The Nephrology Training Program at New England Medical Center/Tufts University School of Medicine was founded by Dr. William B. Schwartz in 1950. Between 1971 and 1982, the training program was headed by Dr. Jordan J. Cohen, who was succeeded by Dr. Nicolaos E. Madias, the current director. Over this period of time, the program has prepared approximately 130 physicians for careers in clinical nephrology and in basic or clinical research. Currently, the training program includes 15 faculty and 9 trainees.

Several training tracks are offered to accommodate variable career aspirations. Trainees can pursue 1 or 2 yr of intensive clinical training depending on career emphasis. Additional training can include 1 or 2 yr of clinical research or at least 2 yr of basic research.

Clinical training encompasses rigorous exposure to all aspects of inpatient practice, including general nephrology, renal complications of pregnancy, transplantation, and the techniques of hemodialysis, peritoneal dialysis, and hemofiltration. In addition, major emphasis is given to outpatient practice, including consultative nephrology, hypertension, and primary management of patients receiving chronic dialysis or after transplantation.

A broad range of research programs are available reflecting the diverse interests of the faculty. Ongoing basic research projects include the transcriptional regulation of the human Na⁺/H⁺ exchanger; the cellular and molecular biology of polycystic kidney disease; the regulation of Na⁺, K⁺ ATPase in uremia; the role of cytokines in vascular pathophysiology; and the molecular genetics of murine lupus. The Nephrology Clinical Research Center, a facility that has centralized the clinical-research resources of the division, provides support for all clinical research. Ongoing projects include participation in national collaborative trials on the progression of renal disease and the morbidity and mortality in hemodialysis; the role of cytokines in the biocompatibility of dialysis membranes and dialysis-related symptoms; interventional trials in acute renal failure; hepatitis C infection in organ transplantation; and the assessment of health status, comorbidity, and outcomes in hemodialysis.

A number of teaching conferences support the educational mission of the program including a clinical conference, journal club, research conference, biopsy conference, and the Nephrology Forum, a conference designed to relate the principles of basic science to clinical problems in nephrology, the proceedings of which are published monthly in Kidney International. Trainees have considerable opportunities to exercise their teaching skills. In addition to sharing with the faculty the responsibility of teaching fourth-year medical students during their renal elective, trainees participate in teaching the Renal Pathophysiology Course to the second-year medical class.

Rapidly Progressive Glomerulonephritis After Immunotherapy for Cancer

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ABSTRACT
Cytokines have been used in experimental and standard protocols for immune enhancement for cancer. The combination of interleukin-2 and interferon-alpha 2β has been used in experimental protocols for met
A 66-yr-old man was evaluated for weight loss, fatigue, anemia, pulmonary nodules, and an enlarging pancreatic mass. Twenty-one years earlier, he had a right nephrectomy for encapsulated renal cell carcinoma. A biopsy of the current pancreatic lesion revealed clear cell carcinoma. Written informed consent was obtained for participation in an investigative protocol of outpatient subcutaneous IL-2 in combination with IFN-α therapies. In this report, we provide the first description of a patient who developed Pauci-immune crescentic glomerulonephritis after treatment with IL-2 and IFN-α 2β for metastatic renal cell carcinoma.

CASE REPORT

Before immunotherapy, a renal evaluation included a serum creatinine of 106.1 μmol/L (1.2 mg/dL), a BUN of 7.1 mmol/L (20 mg/dL), a urinalysis showing a specific gravity of 1.019 (pH 5.5), a dipstick negative for albumin, and a sediment examination revealing no casts. A serum albumin of 22 g/L (2.2 g/dL) was attributed to poor nutritional status. Liver function tests were within normal limits. He had no prior history of proteinuria, and there was no family history of renal disease.

A 2-wk hiatus, a second, identical, 4-wk treatment cycle was given. Renal function was monitored by serum creatinine and urinalysis throughout and after the course of therapy (Figure 1).

On Day 82 after the initiation of therapy (12 days after the last cycle was completed), the serum creatinine was 114.9 μmol/L (1.3 mg/dL). The patient had computed tomography of the chest and abdomen with iv contrast. The pancreatic mass and pulmonary nodules were unchanged, and no further immunotherapy was given.

On Day 103, he was admitted to the hospital with renal failure. Medications included acetaminophen and triazolam. A physical examination revealed hypertension and fluid overload. There were no signs or symptoms of extrarenal vasculitis. A chest radiograph revealed pulmonary vascular congestion, but no focal disease process. The BUN was 16 mmol/L (45 mg/dL), creatinine was 397.8 μmol/L (4.5 mg/dL), and albumin was 19 g/L. A urinalysis showed a specific gravity of 1.012 (pH 5.0), a dipstick with 3+ blood and 3+ protein, and a sediment examination revealing numerous red blood cells, red blood cell casts, and occasional granular casts. The urine culture showed no growth. A 24-h urine collection had 1.42 g of protein, and the creatinine clearance was 10 mL/min. A renal ultrasound showed a 12.6-cm, solitary left kidney with no hydronephrosis. The following serologies were obtained: C3, 1.35 g/L (0.87 to 2.20); C4, 0.50 g/L (0.15 to 0.54); total hemolytic complement (CH50), 299 U (150 to 250), antinuclear antibody titer, 1:140; perinuclear and cytoplasmic antineutrophil cytoplasmic antibody (ANCA) titers by indirect immunofluorescence, 1:8; antistreptolysin O, <200 IU; and the antiglomerular basement membrane antibody titer was negative. On the fourth hospital day, the BUN rose to 19.6 mmol/L (55 mg/dL) and the creatinine rose to 477.4 μmol/L (5.4 mg/dL). Prednisone at 60 mg po each day was initiated. At discharge on hospital day 6, the BUN was 27.5 mmol/L and the creatinine was 477.4 μmol/L.
Seven days later, his BUN was 27.5 mmol/L, creatinine was 274.0 µmol/L (3.1 mg/dL), and albumin was 26 g/L. The urinary sediment revealed 20 to 30 red blood cells per high-power field and no casts. A 24-h urine collection had 2.21 g of protein, and the creatinine clearance was 23 mL/min. His serum creatinine remained stable for approximately 6 wk. Prednisone was slowly tapered to 40 mg/day. A subsequent evaluation of BUN and creatinine were 25.3 mmol/L and 327.1 µmol/L, respectively, and the sediment showed continued hematuria, but no casts.

An open renal biopsy was performed. On light microscopy, 7 of 15 glomeruli revealed cellular and fibrocellular crescents, mostly segmental (Figure 2). There were areas of interstitial fibrosis and tubular atrophy. Small, patchy interstitial infiltrates composed of plasma cells, lymphocytes, and occasional neutrophils were noted (Figure 3). Immunofluorescence was not performed; however, neither immunocytochemical nor electron microscopic analysis revealed evidence of immune deposits. Paraffin sections were stained by immunoperoxidase for immunoglobulin (Ig)G, IgM, and IgA and were negative. Electron microscopy examining four glomeruli (approximately 30 sections) showed only ill-formed densities in the glomerular mesangia, but no discrete deposits (Figure 4). The sections were examined for ultrastructural evidence of glomerular endothelial myxovirus-like microtubular inclusions, and none were present. The biopsy indicated a crescentic glomerulonephritis without immune deposits.

The patient's serum creatinine continued to rise, and glucocorticoid therapy was discontinued. He declined cytotoxic therapy. Serial computed tomography showed no change in his neoplastic lesions. Five months after biopsy, he started hemodialysis. Despite adequate dialysis, he developed progressive cachexia, withdrew from dialysis 2 months later, and died.

**DISCUSSION**

The constellation of rapidly progressive renal failure, red blood cell casts, and proteinuria suggested a crescentic glomerulonephritis after treatment with IL-2 and IFN-α 2β. There had been no evidence of preexisting glomerular disease. The chronicity of exposure to nephrotoxins such as nonsteroidal anti-inflammatory agents or radiocontrast was not appropriate to implicate these etiologies to renal failure. Glomerulonephritis associated with renal cell carcinoma has been associated with immune complex deposition (2,3) and thus is not the likely cause of his disease. The absence of pathogenic serum antibodies or immune deposits suggests cell-mediated injury induced by IL-2 and IFN-α 2β therapy. The initial improvement with glucocorticoid therapy is consistent with disease mediated by immune enhancement.

Over 80% of patients with pauci-immune necrotiz-
ing and crescentic glomerulonephritis have been found to have circulating ANCA (4). The role of ANCA in the mediation of disease remains unclear. Some investigators have proposed that ANCA are pathogenic by inducing neutrophil activation with resultant vascular injury. In cases without ANCA, the pathogenesis is unknown.

There is abundant evidence of extrarenal, cell-mediated autoimmune pathology after treatment with IL-2 alone or in combination with IFN-α. Vasculitic skin reactions, vitiligo, and lymphocytic myocarditis have been described, as has inflammatory arthritis (5,6). Exacerbation of Crohn’s disease has recently been reported (7). Moreover, a spectrum of autoimmune thyroiditis, occurring in approximately 20% of patients treated with IL-2, has been described (8,9). Many of these phenomena are felt to be mediated by the action of specific autoreactive T cells that have been activated by IL-2.

IL-2 and IFN-α 2β have also been associated with renal pathology, although the information for IFN-α 2β has been primarily anecdotal (Table 1). Gresser et al. described glomerulonephritis in mice after IFN treatment at birth (10). Early Phase I and II studies of IFN-α in cancer therapy revealed proteinuria development in 15 to 20% of patients, usually less than 1 g/day (11). Reversible nephrotic syndrome was first described by Selby et al. in a patient treated for myeloma with IFN-α (12). Later reports included a case of allergic interstitial nephritis and minimal change-nephropathy after IFN-α (13) and a membranoproliferative glomerulonephritis developing in a man with hairy cell leukemia, 1 month after the initiation of IFN-α (14). In renal transplantation, high doses of IFN-α for the prevention and treatment of cytomegalovirus infection are associated with an increased frequency of episodes of rejection. In one report, three of these patients had nephrotic-range proteinuria that resolved after the discontinuation of IFN-α (15). Finally, there is a growing experience of IFN-α therapy for hepatitis C virus and cryoglobulinemia. In a recent report, 1 patient of 26 treated with IFN-α for mixed cryoglobulinemia developed glomerulonephritis, although it remains uncertain whether glomerulonephritis was caused by the treatment or the underlying disease (16).

The renal pathophysiology of IL-2 treatment has been more extensively evaluated. A number of reports describe a “capillary-leak” phenomenon characterized by edema, weight gain, hypotension, oliguria, decreased fractional excretion of sodium, azotemia, and a bland urinary sediment consistent with poor renal perfusion (17–20). Local changes in vasoactive mediators, such as decreased prostaglandin excretion or synthesis (19) and increased PRA and aldosterone levels (20), have been demonstrated and postulated to play a role. Shalni et al. have proposed a parenchymal lesion as well, on the basis of the findings in 10 patients of a relatively low BUN-to-creatinine ratio and a decline in GFR with reduced filtration fraction (21). Others have reported parenchymal disease associated with IL-2 therapy (5,22–24) (Table 2). Kragel et al. described postmortem findings of 19 patients treated with IL-2 (5) revealing tubular changes in 13, interstitial lymphoid infiltrates in 6, mesangial changes in 2, and 1 with focal glomerulosclerosis. Hisanaga et al. noted a reversible nephrotic syndrome in a patient receiving human recombinant IL-2 for malignant hemangioepithelioma (22). A histopathologic examination from a patient who died during a course of IL-2 (and lymphokine-activated killer cells) treatment for metastatic melanoma revealed an interstitial nephritis (23). The majority of infiltrating cells identified by monoclonal antibodies were T lymphocytes, suggesting a cell-mediated immune process. Glomerular pathology with IL-2 was observed in a man with hepatocellular carcinoma treated with IL-2 and lymphokine-activated killer cells. He developed a crescentic IgA glomerulonephritis that appeared to remit with the cessation of IL-2 and the initiation of plasmapheresis and steroids (24).

In conclusion, we report the first description of pauci-immune glomerulonephritis after treatment with IL-2 and IFN-α 2β. Our patient had no evidence of the known pathogenic antibodies. We propose a pathogenesis of altered cell-mediated immunity, con-

<table>
<thead>
<tr>
<th>Authors, Year (Ref. No.)</th>
<th>Cancer Type</th>
<th>Functional Change</th>
<th>Pathologic Change</th>
<th>Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selby et al., 1985 (12)</td>
<td>Multiple myeloma</td>
<td>Nephrotic syndrome, renal failure</td>
<td>Not available</td>
<td>Unknown</td>
<td>Renal function recovery</td>
</tr>
<tr>
<td>Auerbach et al., 1984 (13)</td>
<td>Mycosis, fungoides</td>
<td>Nephrotic syndrome, renal failure</td>
<td>Allergic interstitial nephritis, minimal glomerular changes</td>
<td>MPGN*, Type 1</td>
<td>Renal function recovery</td>
</tr>
<tr>
<td>Herman and Gabriel, 1987 (14)</td>
<td>Hairy cell leukemia</td>
<td>Nephrotic syndrome</td>
<td></td>
<td>Unknown</td>
<td>Not available</td>
</tr>
</tbody>
</table>

* MPGN, membranoproliferative glomerulonephritis.
TABLE 2. Renal parenchymal disease reported after cancer therapy with IL-2

<table>
<thead>
<tr>
<th>Authors, Year (Ref. No.)</th>
<th>Cancer Type</th>
<th>Functional Change</th>
<th>Pathologic Change</th>
<th>Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hisanaga et al., 1990 (22)</td>
<td>Hemangioepithelioma</td>
<td>Nephrotic syndrome</td>
<td>Not available</td>
<td>Unknown</td>
<td>Renal function recovery</td>
</tr>
<tr>
<td>Feinfeild et al., 1991 (23)</td>
<td>Malignant melanoma</td>
<td>Renal failure</td>
<td>Interstitial nephritis</td>
<td>Cell-mediated (T lymphocyte infiltration)</td>
<td>Patient death (metastases)</td>
</tr>
<tr>
<td>Chan et al., 1991 (24)</td>
<td>Hepatocellular carcinoma</td>
<td>Proteinuria, renal failure</td>
<td>IgA glomerulonephritis</td>
<td>Unknown</td>
<td>Renal function improvement</td>
</tr>
</tbody>
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Persistent with pathologic changes that have been reported in extrarenal organs after immune modulation.

ACKNOWLEDGEMENTS

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REFERENCES