

EDITORIAL COMMITTEE

Tomas Berl, **Editor**  
Denver, CO

William Henrich  
Dallas, TX

Mark Paller  
Minneapolis, MN

Fred Silva  
Oklahoma City, OK

**THE NEPHROLOGY TRAINING PROGRAM—UNIVERSITY OF MIAMI SCHOOL OF MEDICINE**

The Renal Division of the University of Miami was developed in the mid-1960s by Drs. Gorman Hills and Williams Hulet. It is currently a joint program between the University of Miami/Jackson Memorial Hospital and the Miami Veterans Affairs Medical Center. More than 120 fellows have graduated from this combined clinical and research fellowship program since 1968. Twelve full-time and four part-time faculty members supervise the clinical and research activities at both major hospitals as well as at the University of Miami Hospital and Clinics; all institutions are located within one city block. The division is associated with an active organ transplant program, with a nephrologist coordinating the medical aspects of renal transplantation. Kidney transplants average 100 per year. Other transplants include liver, heart, and combined kidney-pancreas.

The training program provides a 2- or 3-yr clinical and research experience for physicians who have completed their training in internal medicine. Trainees are exposed to a wide range of acute and chronic nephrologic illnesses, extending from the exotic and rare to the most common nephropathies. Training in water, electrolyte, and acid-base disturbances and hypertension is emphasized. About 150 new ESRD patients are seen, and 2,500 consultations, 15,000 dialyses, and 100 renal biopsies are performed each year. Two large dialysis units provide all modalities of dialytic therapy. Research is an integral part of the training process with areas of interest including AIDS and the kidney, the pathophysiology and prevention of progressive renal insufficiency, hepatitis C, drug nephrotoxicity, and renovascular as well as other types of hypertension in various patient populations. These investigations combine studies in patients and whole animals as well as investigation in isolated organs and cultured cells using modern techniques of immunology and molecular biology.

**Secondary Syphilis and the Nephrotic Syndrome<sup>1,2</sup>**

Wishburne Hunte, Fadi Al-Ghraoui, and Robert J. Cohen

W. Hunte, St. Thomas, U.S. Virgin Islands  
F. Al-Ghraoui, R.J. Cohen, Cleveland Clinic Foundation,  
Ft. Lauderdale, FL  
(J. Am. Soc. Nephrol.

ings, compatible with syphilitic nephropathy, are offered to remind internists (nephrologists) that sexually transmitted diseases, like syphilis or hepatitis B, in addition to human immunodeficiency virus, can have important renal manifestations.

*Key Words: Sexual transmission, renal disease*

**ABSTRACT**

A case of nephrotic syndrome in a 21-yr-old black man with secondary syphilis and diabetes mellitus is described. A renal biopsy was performed, which showed membranous glomerulopathy stage I associated with mesangial hyperplasia and mesangial deposits. The clinical course and the histologic find-

Although syphilis has become a rare disease for a large part of the population in the United States, it remains a threatening hazard particularly among blacks and Hispanics (1). Over the last decade, the incidence of primary and secondary syphilis increased 34% to reach its highest levels since 1949 (1). The increase in the incidence of syphilis in the 1980s is likely to lead to an increase in syphilitic renal disease, an entity known since the 18th century (2). With the human immunodeficiency virus (HIV) epidemic at the forefront, we now recognize that the nephrotic syndrome can be the first manifestation of HIV infection. Similarly, the recent in-

<sup>1</sup> Received October 2, 1991. Accepted July 13, 1992.

<sup>2</sup> Correspondence to Dr. J. Bourgoignie, Division of Nephrology (R-126), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.

1046-6673/0307-1351\$03.00/0  
Journal of the American Society of Nephrology  
Copyright © 1993 by the American Society of Nephrology

crement in syphilis incidence may foreshadow an incoming increase in all forms of syphilitic renal involvement from mild transient proteinuria (3) to frank nephrosis associated with minimal change disease (4), membranous glomerulopathy (5), or even diffuse proliferative glomerulonephritis (6) or rapidly progressive crescentic glomerulonephritis (7).

### CASE REPORT

A 21-yr-old black man was admitted to Jackson Memorial Medical Center complaining of swelling of the face, hands, and feet of 1-wk duration, weight gain of at least 15 lbs, skin rash, polyuria, and polydipsia. He first noticed myalgias, headaches, and a sore throat followed by nonpruritic eruption over the forearms, trunk, and feet. There was a negative history of previous renal disease, edema, insect bite, allergy, arthralgias, penile lesion, dysuria, hematuria, or fever. He had insulin-dependent diabetes mellitus for 9 yr and labile hypertension for 3 yr. The only current medication was insulin. He denied a history of alcohol abuse or illicit drug use. He had many heterosexual, but no homosexual, contacts.

Physical examination revealed a moderately obese, edematous patient. Temperature was 97.4°F, pulse was 80 and regular, blood pressure varied between 136/90 and 160/100. Weight was 152 lbs. The fundoscopic examination was normal. Mucous membranes of the mouth and pharynx were normal. There was marked periorbital edema and puffiness in the malar area symmetrically. Multiple, fine, scaly, brown papules and plaques involving the neck, upper back, anterior cubital fossa, and dorsum of the feet bilaterally were seen. There was no involvement of

the mucosa of the mouth, genital region, palms, or soles. The lesions began on the arms and neck simultaneously and had no associated pain, change in color or size, or bleeding (Figure 1). Examination of the lungs, heart, abdomen, and genitalia was normal. Several painless 1- to 2-cm lymph nodes were palpable in the inguinal but not cervical or axillary areas. There was 3+/4+ pretibial, pedal, and hand-pitting edema. The urine was yellow in color with heavy proteinuria and glycosuria without acetonuria. Spun urine sediment showed one to five white blood cells, one to five red blood cells, and numerous hyaline casts per high power field. No red blood cell casts were observed. The erythrocyte sedimentation rate was 110 mm/h. The hematocrit was 36%, and the white blood cell count was 9,900/mm<sup>3</sup> with a normal differential. Blood glucose was 442, BUN was 22, and serum creatinine was 1.2 mg/dL. Serum concentrations of electrolytes, calcium, phosphorus, magnesium, transaminases, alkaline phosphatase, bilirubin, amylase, and lipase were normal. Total serum protein was initially 8.6 g/dL with an albumin of 3.0 g/dL. ASO and ANA were nonreactive, as was an ELISA for HIV antibodies. Complement levels were normal with C3 at 145 and C4 at 15. A 24-h urine collection revealed 4.3 g of protein and a creatinine clearance of 70 mL/min. The chest roentgenogram showed small, bilateral pleural effusions.

The patient was initially treated with insulin and iv fluids and was then placed on a sodium-restricted diet, enalapril, and furosemide. Serum protein electrophoresis confirmed the hypoalbuminemia and the absence of an M component. Serum cholesterol was 245 and triglycerides were 340 mg/dL. A repeat 24-h urine collection contained 6.4 g of protein. Renal



Figure 1. Scaly brown papules and plaques of the forearm.

ultrasonography showed modestly echogenic and normally sized (11 and 12 cm) kidneys. A KOH examination of skin lesions did not reveal any hyphae or spores. A 3-mm punch skin biopsy was obtained and showed mixed granuloma-like infiltration of lymphocytes and plasmacytes at the dermal-epidermal junction with swelling and proliferation of the endothelial cells and a perivascular infiltrate composed of lymphoid and plasma cells consistent with secondary syphilis. These findings prompted serologic testing. The rapid plasma reagin was markedly reactive and quantitated at 1:1,024, and the fluorescent treponemal antibody-absorption test was also reactive at 4+. Therapy with benzathine penicillin (2.4 Units im weekly for 3 wk) was initiated, and a renal biopsy was performed.

By light microscopy, there were approximately 16 glomeruli. Five were obsolescent, and the remaining showed a diffuse and global increase in mesangial matrix and cells. There was also diffuse thickening of the glomerular capillary basement membrane. Interstitial edema, fibrosis, and tubular atrophy were sparse. Arterioles were normal. Electron microscopy revealed subepithelial deposits associated with normal to minimally thickened lamina densa of the glo-

merular basement membrane (Figure 2). Immunofluorescence showed the deposits to consist of immunoglobulin G (IgG)<sup>3+</sup>, IgA<sup>2+</sup>, IgM<sup>2+</sup>, and C3<sup>2+</sup>. The pattern was granular, diffuse, and global, and when compared with electron microscopy findings, was shown to involve the subepithelial space and capillary loops. A diagnosis of membranous glomerulopathy stage 1 was made on the basis of the finding on electron microscopy.

Shortly before hospital discharge, his weight decreased to 140 lbs, his serum albumin was 3.2 g/dL, and his urine contained 2.7 g of protein/24 h. Discharge creatinine clearance was 92 mL/min.

The patient was seen in the outpatient clinic 16 wk after completing antibiotic therapy. He was asymptomatic. Serum albumin was 4.1 g/dL, and the urine had 212 mg of protein/24 h. Creatinine clearance was 97 mL/min.

Resolution of the patient's nephrotic syndrome supports syphilis as the cause of the disease.

## DISCUSSION

The association between syphilis and renal disease has been known for more than 100 yr (2). Although



Figure 2. Electron microscopy showing electron-dense subepithelial deposits.

renal involvement in the modern era is infrequent, proteinuria is probably still the most common manifestation. The incidence of albuminuria in patients with syphilis reported in previous studies varies from 0.3% among 4,000 patients with secondary syphilis (8) to 8% in the patients with secondary syphilis studied by Hermann and Marr (9) and 7% in those with tertiary syphilis. The clinical picture can vary from mild transient albuminuria or nephrotic syndrome to acute nephritic syndrome with hypertension and acute renal failure. Not infrequently, spontaneous diuresis and resolution of proteinuria occur without therapy (3; see reference 17). Complete resolution of renal manifestations after antisyphilitic therapy is the rule in patients with syphilitic nephrotic syndrome or nephritis. Beside albuminuria, reports of renal involvement in syphilis describe membranous glomerulonephritis (5), mesangial and endothelial cell proliferative glomerulonephritis (6), rapidly progressive crescentic glomerulonephritis (7), and minimal-change nephrotic syndrome associated with acute renal failure (4), presumably secondary to renal interstitial edema (10). Finally, renal gumma and amyloid are also reported with late syphilis (2).

Pathologically, most reports of syphilitic nephropathy in infants with congenital syphilis demonstrate membranous glomerulonephritis with subepithelial deposits and occasional intramembranous deposits (5,11-15). All had IgG as the predominant immunoglobulin accompanied by C3. Less often, IgM and IgA were identified. Much less commonly, the glomerular

pathology may be one of mesangial or endocapillary and extracapillary proliferation (12,16). The clinical and pathologic manifestations of syphilitic renal disease are listed in Tables 1 and 2.

In adults with acquired syphilis, membranous glomerulonephritis or diffuse endocapillary glomerulonephritis, sometimes with crescents, is usually found (3,6,7,13,17-19). An immune complex pathogenesis was first suggested by the detection of granular deposits and complement along the glomerular basement membrane by immunofluorescence and electron microscopy (3,6;7,11-15,17-19). The demonstration of hypocomplementemia in patients with congenital syphilis and glomerulonephritis supported such a pathogenesis (5,14,15). Furthermore, eluates from deposits were shown to contain antibody specific for *Treponema pallidum* antigen (5,7,19).

Follow-up renal biopsies after therapy have been performed in few patients (5,7,14,16,17). In patients who recovered clinically, the biopsies showed resolution of mesangial hyperplasia, glomerular basement membrane spikes and deposits, and foot process effacement. In patients with persistent renal abnormalities, glomerular hyalinization or mesangial hypercellularity was seen.

Thus, with the worldwide resurgence of sexually transmitted diseases, our case illustrates that clinicians must be vigilant of the diagnosis of syphilitic nephropathy. Recent epidemiologic data show an important increase in sexually transmitted diseases (1). Syphilis should be considered in the differential diagnosis of nephrotic syndrome.

**TABLE 1. Clinical manifestation of syphilitic renal disease**

Proteinuria (Most Common)
Nephrotic Syndrome
Acute Nephritic Syndrome
Rapidly Progressive Glomerulonephritis
Nephrotic Syndrome With Acute Renal Failure
Chronic Progressive Renal Failure Secondary to Renal Gumma

**TABLE 2. Pathologic findings in syphilitic renal disease**

Immune-Complex Glomerulonephritis
Membranous nephropathy (most common)
Mesangial proliferative glomerulonephritis
Postinfectious endocapillary proliferative glomerulonephritis
Rapidly progressive glomerulonephritis with crescents
Minimal change disease with acute renal failure secondary to interstitial edema
Renal gumma
Amyloid renal disease

## ACKNOWLEDGMENTS

The authors are indebted to Dr. Jacques J. Bourgoignie for his help and guidance in writing the manuscript.

## REFERENCES

1. Rolfs R, Nakashima A: Epidemiology of primary and secondary syphilis in the United States, 1981 through 1989. *JAMA* 1990; 264:1432-1437.
2. Thompson L: Syphilis of the kidney. *JAMA* 1920;75:17-20.
3. Braunstein GD, Lewis EJ, Galvanek EG, Hamilton A, Belle WR: The nephrotic syndrome associated with secondary syphilis: An immune deposit disease. *Am J Med* 1970;48:643-648.
4. Krane NK, Espenan P, Walker PD, Bergman SM, Wallin JD: Renal disease and syphilis: A report of nephrotic syndrome with minimal change disease. *Am J Kidney Dis* 1987;9: 176-179.
5. Losito A, Bucciarelli E, Massi-Benedetti F, Lato M: Membranous glomerulonephritis in congenital syphilis. *Clin Nephrol* 1979;12:32-37.
6. Bhorade MD, Carag HB, Lee HJ, Potter EV,

- Dunea G:** Nephropathy of secondary syphilis. A clinical and pathological spectrum. *JAMA* 1971; 216:1159-1166.
7. **Walker P, Deeves E, Sahba G, Wallin J, O'Neill W:** Rapidly progressive glomerulonephritis in a patient with syphilis. Identification of antitreponemal antibody and treponemal antigen in renal tissue. *Am J Med* 1984;76:1106-1112.
  8. **Thomas EW, Schur M:** Clinical nephropathies in early syphilis. *Arch Intern Med* 1946;78: 679-686.
  9. **Hermann G, Marr WL:** Clinical syphilitic nephropathies. A study of new cases and survey of reported cases. *Am J Syph Neurol* 1935;19: 1-29.
  10. **Lowenstein J, Schacht RG, Baldwin DS:** Renal failure in minimal change nephrotic syndrome. *Am J Med* 1981;70:227-233.
  11. **Kaplan BS, Wigglesworth F, Drummond KN:** The glomerulopathy of congenital syphilis: An immune deposit disease. *J Pediatr* 1972;81: 1154-1156.
  12. **Kaschula OC, Uys CJ, Kuiften RH, Dole JRP, Wiggelinkhuizen J:** Nephrotic syndrome of congenital syphilis. Biopsy studies in four cases. *Arch Pathol* 1974;97:289-296.
  13. **O'Regan S, Fong JSC, de Chadaverian JP, Rishikof JR, Drummond KN:** Treponemal antigens in congenital and acquired syphilitic nephritis. Demonstration by immunofluorescence studies. *Ann Intern Med* 1976;85:325-327.
  14. **Yuceogula AM, Sagel I, Tresser G, Wasserman E, Longe K:** The glomerulopathy of congenital syphilis. A curable immune deposit disease. *JAMA* 1974;229:1085-1089.
  15. **Sanchez-Bayle M, Ecija JL, Estepa R, Combrenero MJ, Martinez MA:** Incidence of glomerulonephritis in congenital syphilis. *Clin Nephrol* 1983;20:27-31.
  16. **Wiggelinkhuizen J, Kaschula OC, Uys CJ, Kuiften RH, Dale J:** Congenital syphilis and glomerulonephritis with evidence for immune pathogenesis. *Arch Dis Child* 1973;48:375-381.
  17. **Falls WF, Ford KL, Ashworth CT:** The nephrotic syndrome in secondary syphilis. Report of a case with renal biopsy findings. *Ann Intern Med* 1965;6:1047-1057.
  18. **Gamble CN, Reardon JB:** Immunopathogenesis of syphilitic glomerulonephritis. Elution of antitreponemal antibody from glomerular immune-complex deposits. *N Engl J Med* 1975;292: 449-454.
  19. **Tourville DR, Byrd IH, Kim DU, Zald D, Lee I:** Treponemal antigen in immunopathogenesis of syphilitic glomerulonephritis. *Am J Pathol* 1976; 82:479-487.