要時可輔以類固醇治療。此類病人最後多半能恢復部分、甚至全部的腎功能，但倘若病程延長，可能進展至慢性腎小管間質腎炎，腎功能也可能永久性地喪失。在文獻紀錄上，因服樂洩麥引起腎小管間質腎炎的案例報告並不常見，吾人藉此案例報告強調，在服樂洩麥被廣為使用的今日，要謹慎注意該藥可能對腎功能造成的不良影響。