Lupus Nephropathy as the Initial Manifestation of Systemic Lupus Erythematosus

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The present report documents the occurrence of lupus nephropathy as the sole initial manifestation of systemic lupus erythematosus (SLE). Despite the absence of initial systemic signs characteristic of SLE, the diagnosis was confirmed on the basis of the renal histopathologic features and serological studies. Subsequent follow-up demonstrated systemic features of the disease in each of the four patients.

The report shows that the diagnostic criteria for SLE proposed by the American Rheumatology Association may not be fulfilled at the time of the initial evaluation in all cases, and that some patients may exhibit signs attributable to primary renal disease. These data emphasize the importance of careful assessment of the pattern of glomerular ultrastructural changes and usefulness of appropriate serological studies.

INTRODUCTION

Clinical recognition of systemic lupus erythematosus (SLE) in individual patients is often complicated by the wide spectrum of clinical manifestations which may simulate other disease entities. Conversely, the systemic features of SLE may be masked, at least initially, when clinical signs are restricted to a single organ system. To establish a uniform means to identify and classify patients with SLE, the American Rheumatology Association (ARA) published diagnostic criteria in 1971 which included 14 criteria, eight of which were clinical and six were laboratory [1]. The presence of four or more criteria in an individual patient was construed to be compatible with the diagnosis of SLE.

Despite the usefulness of the criteria proposed by the ARA, occasional patients with SLE have been reported in whom these criteria were not fulfilled at the time of initial clinical presentation [2,3]. Since SLE exhibits a variable natural course and the criteria proposed by the ARA were derived from patients attending rheumatology clinics, it is not surprising that exceptions to the classification occur.

Although previous reports have stated that lupus nephropathy may occur as the sole presenting sign of SLE in three to six percent of cases [2,3], documentation has not been provided to establish the existence of lupus nephropathy in the absence of non-renal manifestations at onset of disease. Recognition of this possible clinical variant of SLE has important clinical implications since treatment with glucocorti-
coids and/or cytotoxic drugs may alter the renal histopathology and clinical course of lupus nephropathy [4].

In the present report, we describe four patients with SLE in whom the initial clinical manifestation was restricted to signs of renal disease. Although the published criteria of the ARA for SLE were not fulfilled at the time of initial evaluation, specific serological studies, renal histopathological features, and/or subsequent clinical manifestations ultimately led to the recognition of SLE.

Case 1

R.B., a 61-year-old woman, was in good general health until March 1970, when she was admitted to a community hospital complaining of a 30-pound weight loss, nervousness, and fever. Physical examination demonstrated a temperature of 103.6°F. and a diffusely enlarged thyroid gland. There was no evidence of rash or arthritis. Laboratory evaluation included a protein-bound iodine of 10 micrograms (normal 4–8 micrograms) and a T3 resin uptake of 45 percent. Urinalysis showed 1+ protein, 6–8 RBC and 4–6 WBC/HPF. BUN was 19 mg/dl, Hg 11.5 gm/dl, and WBC was 3700/ml. Several LE preparations were negative. The diagnosis of hyperthyroidism was made and the patient was begun on propylthiouracil. Within several days, the patient developed leukopenia characterized by a white blood cell count of 1800/ml with 12 percent polymorphonuclear cells and 74 percent lymphocytes. Propylthiouracil was discontinued and methimazole was begun. Following the change in therapy, the patient's temperature fell to normal levels and white blood cell count rose to 4700 with 42 percent polymorphonuclear cells.

She remained asymptomatic until October 1971 when she was readmitted to the hospital for evaluation of dependent edema of one month's duration. With the exception of edema to the level of her knees and mild hypertension, the physical examination was normal. The patient denied systemic manifestations including rash, arthritis, or arthralgia. Laboratory studies showed the following: Hct 34 percent, WBC 4800/ml, serum creatinine 1.0 mg/dl, creatinine clearance 60 ml/min, serum albumin 2.6 gm/dl, and urinary protein 4.8 gm/day. A percutaneous renal biopsy was performed and demonstrated a severe diffuse proliferative and focally necrotizing glomerulonephritis with acute necrotizing periarteritis by light microscopy. Examination by electronmicroscopy showed massive subendothelial deposits and electron-dense deposits in subepithelial and mesangial loci. Since the renal histopathological features were considered to be characteristic of lupus glomerulonephritis, serological studies were performed and showed a positive antinuclear factor (ANF) of 1:256, and a C3 of 36 mg/dl (normal values 78–150 mg/dl).

Treatment was begun with azathioprine 100 mg/day and prednisone 10 mg/day. Within two months of initiating treatment, the urinary protein excretion fell to less than 300 mg/day. During the ensuing four years, she remained asymptomatic and the levels of serum creatinine, urinary protein excretion, and C3 were within normal limits and ANF titers were less than 1:40. Determination of DNA binding capacity (DNA-bc) was first performed in February 1973 and was 12 percent and remained less than 15 percent on subsequent studies (normal values < 20 percent [5]). Renal biopsies performed in 1973 and 1975 showed a marked reduction in the intraglomerular inflammatory reaction, complete resolution of subendothelial deposits, and persistence of subepithelial and mesangial deposits. Azathioprine was discontinued in November 1975 and prednisone was continued in a dose of 5 mg/day.

In June 1977, while asymptomatic, the DNA-bc rose to 34 percent and C3 fell to 26 mg/dl. Urinary protein excretion was 300 mg/day. With six weeks, a macular
Clinical improvement, the azathioprine protein leukocytoclastic proliferation erythematous rash was evident on two general evaluations. Case K.A., a five-year-old girl, was transferred from a community hospital for evaluation of proteinuria and generalized edema of two months' duration. During the two weeks prior to admission, she had had occasional temperatures of 101°F. There was no antecedent history of throat or skin infection. In addition, there was no history of drug ingestion, rash, arthritis, or mucosal lesions. Physical examination was notable for a temperature of 102.4°F, ascites, and peripheral edema. Laboratory tests showed the following: Hg 8.0 gm/dl, WBC 10,400/ml, platelets 550,000, urinalysis 4+ protein, many RBC and RBC casts, serum albumin 1.3 gm/dl, serum creatinine of 2.6 mg/dl, ANF titer 1:512, DNA-bc 78 percent, C3 22 mg/dl, C4 20 mg/dl (normal 21–50 mg/dl). A percutaneous renal biopsy revealed a severe proliferative glomerulonephritis with focal necrosis and numerous cellular crescents. Electronmicroscopy showed massive subendothelial deposits and focal mesangial and intramembranous deposits. Several deposits had a fingerprint pattern. On immunofluorescent staining, there was a marked deposition of IgG, IgM, IgA, C3, C4, and fibrin in a granular pattern. Over the next five days the patient became oliguric, the serum creatinine level rose further, and peritoneal dialysis was instituted.

Therapy was begun with cyclophosphamide, 25 mg/day and glucocorticoids were administered on alternate days as 40 mg of prednisone orally and 600 mg of methylprednisolone intravenously for a 12-day period. On the ninth day of therapy, a diuresis occurred. Serum creatinine levels which had risen to 3.2 mg/dl fell to 1.2 mg/dl and peritoneal dialysis was discontinued. She was subsequently maintained on cyclophosphamide 25 mg/day and prednisone 40 mg/day. Over the next nine months, renal function continued to improve and prednisone was tapered to 5 mg/day. She continues to be free of edema without salt restriction or diuretics, and she has no signs or symptoms of SLE. Current laboratory studies include: serum creatinine 0.5 mg/dl, 24-hour urinary protein excretion 3.0 grams, ANF titer 1:4, DNA-bc 5 percent, C3 93 mg/dl, C4 46 mg/dl.

Comment

The diagnosis of SLE is based on the characteristic renal histopathology, elevated titers of ANF and DNA-bc, and reduced C3 levels. Fever at the time of her initial presentation may have represented another manifestation of SLE.
Case 3

Mr. K.F., a 53-year-old white male, was admitted to a community hospital in April 1973 complaining of left-sided scrotal pain. A urinalysis at that time revealed 1+ protein, 10–14 RBC/HPF, 6–8 WBC/HPF. The diagnosis of acute epididymitis was made and antibiotic therapy was initiated with apparent resolution of symptoms. He was readmitted two weeks later with fatigue and periorbital edema. Repeat urinalysis showed 4+ protein, 25 RBC/HPF, 8 WBC/HPF. BUN was 20 mg/dl. On May 5, 1973, he was admitted to Yale-New Haven Hospital for a percutaneous renal biopsy. Aside from an admission blood pressure of 160/110 mm Hg, physical examination was normal. Laboratory studies included the following: serum creatinine 2.0 mg/dl, creatinine clearance 32 ml/min, serum albumin 1.8 gm/dl, urinalysis 2+ protein, 5–10 RBC/HPF, 5–10 WBC/HPF, 24-hour urinary protein excretion of 5.0 gm, ANF 1:128, LE preparation +, C3 30 mg/dl. Renal biopsy showed diffuse proliferative glomerulonephritis with focal necrosis and an accentuation of the glomerular lobules, with thickening of the capillary walls. Electronmicroscopy revealed extensive deposits in subendothelial, mesangial, and epimembranous positions. On immunofluorescent staining, there was a granular deposition of C3 in capillary walls.

Because of the renal biopsy findings and serological tests, the patient was begun on azathioprine 100 mg/day and prednisone 30 mg/day. Approximately one month later, he developed daily temperature elevations to 103°F and generalized pruritus. Azathioprine was discontinued with resolution of symptoms. When azathioprine was restarted, fever recurred. The cytotoxic agent was changed to cyclophosphamide, 75 mg/day. Over the next year, C3 levels normalized, but daily protein excretion of 3.0 grams persisted. Serum creatinine decreased to 1.4 mg/dl. DNA-bc was 11 percent when first assayed six months following presentation while the patient was on prednisone and cyclophosphamide therapy. In September 1974, he sustained an acute myocardial infarction and recovery was uncomplicated.

In December 1974, he underwent a second percutaneous renal biopsy which revealed a marked decrease in glomerular hypercellularity and persistent capillary wall thickening. Electronmicroscopy showed abundant intramembranous deposits and areas of glomerular basement membrane rarefaction. No subendothelial or mesangial deposits were seen. In August 1975, he was admitted for evaluation of fever. Laboratory studies showed the following: serum creatinine 1.5 mg/dl, urinary protein excretion less than 100 mg/day, DNA-bc 2 percent. Cyclophosphamide was discontinued, prednisone was increased to 20 mg/day, and his fever resolved. In November 1975, he was readmitted with dizziness. Neurological examination showed an abnormal mental status and right-sided pyramidal symptoms. Laboratory evaluation included: normal brain scan and electroencephalogram, ANF 1:8, DNA-bc 0 percent, C3 94 mg/dl. The etiology of the dizziness was not clearly defined and he was discharged without a change in medication. Aside from intermittent symptoms of dizziness, he remained well until August 1978 when he sustained a second acute myocardial infarction and died. An autopsy was not obtained.

Comment

The diagnosis of SLE was established by the positive LE preparation, low C3 levels, and characteristic renal histopathological findings. Although fever early in his course was clearly related to a drug-induced hypersensitivity reaction, the onset of fever six months prior to his death and subsequent neurological manifestations may have been related to SLE.
Case 4

M.M., a 23-year-old woman, sought medical attention in 1976 for dependent edema of three months' duration. Except for evidence of generalized edema, physical examination was normal. She denied malaise, fever, rash, or arthritis. Laboratory studies included: urinalysis 4+ protein with normal urinary sediment, urinary protein excretion 7.0 gm/dl, ANF 1:4, DNA-bc 27 percent, serum albumin 2.6 gm/dl, serum creatinine 0.8 mg/dl and creatinine clearance was 90 ml/min. A percutaneous renal biopsy was performed. By light microscopy, there was basement membrane thickening with focal reduplication. The mesangium was prominent due to focal hyperplasia. Electronmicroscopy revealed foot process fusion, epimembranous deposits, and moderate hyperplastic mesangium with focal sclerosis and mesangial deposits. Immunofluorescent staining showed granular depositions of IgG and C3 in capillary walls.

The patient was discharged on diuretic therapy alone. The following year she became pregnant. The delivery was complicated by hypertension and increased edema. Laboratory studies included: ANF 1:128, DNA-bc 13 percent. One month post partum, she was hospitalized because of fever, persistent hypertension, and signs of congestive heart failure. Physical examination revealed S3 and S4 gallops and bilateral dullness to percussion with absent breath sounds at the lung bases. Laboratory tests included: urinalysis 4+ protein, normal urinary sediment, urinary protein excretion 9.3 gm/day, serum creatinine 0.7 mg/dl, creatinine clearance 130 ml/min, ANF 1:128, LE preparation +, C3 51 mg/dl, C4 11 mg/dl. A 99 M Tc sodium pertechnetate first pass dynamic heart scan was performed and showed an ejection fraction of 36 percent (normal value > 55 percent). During the first week of hospitalization, the patient continued to have temperatures to 103.6°F. The patient was placed on prednisone, 90 mg/day, which resulted in rapid defervescence. She was discharged on prednisone, digitalis, and furosemide. She was readmitted several months later with fever and a right lower lobe infiltrate on chest roentgenogram. Laboratory studies showed: serum creatinine 0.9 mg/dl, ANF 1:64, DNA-bc 4 percent, C3 98 mg/dl, C4 33 mg/dl. She was treated with antibiotics, recovered rapidly, and was discharged on the sixth hospital day. Since that time her clinical condition has remained stable.

Comment

The elevated DNA-bc level and mesangial deposits, in association with epimembranous deposits, by renal biopsy, strongly suggested the possibility of SLE in 1976 when this patient was first evaluated for nephrotic syndrome. The diagnosis of SLE was established subsequently by the positive LE preparation. The fever and cardiomyopathy which occurred post partum probably represent systemic manifestations of SLE.

DISCUSSION

The four patients described in this report initially sought medical care because of generalized edema due to nephrotic syndrome. Except for patient 2, in whom fever occurred initially, there were no signs or symptoms suggestive of SLE at the time of initial presentation. During follow-up, however, each of the other three patients ultimately developed clinical findings frequently associated with the systemic manifestations of SLE: Patient 1 had a rash due to a leukocytoclastic angiitis, patient 3 developed a recurrent fever of unknown etiology, and patient 4 had fever and
myocardopathy. It is noteworthy that the hallmark findings of SLE, such as facial erythema, Raynaud's phenomena, alopecia, photosensitivity, and arthritis, did not occur in any of these four patients.

The diagnosis of SLE in these cases was established on the basis of serological studies and renal histopathological findings. In cases 1–3, the finding of a proliferative glomerulonephritis with electron-dense deposits in subendothelial, subepithelial, and mesangial loci was considered to be highly suggestive of lupus nephropathy [6,7]. The combination of clinical features and renal histopathology were not compatible with other entities in which subendothelial deposits are also found, such as post-infectious glomerulonephritis [8], mesangiocapillary glomerulonephritis [9], and Henoch-Schölein purpura [10]. The renal biopsy findings in case 4 were also suggestive of lupus nephropathy because of the association of mesangial and epimembranous electron-dense deposits. Mesangial deposits have not been described, characteristically, in idiopathic membranous nephropathy [6], but are commonly found in patients with membranous lupus nephropathy [7].

Serological studies were used to confirm the diagnosis of SLE. In each case, an antinuclear factor was found and either identified as an anti-DNA antibody or associated with a positive LE preparation. Patient 1 had an elevated ANF titer and reduced C3 on initial evaluation, and subsequently an elevated DNA-bc. Patient 2 had elevated ANF titer, increased DNA-bc, and reduced C3. Patient 3 had elevated ANF titer, positive LE preparation, and reduced C3. Patient 4 had elevated DNA-bc initially, and later a positive LE preparation, elevated ANF titer, and reduced C3. A DNA-bc level greater than 20 percent was considered highly specific for SLE. Adler and associates, working in our laboratory, previously reported that levels of DNA-bc did not exceed 20 percent in normal individuals or patients with rheumatoid arthritis or rheumatoid variants [5]. Moreover, except for the report by Pincus and associates [11], other groups have also reported that DNA-bc greater than 20 percent is highly discriminatory for SLE in untreated patients [12,13,14,15,16,17].

Several reports of large series of patients have stated that lupus nephropathy may represent the initial clinical manifestation of SLE in three to six percent of cases [2,3]. This type of clinical presentation of SLE, however, has not been documented since data were not included that either demonstrated the diagnosis of SLE or the type of renal disease at onset of illness. Lupus nephropathy as the sole presenting manifestation of SLE was also suggested by two recent reports. Libit and associates described three children, ages 10 to 14 years, with epimembranous nephropathy who developed clinical and serological evidence of SLE which included the appearance of rash and multisystem disease one and a half to three and a half years after the first evidence of renal disease [18]. In contrast to the cases in the present report, serological studies for SLE were negative at the time of the initial evaluation. Two similar cases were reported by Kallen and associates [19], in which the nephrotic syndrome, due to typical epimembranous nephropathy, developed in the absence of serological evidence of SLE. One and three years later, respectively, both children developed systemic manifestations and serological evidence of SLE. Re-evaluation, by renal biopsy, demonstrated a proliferative glomerulonephritis with electron-dense deposits in subendothelial and mesangial loci, in addition to epimembranous deposits in both cases. Although there was no direct evidence that the initial glomerulonephropathy in these previously reported cases was caused by SLE, the authors suggested a causal relationship since both membranous nephropathy and SLE, as separate disease entities, are relatively uncommon in children.

The present report documents the occurrence of lupus nephropathy as the sole
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Initial manifestation of SLE. It becomes evident, therefore, that under certain circumstances, the diagnostic criteria established by the ARA may not be sufficiently inclusive for all cases of SLE. These findings emphasize the importance of considering the possibility of SLE even in patients with apparent primary renal disease. Observations made in the present series of patients suggest that important clues to the eventual diagnosis of SLE may be provided by careful assessment of the pattern of glomerular ultrastructural changes and that confirming evidence can be obtained by appropriate serological studies.

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