Uric Acid Nephropathy Superimposed on Lupus Nephritis

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Hyperuricaemia and gout are predominant diseases of middle-aged men and postmenopausal women. Systemic lupus erythematosus is primarily a disease of young women, with a female: male ratio of about 9:1. Uric acid nephropathy and lupus nephritis are often the cause of renal failure. The incidence and prevalence of these two diseases are low in young men. We report a 29-year-old man who presented with anasarca, gross hematuria, proteinuria, mild anaemia, hyperuricaemia and acute renal failure. He had developed a rash on his face and right hand, and pain in both knee joints six months prior to presentation. Gouty arthritis was diagnosed because of coexistent hyperuricaemia. He was admitted to hospital because of exacerbated anasarca which had been progressing slowly for over half a year. Severe proteinuria and hematuria were also noted and a renal biopsy revealed uric acid nephropathy superimposed on lupus nephritis. Long term medication with immunosuppressants and a uric acid-lowering agent were prescribed after the pathohistologic diagnosis. The patient's serum creatinine level had improved after six months of therapy. **(Mid Taiwan J Med 2004;9:249-54)**

Key words

lupus nephritis, renal failure, uric acid nephropathy

INTRODUCTION

Systemic lupus erythematosus (SLE), an autoimmune disorder of unknown etiology, demonstrates a chronic inflammatory character and can occur at almost any age. It may affect the skin, joints, lungs, heart, serous membranes, nervous system, and other organs. Renal involvement is common and can influence the patient's prognosis. SLE is predominantly a disease of women, with a female: male ratio of about 9:1 [1]. Overt clinical prevalence of renal disease varies from 35% to 75% of patients with well-documented SLE [2]. Results of renal biopsies have shown that SLE involves the kidney in almost all cases even in the absence of proteinuria or abnormal urinary sediment [3].

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Hyperuricaemia is associated with renal disease. Approximately 20% to 60% of patients with gout have mild or moderate renal insufficiency [4]. There is strong evidence that in the overwhelming majority of middle-aged, predominantly male patients with gout, hyperuricaemia results from an inherited decreased fractional clearance of urate in the kidney.

Although some patients with SLE may have hyperuricaemia due to renal insufficiency, they seldom develop gout. We recently diagnosed uric acid nephropathy in a young man with lupus nephritis. This case prompted us to examine the frequency of gout and hyperuricaemia in SLE patients and to explain the factors which may predispose individuals to its development.

CASE REPORT

A 29-year-old man, without a familial history of lupus, gout or nephritis, was diagnosed

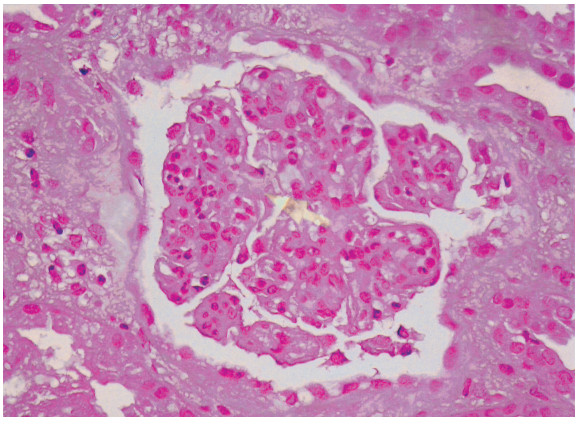

Fig. 1. Marked intraglomerular cellular proliferation, lobular accentuation and mild to focally moderate karyorrhexis. (H & E stain, 400 ×)

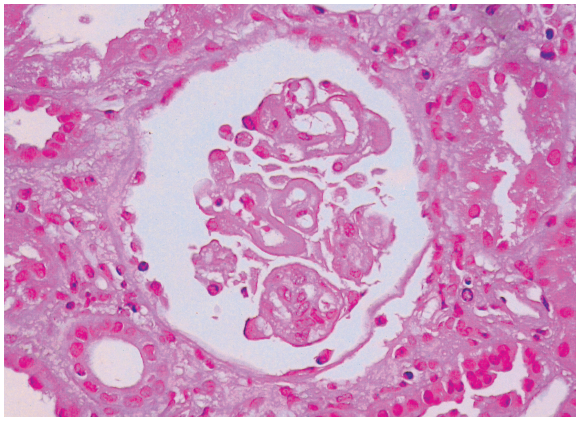

Fig. 2. Subendothelial deposits in a wire loop pattern and fibrinoid necrosis were present in the intraglomerular area. (H & E stain, 400 ×)

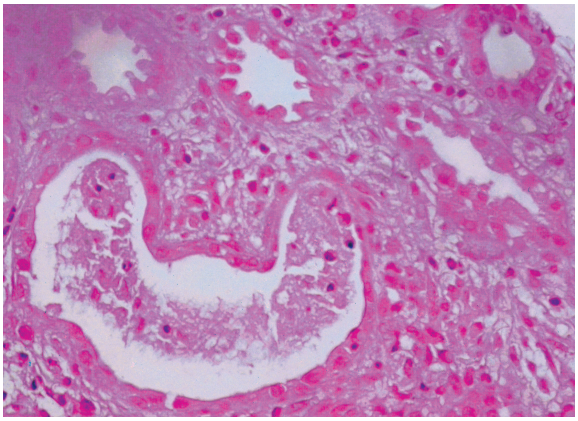

Fig. 3. Alternating degenerative and regenerative changes of the lining epithelium. (H & E stain, 400 ×)

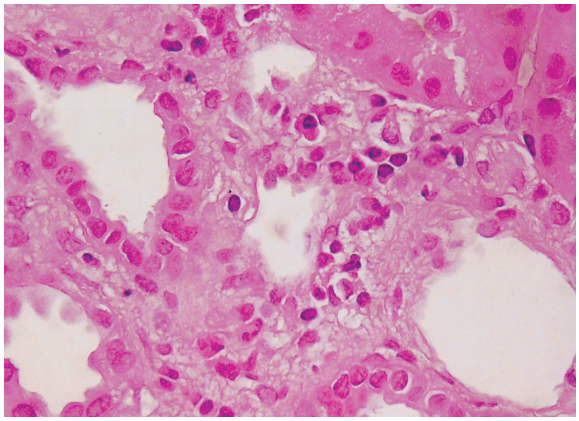

Fig. 4. Mild to moderate interstitial infiltration composed primarily of mononuclear cells. (H & E stain, 400 ×)

as having primary hypertension at age 20. His blood pressure was poorly controlled between 140-160/70-90 mmHg by atenolol 100 mg daily. About six months prior to this admission, he presented with moderately painful erythema in his right hand and para-oral area, followed by arthralgias in both knee joints. Gouty arthritis was diagnosed because of coexistent hyperuricaemia and treated with allopurinol and benzbromarone. Urinalysis revealed microscopic hematuria and proteinuria. However, three months prior to this admission, he had developed eyelid puffiness, gross hematuria, stiffness in both ankle joints and occasional bilateral flank pain. Anasarca had also been developing for over half a year. Upon admission, the white blood cell count was 6.74 × 10^9/L (6.74 × 10^3/μL), hemoglobin 6.88 mmol/L (11.1 g/dL), platelet 76 × 10^9/L (76 × 10^3/μL), blood urea nitrogen 42.8 mmol/L (120 mg/dL), creatinine level 469 μmol/L (5.3 mg/dL), albumin 22 g/L (2.2 g/dL), uric acid 964 μmol/L (16.2 mg/dL), 24 h urinary protein 10.64 g, creatinine clearance 29.9 ml/min, 24 h urinary uric acid 280 mg. Urinalysis showed proteinuria (3+), pyuria (25-30 white blood cells per high power field) and hematuria (numerous red blood cells per high power field). Immuological tests were normal except for a low C3 complement (0.078 g/L; N: 0.85-1.85) (7.82 mg/dL; N: 79-152), a low C4 complement (0.112 g/L; N: 0.12-0.54) (11.2 mg/dL; N: 16-38) and a positive antinuclear antibody titer at 1:80 with a speckled pattern.

A renal biopsy specimen showed diffuse proliferative glomerulonephritis, manifested by a

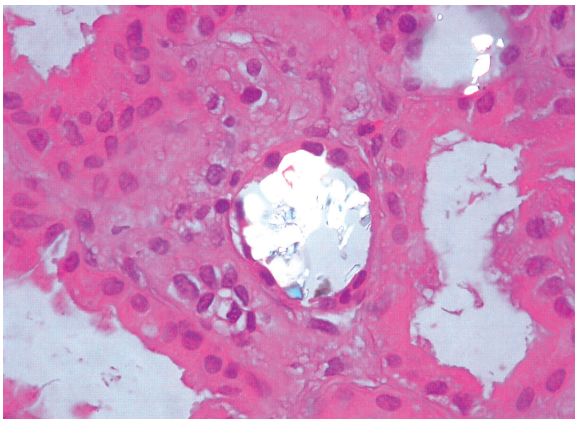

Fig. 5. Discernible needle to rectangular sodium urate crystals in the injuried tubules under a polarized microscope. (H & E stain, 400 ×)

marked intraglomerular cellular proliferation, lobular accentuation and mild to focally moderate karyorrhexis (Fig. 1). Subendothelial deposits in a wire loop pattern and fibrinoid necrosis were also noted (Fig. 2). The tubulointerstitial compartment showed patchy tubular epithelial cell injury with simplification and alternating degenerative and regenerative changes of the epithelial lining (Fig. 3). Mild to moderate interstitial inflammatory infiltration in the interstitial area was also noted (Fig. 4). Discernible needle to rectangular sodium urate crystals could be seen in the injuried tubules under a polarized microscope (Fig. 5). The immune fluorescent study demonstrated a strong granular "full-house" deposition of IgG, IgM, IgA, C3, C1q and C4 in the subendothelial and mesangial regions. Based on the histopathological and immunofluorescent features, lupus nephritis class IVc (modified World Health Organization classification) and tubulointerstitial injuries caused by acute uric acid nephropathy were suspected. The patient's serum creatinine had decreased to around 265.2 μmol/L after six-months of treatment with immunosuppressants and a uric acid-lowering agent (prednisolone 10 mg daily, cyclosporine 50 mg bid, and allopurinol 100 mg daily).

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder characterized by overproduction of autoantibodies and other distinct immunological abnormalities. It may be multisystemic or may involve only one organ system with additional manifestations occurring later. Lupus nephritis usually develops within 3 years after diagnosis of SLE [3] and only one-quarter of patients with renal lupus presents with renal disease as the first manifestation. Arthritis and facial rash usually precede nephritis [5].

Our patient, who fulfilled the American Rheumatism Association criteria for SLE, clinically presented with acute renal failure, severe proteinuria, hematuria and hyperuricemia on admission. He had sudden onset of arthralgia attacks in both knees and gouty arthritis was diagnosed without arthrocentesis six months prior to presentation. Patients with SLE are predominantly young and female. Coexistent SLE and gout, as in our case, is uncommon. The common clinical features of this group include nephritis manifested by proteinuria. Diuretic and corticosteroid therapy is the most common treatment. Patients with coexistent SLE and gout tend to be older and more frequently male than the general population of SLE patients [6]. It has been reported that most patients develop gout after the onset of SLE and many of them have hypertension and serious cardiovascular diseases. In one study, serum uric acid and 24-h urine uric acid indicated that all of the patients were hyperuricaemic and underexcretors of uric acid [7]. Most of the above clinical features were also seen in our case.

Hyperuricaemic SLE patients often present with the same clinical features associated with gout. One study reported that hyperuricaemia was found in 29% of patients and that it was closely associated with renal involvement and diuretic therapy. Particularly striking was the very high prevalence of proteinuria in these patients, although most of them had normal serum creatinine levels [6]. Thus the major factors contributing to hyperuricaemia in our patient appeared to be decreased clearance of uric acid, including decreased glomerular filtration rate and impaired tubular secretion, and enhanced tubular reabsorption due to intravascular volume contraction. The uricosuric effect of

benzbromarone, NSAIDs and corticosteroid could also have been a factor. Recent studies have reported that hyperuricaemia induces hypertension, intrarenal vascular disease and renal injury. Despite the association between hyperuricaemia and renal disease, controversy exists as to whether uric acid plays an etiologic role [8-10]. In this study, the rectangular sodium urate crystals within the tubular lumen seen under polarized microscopy were mainly uric acid crystals. Tubular blockage and tubular ingestion of crystals, which induce tubular injury, tubular inflammation and minimal interstitial cellular infiltraton, lead to acute uric acid nephropathy and may exacerbate acute renal failure. About 60% to 70% of patients with lupus nephritis show some degree of interstitial inflammation, tubular damage, and interstitial fibrosis. Together with inflammatory lesions, some 30% to 50% of cases show immune deposits (mostly IgG and C3) along tubular basement membranes, in the interstitium, and along the peritubular capillary and arteriolar walls. Usually the degree of interstitial lesions correlates with the severity of glomerular changes. The presence of immune deposits in these structures has suggested that tubulointerstitial damage may be immune complex-mediated [11]. Therefore, acute uric acid nephropathy seen in our patient is different from typical lupus interstitial nephritis.

Gout with renal failure in young patients is possibly due to hereditary nephritis, a hypoxanthine guanine phosphoribosyltransferase (HGPRTase) defect leading to purine over-production, or an inherited defect in the tubular handling of urates which reduces urate excretion [12,13]. Although our patient was an underexcretor, calculation of fractional urate excretion (FEur) and red cell HGPRTase deficiency testing would have provided additional information to help rule out hereditary nephritis.

The severity of proteinuria, ranging from the minimal to nephrotic usually correlates with the histologic type of lesion in lupus nephritis. The main cause of overt proteinuria in our patient was attributed to class IVc lupus nephritis. Neither acute uric acid nephropathy nor chronic urate nephropathy would have been able to induce nephrotic proteinuria. Acute nephritic syndrome, which is characterized by the abrupt onset of hematuria, proteinuria temporally associated with acute renal failure resulting in the development of oligouria, salt and water retention, and hypertension as seen in our case, is most commonly due to proliferative glomerulonephritis and less commonly due to acute interstitial nephritis. We believe that active immunosuppressive therapy for his class IVc lupus nephritis led to improved renal function, decreasing the the serum creatinine level from 469 μmol/L (5.3 mg/dL) to 265 μmol/L (3.0 mg/dL). This implies that acute uric acid nephropathy was simply superimposed on lupus nephritis and not the main cause of his acute renal failure.

Renal biopsies of lesions in SLE patients with gout and hyperuricacemia offen reveal membranous nephritis [6,7], membrano-proliferative nephritis and diffuse proliferative nephritis [6]. Acute uric acid nephropathy superimposed on diffuse proliferative nephritis has never been reported. Based on the epidemiology of uric acid nephropathy and lupus nephritis, young males have a relatively low incidence of developing those two diseases. Renal biopsy plays a crucial role in identifying these lesions and may have prognostic and therapeutic implications.

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尿酸性腎病變合併狼瘡性腎炎表現於一年輕男性病人

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高尿酸血症和痛風常發生在中年男性或停經後的婦女。紅斑性狼瘡則常常好發於年輕女性，女性和男性的比例約爲9：1。尿酸性腎病變和狼瘡性腎炎常常是腎衰竭的原因。年輕男性對上述兩種疾病有較低的發生率與盛行率。我們報告一位29歲的男性病人，臨床表現爲全身水腫，巨觀血尿，蛋白尿，輕微貧血，高尿酸血症和急性腎衰竭。大約在住院前六個月左右，這位病人發生位於臉及右手的皮疹和兩側膝關節疼痛，因爲同時合併高尿酸血症，當時開業醫師診斷爲痛風性關節炎。這次住院是因爲全身水腫在最近半年內逐漸惡化，並發現嚴重蛋白尿和血尿。腎臟切片檢查結果顯示這位病人罹患急性尿酸性腎病變合併狼瘡性腎炎。開始長期給予降尿酸藥物和免疫抑制劑治療，經六個月之後，病人血中肌酸酐濃度明顯改善。（中台灣醫誌 2004;9:249-54）

關鍵詞

狼瘡性腎炎，腎衰竭，尿酸性腎病變

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