ing to recognition of a metastatic islet cell tumor. Fasting plasma immunoreactive glucagon (IRG) was 800 pg per ml, and 70 percent of this consisted of normal (3,500) molecular weight IRG. Faulty regulation of plasma IRG included pronounced increases after mixed meals and orally given fat. Tumor cell morphology was heterogeneous, and while glucagon immunofluorescence was shown, insulin and somatostatin immunofluorescence were lacking. A clinical remission was induced and sustained by surgical therapy and chemotherapy. The case documents the occurrence of this syndrome in the second decade of life, a favorable response to palliative therapy, and a relationship between meal composition and plasma IRG that may have clinical importance for this patient.

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Idiopathic Acute Interstitial Nephritis

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ACUTE INTERSTITIAL NEPHRITIS (AIN) must be considered in any patient presenting with acute renal failure; the pathologic inflammation may resolve and the prognosis is generally favorable. Previous reports emphasize that AIN with acute renal failure is most frequently seen as a manifestation of drug hypersensitivity, or rarely in association with overt infection. We report the case of a patient with reversible acute renal failure and biopsy-confirmed AIN in whom none of the known pharmacologic or infectious associations of AIN were identifiable. Fluorescent antiglobulin studies showed intense interstitial staining for IgM, with staining of both tubular and glomerular basement membranes for IgG, IgM and complement. We believe that the AIN in this case may represent virus induced immunologic injury.

Report of a Case

A 36-year-old woman, a schoolteacher, had a three-week illness characterized by fatigue, low grade fever, nasal congestion, cough and mild diarrhea. Findings on physical examination were

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unremarkable. The sedimentation rate was 103 mm per hour and the blood urea nitrogen (BUN) was 30 mg per dl. Despite resolution of all symptoms in five days, the BUN had risen to 60 mg per dl, and the patient was admitted to hospital.

The patient had not noted pharyngitis, rash, arthralgias, photosensitivity or ocular symptoms. There was no history of flank pain or dysuria, and urinary volumes had been normal. The patient distrusted drugs, and had used none in the months before admission.

She had previously been healthy except for borderline hypertension. One year earlier, results of a complete blood count, analysis of urine and serum chemistry screen were normal, and the BUN was 12 mg per dl.

On physical examination at admission, the patient appeared healthy. Blood pressure was 140/96 mm of mercury, there was no fever and the examination showed no abnormalities.

Findings on an electrocardiogram and x-ray study of the chest were normal. The hemoglobin value was 10.9 grams per dl, the leukocyte count was 13,000 with 83 percent neutrophils, 11 percent lymphocytes, 4 percent monocytes, 2 percent basophils and no eosinophils. The uric acid, phosphorus and serum chemistries were normal. The sodium level was 134, potassium was 4.3, chloride was 96 and bicarbonate was 22 mEq per liter. The BUN was 59 and the creatinine level was 7.6 mg per dl. Analysis of urine showed a pH of 7, a specific gravity of 1.003, + + protein and + + + glucose with a simultaneous plasma glucose of 112 mg per dl. Occasional granular and white cell casts, 5 to 10 leukocytes and 2 to 4 red blood cells were seen per high power field. The 24-hour protein excretion was 800 mg, of which less than 10 percent was albumin on acrylamide gel electrophoresis. Intravenous urography showed 17 cm kidneys and no obstruction.

Coombs, antinuclear antibody and lupus erythematosus cell tests were negative. Cryoglobulins were not demonstrable. Complement (C3 and C4) levels were normal. The IgA value was 148 mg per dl (normal 60 to 330); the IgM, 268 mg per dl (47 to 147); the IgG, 1,760 mg per dl (570 to 1,900), and the IgE, 104 units per ml (normal, less than 300). Bone marrow aspirate and biopsy findings were normal. Liver-spleen radionuclide imaging showed the spleen to be grossly enlarged.

Urine and blood cultures were sterile. Rare beta hemolytic streptococcus group C was recovered from the throat. Viral and mycobacterial

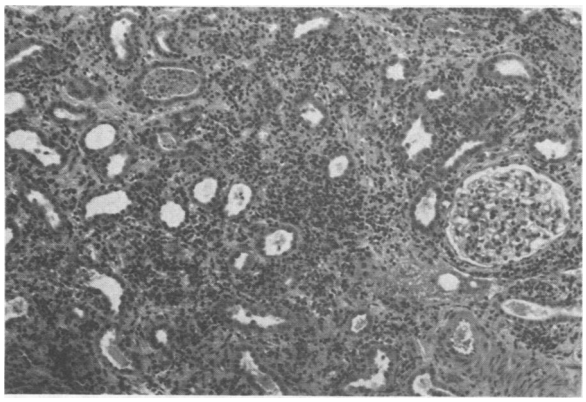

Figure 1.—Low-power view of patient's kidney showing severe interstitial nephritis and a representative normal glomerulus (reduced from ×125).

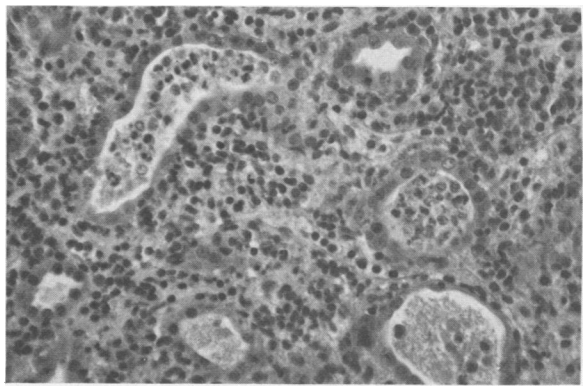

Figure 2.—Light microscopic picture showing interstitial nephritis with tubulitis (reduced from ×325).

cultures of sputum, marrow and urine were sterile. There was no reaction to intermediate purified protein derivative. A Venereal Disease Research Laboratories test and a mononucleosis screen were negative. Hepatitis B antigen was not present on radioimmunoassay, and there was no rise in the convalescent titers of antibodies to leptospirosis, Epstein-Barr virus, mumps, adenovirus, influenza A or B, parainfluenza virus or Toxoplasma. An antistreptolysin O titer was normal. Heavy metal screens were negative.

Percutaneous renal biopsy showed the histologic features (Figures 1 and 2) of AIN. The interstitium was densely packed with lymphocytes, plasma cells and rare eosinophils, and there was no evidence of fibrosis. Focal tubulitis was present. All 24 glomeruli were normal in appearance on light microscopy. Electron microscopy confirmed the tubular injury, and showed in some glomeruli extension of mesangium into the subendothelial space. Electron-dense deposits were absent. Findings on immunofluorescent

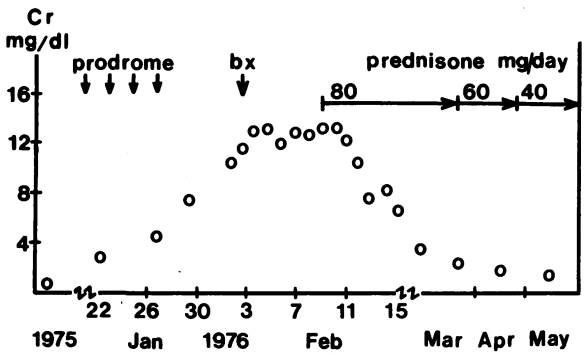

Figure 3.—Clinical course of patient showing progressive improvement in renal function following onset of prednisone therapy.

studies were most remarkable for prominent diffuse interstitial staining for IgM. Intense depostion of IgG, IgM and C3 was observed along both glomerular and tubular basement membranes. The staining was predominantly linear, with some areas suggestive of a granular overlay.

The clinical course is diagramed in Figure 3. The creatinine value initially rose one mg per dl per day, associated with progressive acidosis, hyperkalemia, hyperphosphatemia and return of the blood pressure to normal levels. Urinary output ranged from 2 to 3.5 liters per day, and glucosuria persisted. Despite progressive azotemia, the patient remained free of symptoms, her weight was stable and the results of physical examination were unchanged. After the creatinine had stabilized at 13 mg per dl, prednisone therapy was instituted at 80 mg per day. The creatinine value fell to a level of 2 mg per dl over five months.

Comment

Several features of our case are typical of AIN-induced acute renal failure. The urinary sediment was benign, the biopsy was characteristic and clinical recovery was seen. The renal failure in our patient was of the nonoliguric type, previous reports recording urinary volumes ranging from several liters per day[1,2] to anuric levels.[3-6] Eosinophilia[7] and elevated IgE,[8] common findings in drug-associated AIN, were not present. The renal biopsy showed classic changes[7,9] of AIN: tubulitis accompanied a dense interstitial infiltrate of lymphocytes, plasma cells and eosinophils. Glomerular changes were minimal, as reported in other cases,[1,6,7,10-13] and were shown only by electron microscopy.

There was no history of drug exposure, nor could infection with Toxoplasma, spirochetes, bacteria or mycobacteria be shown present. As suggested by the prodromal illness, the splenomegaly, the elevated IgM and the similarity of this patient's illness to that described with viral-associated AIN, a causative viral agent was suspected but could not be identified.

The immunofluorescence stains, showing complement and immunoglobulin along basement membranes, suggest that the renal injury in this patient was immunologically mediated. The linear immunofluorescence pattern and lack of electron dense deposits further suggests, but does not prove, that the immunoglobulin is directed against basement membrane, as opposed to originating from deposited immune complexes. Both varieties have previously been reported with AIN. The linear pattern immunofluorescence, often with hapten bound in the same distribution, has been observed with drug-associated AIN,[14-16] and linear staining has been described in a single case of AIN following poststreptococcal nephritis.[17] The granular pattern, representing immune complex deposition, has been described with the interstitial inflammation accompanying systemic lupus erythematosus[18,19] or primary glomerular disease.[20] For perspective, it should be noted that numerous groups have found no evidence of immunologic injury, as judged by immunofluorescence, in their cases of drug-associated,[7,12] viral[1] or idiopathic[17,21] AIN.

Discussion

A classification of AIN is presented in Table 1. Most cases of AIN have been associated with drug therapy; more than 100 cases have been attributed to methicillin therapy, and other agents have been sporadically incriminated. The clinical course of drug-associated AIN is fairly uniform in that evidence of hypersensitivity (fever, rash, eosinophilia) develops in the patient and progressive acute renal failure which is largely reversible is seen. The etiologic role of the drug is suggested by epidemiologic data,[22] by the presence of dermal-bound[14,17,23] or circulating[14,24] drug-specific antibody, by the presence of the drug or its metabolites bound with complement and antibody to renal tubules,[14,15,17] and most specifically by rechallenge.[3,11,25]

There is, however, reason to suspect that AIN associated with antimicrobials may be induced by the infection itself. Autopsy series in the preantibiotic era frequently noted interstitial nephritis

with bacterial sepsis,[26-28] but these early reports were often inadequate to exclude pyelonephritis, acute tubular necrosis, endovasculitis or actual parenchymal infection. More recently the case reported by Knepshield and associates[29] and the ten cases of Brass and co-workers[30] lend support to Kimmelstiel's hypothesis[31] that nonrenal bacterial infection can induce a hypersensitivity response that culminates in AIN.

Infection-associated AIN is clearly documented in cases of leptospirosis, toxoplasmosis and tuberculosis (see Table 1). Viral infections, especially mononucleosis, may also evoke AIN, with prominent glomerular injury usually present in addition to the interstitial inflammation.[32]

Renal tubular damage mediated by immunologic injury appears to be the pathogenetic mechanism in many cases of AIN.[16,33-36] With drug-associated AIN, the inciting antigen is presumably the drug or its metabolites functioning as haptens.[14,15,37,38] In transplant rejection, AIN may result from immunity directed against autologous renal antigens.[39] Autoantigens may also evoke interstitial nephritis; this is the predominant renal lesion in Sjögren's syndrome,[40,41] and is increasingly appreciated with systemic lupus erythematosus.[18,19,21] In both of these diseases, however, the interstitial nephritis is of the chronic variety in that fibrosis is a constant feature, and renal failure, if present, is persistent.

Eight cases of reversible acute renal failure and idiopathic AIN have been reported. Three of these were described without clinical detail except to mention that iridocyclitis was present in two of them.[9,44]

In two of the five cases reviewed by Chazan and co-workers,[45] the patients had received antibiotics. The remaining three patients were middle-aged women who presented with severe renal failure and AIN on renal biopsy, and whose conditions seemed to respond to steroid therapy.

Dobrin and associates[21] reported the cases of two young women in whom acute renal failure and AIN developed following prodromal illnesses. In one there was response to therapy with systemic steroids, while in the other there was spontaneous resolution. Both had received antibiotics, but the drugs were thought to be unrelated to the development of renal failure. An immunofluorescence study in one case was negative. Complete evaluation showed no discernible cause for the renal failure, and no explanation for the uveitis and bone barrow granulomata present in both cases.

The splenomegaly in our case and the granulomatous marrow and uveal involvement in Dobrin's cases are the only features that distinguish these cases from each other. The similarities of Chazan's and Dobrin's cases and the case we report are many: all of the patients were women, and five of six had prodromal illnesses preceding the development of acute renal failure associated with AIN. Urinalysis in each showed proteinuria and microscopic hematuria. Where measured, there was no eosinophilia, the complement levels were

TABLE 1.—*Acute Renal Interstitial Inflammation**

- Acute interstitial nephritis
  - Associated with drugs:
    - Methicillin
    - Penicillin derivatives
    - Cephalosporins
    - Sulfa derivatives
    - Polymyxin
    - Antituberculars
    - Phenindione
    - Diuretics
    - Diphenylhydantoin
    - Phenazone
    - Glafenine
    - Azathioprine
    - Phenacetin
    - Phenobarbital
    - Allopurinol
  - Associated with infection
    - Bacterial
      - Streptococcus
      - Salmonella
      - Diphtheria
      - Staphylococcus
      - Brucella
      - Meningococcus
    - Granulomatous
      - Tuberculosis
      - Sarcoid
      - Mycetoma
      - Toxoplasmosis
      - Leptospirosis
      - Syphilis
    - Viruses, especially mononucleosis
  - Associated with immunologic disease
    - Transplant rejection
    - Sjögren syndrome
    - Systemic lupus
  - Idiopathic
- Secondary renal interstitial inflammation
  - Associated with primary tubular disease
    - Pyelonephritis
    - Acute tubular necrosis
    - Toxic nephritis
  - Associated with primary glomerular disease
  - Associated with vasculitis

*Documentary bibliography available upon request to authors.

normal and immunoglobulins were elevated. In each case the renal failure resolved, albeit with some residual impairment.

These cases are too few in number, and the immunofluorescence data too infrequent, to postulate any common mechanism. They suggest, however, that AIN may be induced by agents besides those previously described, and these agents should be diligently sought in future cases. Clinically, the nonspecific presentation of idiopathic AIN and the favorable prognosis mandates that the diagnosis be considered in every patient with acute renal failure in whom the cause of the renal lesion is in doubt.

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