CASE REPORTS

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Renal Tubular Abnormalities in a Patient with Lupus Nephritis

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THE GLOMERULAR LESIONS present in patients with systemic lupus erythematosus with nephritis have been well described. Electron-dense deposits, believed to represent complement-fixing immune complexes, occur in a granular pattern along the glomerular basement membrane and in a subendothelial position in glomerular capillaries. These deposits are assumed to be causally related to the decreased creatinine clearance that develops in lupus nephritis. The tubular defects that occur in patients with lupus renal disease, both anatomic and physiologic, have received relatively little attention in the literature. A case is reported of a patient with acute systemic lupus erythematosus in whom findings from renal biopsy studies showed deposits of electron-dense material along the peritubular basement membrane and in a subendothelial distribution in peritubular capillaries. In this patient, metabolic abnormalities were also present suggestive of renal tubular dysfunction that may have been related to these deposits.

Report of a Case

A 57-year-old black woman was admitted to San Francisco General Hospital in July 1974 because of a three-month history of anorexia, malaise, recurrent fever, night sweats, polyarthralgias, pedal edema, dull substernal chest pain and a 15 pound weight loss. Except for an episode of pneumonia in 1940, a hysterectomy-salpingo-oophorectomy in 1965, and allergies to penicillin and sulfa drugs, the medical history was unremarkable.

On admission, blood pressure was 120/76 mm of mercury and other vital signs were within normal limits. The patient was cachectic but in no distress. On examination of the eyes, bilateral early cataract formation, fundic arteriolar narrowing and a fundic drusen in the right eye were noted. Many small nontender cervical nodes were found bilaterally. Chest excursion was decreased, but no rales or rhonchi were heard. Heart sounds were normal. The liver was palpable at the right costal margin. There was no tenderness at the costovertebral angles and no tenderness, erythema or effusion at the joints.

Initial laboratory data were as follows: hematocrit reading, 37.2 percent; leukocyte count, 5,000 per cu mm with a normal differential, and platelet count 310,000 per cu mm. Urinalysis showed 3+ protein, five to ten red blood cells per high power field, five to ten leukocytes per high power field and occasional granular and cellular casts. The nonfasting blood glucose level was 167 mg per 100 ml, creatinine 1.1 mg per 100 ml and blood urea nitrogen 28 mg per 100 ml, with a creatinine clearance of 28 ml per minute (it ranged between 28 and 54 ml per minute while the patient was in hospital). The albumin to globulin ratio was 3.1:4.4, and the erythrocyte sedimentation rate was 56 mm per hour. Values for serum electrolytes, hepatic enzymes, uric acid, prothrombin time, partial thromboplastin time, fibrinogen screen and fibrin-split products were all within normal limits. On roentgenograms of the chest, biapical pleural thickening, an infiltrate in the right upper lobe and a right pleural effusion were seen. No abnormalities were noted on an electrocardiogram.

Reactions on skin tests for purified protein derivative (PPD) and mumps were initially negative, although on a second PPD test the reaction was positive to 7 mm. Thoracentesis yielded clear exudative fluid with a cell count of 122 leukocytes

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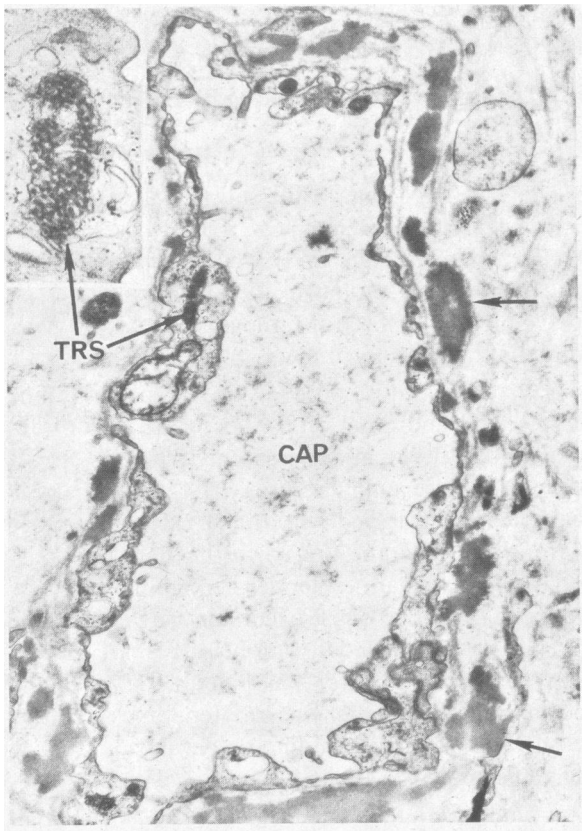

Figure 1.—Electron micrograph showing tubuloreticular structures (TRS) within the endothelial cells of a peritubular capillary (CAP). Electron-dense material is also present within the basement membrane (arrows). (Reduced from original magnification × 17,500, insert magnification × 47,900.)

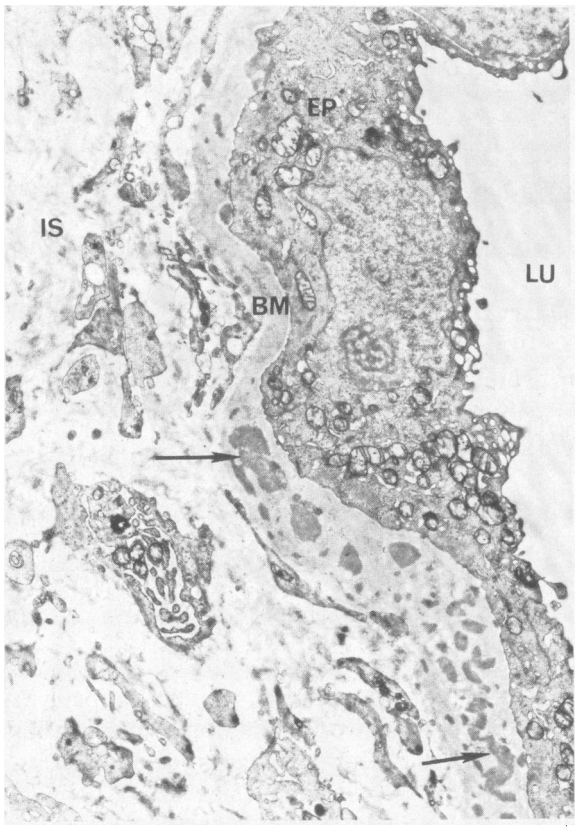

Figure 2.—Electron micrograph of a renal tubule showing the tubular lumen (LU), tubular epithelium (EP), and interstitium (IS). Electron-dense material (arrows) is seen within the basement membrane (BM). (Reduced from original magnification × 9,000.)

per cu mm (64 percent mononuclear and 36 percent polynuclear cells) and 49 red blood cells per cu mm; sputum and pleural fluid smears and cultures for acid-fast bacilli were negative. Treatment with isoniazid, 300 mg per day given orally, and ethambutol, 500 mg per day given orally, was begun.

On day 4, the temperature became elevated, and a vasculitic lesion on the right conjunctiva, muscle pain in the shoulder and pelvic girdle, and multiple arthralgias and arthritis in the right knee developed. Findings on analysis of synovial fluid included 1,130 leukocytes per cu mm (60 percent mononuclear and 40 percent polynuclear cells), 1,130 red blood cells per cu mm and a C′3 complement of 10 with a serum value of 40 mg per 100 ml. On serologic studies, findings included a positive lupus erythematosus preparation, a positive antinuclear antibody in an outline pattern (titer 1:64), a diffuse elevation of immunoglobulin G (IgG) and immunoglobulin A (IgA) fractions, and an anti-double stranded deoxyribonucleic acid (DNA) antibody titer of 517 counts per minute (normal = 150). A biopsy study of visually uninvolved skin showed immunoglobulin and complement deposition in dermal vessels.

The urinary sediment continued to reflect active glomerulonephritis and creatinine clearance remained stable at 25 ml per minute. A 24-hour urine collection yielded 1.1 grams of protein. On light microscopy of a renal biopsy specimen, focal local glomerulonephritis with endothelial and mesangial cell proliferation was noted. In some areas focal fibrosis of the involved segment of the glomerular tuft was also present. There was rare glomerular hyalinization. The tubular cells were unremarkable on light microscopy. Immunofluorescence studies showed deposits of IgG and C1q along glomerular and tubular basement membranes and in some glomerular and peritubular vessels. A few deposits of IgA and immunoglobulin M (IgM) were found in some glomerular

basement membranes and a few deposits of fibrin were present in glomerular and peritubular capillaries. Electron microscopy showed tubuloreticular structures typical of lupus erythematosus within endothelial cells in both glomerular and peritubular capillaries (Figure 1). Electron-dense material was present in subendothelial and subepithelial deposits along both glomerular and peritubular basement membranes (Figure 2). Therapy with prednisone, 60 mg per day, was begun and resulted in prompt improvement in systemic and joint symptoms although renal disease persisted.

Because a culture of urine obtained on admission showed significant numbers of Proteus mirabilis, kanamycin, 500 mg, was administered intramuscularly twice a day for seven doses. On day 14, hyperkalemia developed (6 mEq per liter) and persisted through discharge on day 54 ranging between 4.3 and 6.4 mEq per liter during sodium polystyrene sulfonate (Kayexalate®) therapy. Hyperchloremia ranging from 115 to 124 mEq per liter also developed and persisted well after therapy was begun and the levels of serum sodium ranged between 136 and 145 and bicarbonate ranged between 16 and 25 mEq per liter, respectively. These occurred without evidence of extra renal loss. Findings on urinalysis included a pH range of from 5.0 to 7.0 and intermittent glycosuria associated with blood glucose concentrations as low as 74 mg per 100 ml. Urinary 17-hydroxycorticosteroids and aldosterone levels were low (2.2 mg per 24 hours and 1.0 μg per 24 hours, respectively), but the plasma cortisol level showed a normal response to stimulation by adrenocorticotropin (from 11.0 to 32.0 micrograms per 100 ml). While the patient was on a regulated normal sodium intake, renin concentrations were low: 0.92 nanogram (ng) per ml in three hours supine (normal mean 5.5 ± 0.9 SEM) and 1.5 ng per ml in three hours erect (normal mean 13.9 ± 3.2 SEM).

Discussion

The deposition of immunoglobulin and complement along renal tubular basement membrane has been described previously. Two patterns of deposition have been shown in both human beings with disease and animal models. Steblay and Rudofsky[1] described the formation of antitubular basement membrane antibodies in guinea pigs after multiple injections of rabbit kidney basement membrane incorporated with complete Freund's adjuvant. These antibodies led to a linear pattern of proximal tubular basement membrane staining with fluorescein-labeled anti-IgG and β1C. Such linear staining along tubular basement membrane has been described for persons with Goodpasture's syndrome,[2] methicillin-associated interstitial nephritis,[3] progressive poststreptococcal glomerulonephritis[4] and human renal allografts.[5,6]

The second, or granular, pattern of immunoglobulin and complement deposition has also been observed in both human and animal tissues. Klassen and co-workers induced granular deposition of IgG along tubular basement membrane in rabbits after repeated renal allografts[7] and after repeated immunization with homologous renal tissue in complete Freund's adjuvant.[8] Klassen's group also induced granular tubular basement membrane deposition in rats immunized with homologous kidney in Freund's adjuvant.[9] They did not find circulating or fixed renal tissue antibodies that would react with normal tubular basement membrane, but they did find circulating antibodies against antigens present within the cytoplasm of proximal tubular cells. They postulated that antigen-antibody complexes diffused out of the proximal tubular cells and were deposited along the peritubular basement membrane. Granular deposits of IgG and β1C along the tubular basement membrane of proximal convoluted tubules have been observed in persons with systemic lupus erythematosus, rapidly progressive glomerulonephritis, lipoid nephrosis, and idiopathic interstitial and tubular disease.[10] Almost half the patients who have had this tubular defect have had systemic lupus erythematosus.

There have been no systematic studies correlating physiologic abnormalities with tubular deposition of immunoglobulin and complement. However, many authors have observed clinical phenomena suggestive of tubular dysfunction associated with such deposits. Klassen and associates[8] and Steblay and Rudofsky[1] documented glycosuria in animal models. Glycosuria,[2] aminoaciduria,[3] proteinuria,[2,9] hematuria[2,3,9] and a possible renal tubular acidification defect[3] have all been observed in human beings with tubular basement membrane deposition of immunoglobulin and complement. However, the patient described by Border and co-workers,[3] who was unable to acidify urine adequately even after the adminis-

tration of 7 grams of ammonium chloride, was studied after having received multiple doses of penicillin and aminoglycoside antibiotic drugs and when the serum creatinine level was 3.9 mg per 100 ml. The acidification defect might, therefore, have been due to interstitial nephritis and not tubular IgG or β1C deposition.

In our patient, electron microscopy showed pronounced granular deposition of electron-dense material along the tubular basement membrane and in a subendothelial pattern along the peritubular capillaries. Immunofluorescence proved this material was IgG, complement and fibrinogen. In our patient, the similarity of the subendothelial deposits in peritubular capillaries to those seen in the glomeruli was dramatic. Such similarity has not been emphasized previously. Tubular virus-like particles were also identified in both tubular epithelial cells and the glomeruli. Hyperchloremia, low serum bicarbonate level with a normal urinary pH and intermittent glycosuria present in our patient suggest renal tubular dysfunction. Because the juxtaglomerular apparatus was in the area involved by the tubular deposits, we raised the question of possible dysfunction of the juxtaglomerular apparatus. In our patient, there were two low 24-hour urinary aldosterone levels, resistant hyperkalemia and normal blood pressure despite the lupus nephritis. We believe she may have had transient hyporeninemic hypoaldosteronism indicative of juxtaglomerular dysfunction. Unfortunately, steroids and aminoglycosides were administered before renal tubular function and juxtaglomerular apparatus function could be evaluated adequately, and the tubular dysfunction had either responded to steroid therapy or was masked by the effects of the aminoglycosides. However, the occurrence of tubular dysfunction in patients with lupus erythematosus with peritubular deposits is likely and merits further study.

Summary

A patient with systemic lupus erythematosus and nephritis is reported in whom deposits of electron-dense material were present in glomeruli, along the peritubular basement membrane and in peritubular capillaries of a renal biopsy specimen. Hyperchloremia, a low serum bicarbonate level with a normal pH and intermittent glycosuria were noted. Transient hyporeninemic hypoaldosteronism also appeared to be present. It is likely that tubular dysfunction occurs in patients with lupus erythematosus and peritubular deposits and merits further study.

Addendum

Since our paper was submitted, peritubular deposition of immune complex material in a large group of patients has been reported (Lehman DH, Wilson CB, Dixon FJ: Extraglomerular immunoglobulin deposits in human nephritis. Am J Med 58:765-786, 1975).

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