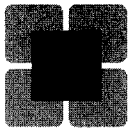

Acute tubulointerstitial nephritis

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■ Between 1980 and 1988, 12 patients at the Cleveland Clinic had biopsy-proven acute tubulointerstitial nephritis. Etiologies of the disease included drugs, systemic illness, and idiopathic causes. Clinical features were nonspecific, and the diagnosis of acute tubulointerstitial nephritis was seldom entertained in these patients prior to biopsy. Seven patients had unrelated underlying renal disease. Treatment included discontinuation of the offending agent and/or a trial of steroids. All patients had final creatinine levels lower than at diagnosis. Because the condition is potentially reversible, this disease should be considered in all patients with new azotemia who do not exhibit prerenal factors, features typical of acute tubular necrosis, red blood cell casts heralding a glomerular process, or evidence of obstructive uropathy.

□ INDEX TERMS: NEPHRITIS, INTERSTITIAL □ CLEVE CLIN J MED 1992; 59:27–32

ACUTE tubulointerstitial nephritis (AIN) is a confusing cause of renal failure which, if not recognized, can be devastating. AIN is characterized by immunologically mediated cellular infiltration of the renal interstitium and tubules. The infiltrating cells are eosinophils and T lymphocytes rather than the polymorphonuclear leukocytes that would be predominantly seen in bacterial pyelonephritis. AIN can occur as a primary disease entity which is initiated by certain systemic diseases or infections, drugs, or unknown factors. Correct diagnosis is important because the resulting renal failure can often be reversed by identifying and removing the etiologic agent responsible for AIN. This is also important in patients with underlying glomerular or other renal disease, since a superimposed primary tubulointerstitial nephritis can cause worsening of renal function from baseline values.

This study retrospectively examined cases of AIN in patients with and without underlying renal disease in order to determine common clinical and laboratory features that may be characteristic of the disease.

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PATIENTS AND METHODS

We reviewed 120 charts which carried the diagnosis of interstitial nephritis from January 1980 to December 1988 in the computerized files of the medical records and pathology departments at The Cleveland Clinic Foundation. Excluded from this group were cases of transplant rejection, chronic interstitial nephritis, crescentic glomerulonephritis, systemic lupus erythematosus, sarcoidosis, acute pyelonephritis with positive cultures, and patients on cytotoxic therapy. Several patients were excluded whose interstitial nephritis was presumed by their physicians to be secondary to underlying renal disease—including diabetes, nephrosclerosis, focal glomerulosclerosis and membranoproliferative glomerulonephritis. Whether these presumptions were in error is not known, since withdrawal of possibly offending drugs was not tried in these patients. Patients for whom renal biopsy data were unavailable were also excluded. This study includes data from 12 patients, with ages ranging from 15 to 73, with biopsy-

TABLE 1
PATIENT PROFILES AND CLINICAL COURSES

Pt. #	Age	Suspected etiology of AIN	Underlying renal disease	Associated diseases	Creatinine (initial/ peak/final)	Time from peak to final creatinine	Therapy
1	31	Pyrimethamine and sulfadoxine for 3 weeks; typhoid-like illness.	–	–	1/4.3/1	1 month	Discontinued pyrimethamine and sulfadoxine
2	19	Idiopathic	–	Uveitis	?/?/0.9		Prednisone
3	41	Indomethacin for 1.5 years; analgesics many years	Amyloid in kidney	Crohn's, uveitis, arthritis	1.9/5.5/4.7	2 months	Prednisone; discontinued indocin and analgesics
4	48	Furosemide for 2 months.	MPGN type I	–	2.6/14.5/3.1	1 month	Steroids; temporary dialysis; discontinued furosemide
5	31	Sulfa eye drops for 2 months	–	Uveitis for 1 month before acute renal failure	0.8/4.1/1.3	5 months	Prednisone; discontinued eye drops
6	59	Sulfasalazine for 1 week	? Hemolytic uremic syndrome	? Inflammatory bowel disease, microangiopathy, adult-onset diabetes mellitus	0.9/9.5/1.1	1 month	Prednisone; temporary dialysis; discontinued sulfasalazine; plasmapheresis
7	73	Furosemide for 2 months	Focal and segmental glomerulo-nephritis	–	0.6/4/0.9	1 month	Prednisone; furosemide was discontinued after creatinine normalized
8	52	Furosemide, metolazone, spironolactone for 5 months	MGN type II	–	4.5/16.3/2.5	2 months	Prednisone; discontinued diuretics, temporary dialysis
9	64	Idiopathic	MPGN type II	Rheumatoid arthritis, hypertension	2/4.2/2.5	1 month	Prednisone
10	65	Tolmetin	MGN type I	–	0.9/2/1.7	4 months	Discontinued Tolmetin
11	15	Idiopathic	–		?/4.3/1.2	2 weeks	Steroid
12	16	Nonbacterial infection	–	Acute systemic viral illness	0.9/4.2/1.7	4 months	None

MGN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis

proven AIN. The cases are compared with respect to their clinical presentation, laboratory features, and course.

RESULTS

Profiles of the 12 patients and their clinical courses are summarized in Table 1. Underlying renal disease was present in 7 of these patients. Specific conditions included Crohn's disease with amyloid deposition in the kidney; microangiopathy, with clinical features of hemolytic-uremic syndrome as well as AIN; membranous glomerulonephritis, type I and type II; membranoproliferative glomerulonephritis, type I and type II; and focal and segmental glomerulonephritis. In these patients, the interstitial nephritis was thought to be a superimposed primary process—not simply due to the underlying disease—because their renal function improved with discontinuation of the offending agent or with the use of steroids, or both. However, we do not have second biopsies to prove that the interstitial component of their disease resolved with these measures.

Etiology

The 12 patients were categorized with respect to the probable etiology of their AIN—infection-related, drug-related, or idiopathic, depending on whether there was a new drug or systemic illness which preceded the decline of renal function.

The drug-related category of patients was the largest. Seven of the 12 patients gave a history of ingesting a new drug between 1 week and 2 years prior to diagnosis of AIN. The implicated drugs included sulfonamide antibiotics, sulfasalazine, furosemide, indomethacin, tolmetin, and other diuretics. One patient had been using sulfonamide eye drops; it is unclear whether these could produce sufficient systemic absorption of the drug to have led to AIN. Another patient with a typhoid-like illness had been newly started on pyrimethamine and sulfadoxine when he developed AIN. The classification of this patient is uncertain, and he is included in both the infection-induced and in the drug-induced groups.

The infection-related group also included a teenager who developed an unidentified systemic viral-like illness with fever, nausea, vomiting, diarrhea, jaundice, and anemia. Studies for bacterial infection, hepatitis A and B, rickettsia, Epstein-Barr anti-VCA immunoglobulin M titer, and *Leptospira* were negative. The patient had evidence of cytomegalovirus superinfection in the kidney, but this was not felt to be the primary illness because cytomegalovirus is not known to produce this constellation of symptoms in a normal host. Moreover, his cytomegalovirus IgG acute and convalescent titers were the same. He recovered without treatment specific for cytomegalovirus.

Three patients in whom neither drug nor infection preceded the onset of AIN were placed in the idiopathic group.

Clinical features

The 12 patients presented with very nonspecific features: 50% or more had pain in the flank or abdomen, fatigue, nausea, and anorexia. Other symptoms (fever, rash, arthralgias, gross hematuria, vomiting, edema, new hypertension, oliguria, or uveitis) were shared by fewer than 50% of the patients, and it is not certain that these symptoms were related to the underlying diseases. Only one patient had the classic triad of drug hypersensitivity AIN (ie, fever, rash, and eosinophilia). Three patients had uveitis. Two of the patients in the idiopathic group were asymptomatic, with unexplained worsening of renal function being the principal reason for performing kidney biopsies. In 10 of the 12 cases, AIN was not suspected prior to biopsy.

TABLE 2
LABORATORY DATA

	No. of Patients
Anemia (Hgb 12 g/dL)	8/12
Eosinophilia (400 cells/mm^3)	6/12
ESR (50 mm/h)	3/6*
Hyperkalemia (5.3 mEq/L)	0/12
Metabolic acidosis (HCO_3 24mEq/L)	5/12
Low complement (CH_{50})	3/12
Specific gravity (1.012)	1/12
Hematuria (3 red blood cells/high-powered field)	9/12
Proteinuria	
Nephrotic (>3.5 gm/dL)	6/12
Non-nephrotic (<3.5 gm/dL)	6/12
Sterile pyuria (4 white blood cells/high-powered field)	11/12
Granular casts (2-3/ high-powered field)	8/12
Glucosuria (trace or more)	4/12
Eosinophiluria (trace or more)	5/7†
>8%	2/7†

*Data not available for 6 patients
†Data not available for 5 patients

Laboratory features

Of the 12 patients, 50% or more had anemia, eosinophilia, microscopic hematuria, proteinuria (six were low-grade and six were in the nephrotic range), sterile pyuria, and granular casts (*Table 2*). Smaller percentages had elevated sedimentation rate, metabolic acidosis, hypocomplementemia, glucosuria, and isosthenuria. Of seven patients with eosinophiluria, only two had more than 5% eosinophils noted on Wright stain of the urine sediment. Three patients had nephrotic proteinuria prior to the onset of AIN which worsened in degree with the development of AIN. Patients 6,7, and 12 developed nephrotic range proteinuria after the onset of AIN; only patient 7 had underlying glomerular disease (*Table 3*). All six patients with nephrotic-range proteinuria experienced marked reduction in the level of proteinuria as AIN resolved.

Evaluation of the kidneys and upper bladder with laminagrams, ultrasound, or intravenous pyelography was undertaken in all patients. Three patients had enlarged kidneys, and the remaining nine patients had normal renal size.

Pathological data

Light and electron microscopic data were available for 10 of the patients (*Table 4*), but biopsy details for patients 2 and 11 were less complete than for the others. Patient 11 had a frozen biopsy specimen inter-

TABLE 3
CORRELATION OF NEPHROTIC CONDITIONS

Patient	Proteinuria (dipstick)	Glomerular disease	Foot process broadening
1	1+	None	absent
2	1+	None	absent
3	1+	None	present
4	4+	MPGN I	Podocytes obliterated
5	1+	None	absent
6	4+	None	absent
7	4+	FSGS	present
8	4+	MGN II	present
9	1+	MPGN III	present
10	4+	MGN I	present
11	1+	None	No data
12	4+	None	No data

MPGN, membranoproliferative glomerulonephritis
FSGS, focal segmental glomerulosclerosis
MGN, membranous glomerulonephritis

TABLE 4
PATHOLOGICAL FINDINGS*

	No. of patients
Interstitial infiltrate	
Lymphocytes	10/10†
Monocytes	10/10†
Plasma cells	10/10†
Neutrophils	2/10†
Eosinophils	9/11
Interstitial edema	5/10†
Interstitial fibrosis	3/10†
Tubulitis and/or tubular dropout	8/11
Glomerular sclerosis	6/11
Vessel sclerosis	6/11
Foot process broadening	6/11
Immunofluorescence - C3 complement along TBM	3/11
Nonnecrotizing granulomas	4/11
Microangiopathy	1/10†
Amyloid	1/10†

*Data not available for patient 2
†Data not available for patient 11
TBM, tubular basement membrane

preted as AIN with tissue eosinophilia, and patient 2 had a biopsy performed at another institution which was read as AIN, with follow-up biopsy 1 year later which was normal.

All 10 patients for whom there was data had lymphocytes, monocytes, and plasma cells in the interstitium of the kidney, which is consistent with the pathological findings of AIN. Nine out of 11 patients also had eosinophils present. Two out of 10 had neutrophils. Five of 10 cases had interstitial edema, which, along with a mononuclear cellular infiltrate, is characteristic of AIN. Three out of 10 had patchy fibrosis in the interstitium. Tubulitis and tubular dropout were fairly common findings. Foot process broadening occurred in four patients with underlying glomerular disease and also in one patient without such glomerular involvement. This patient did not have nephrotic-range proteinuria (*Table 3*).

Other striking features found on pathology included non-necrotizing granulomas in four cases, and the paucity of positive findings on routine immunofluorescence studies. Only 3 of 11 patients were noted to have C3 complement along the tubular basement membrane. Miscellaneous findings included microangiopathy in one patient, amyloid in another, and vessel sclerosis in two.

Clinical course

AIN can be reversed. Eleven patients had final creatinine levels lower than at the peak of their disease (the data are missing for patient 2). In virtually all patients, the improvement in renal function occurred 1 to 5 months after withdrawal of the offending drug, resolution of infection, or initiation of steroid therapy. Nine of the 12 patients had a trial of steroids. Whether the patients' conditions would have improved without steroids is not known. Patient 7's renal function normalized while on prednisone even before the presumed offending drug, furosemide, was discontinued. In this patient, AIN might not have been secondary to furosemide after all, although the rise in creatinine correlated with the initiation of this drug. Six patients had normal final creatinine values. Five patients had final creatinine levels slightly higher than baseline, but lower than their peak creatinine values. One patient had a final creatinine value that was abnormally high but less than at baseline. Thus, recovery was not complete in all patients.

Data for initial and final 24-hour protein excretion were available for patients 10 and 12. In both cases heavy proteinuria (14 g and 17 g) diminished (0.1 g and 2.8 g) as AIN resolved. Neither patient had been given steroids.

DISCUSSION

Etiology

In this study, drugs were implicated more frequently than any other etiology of AIN. Penicillin and sulfonamide derivatives are often cited as causes of AIN,[1] and methicillin-induced AIN was well described in the

days when that drug was used extensively.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) are well-known culprits in this disease,[3–5] and diuretics such as the thiazides,[6] furosemide,[7] and chlorthalidone[8] have been implicated, as have a variety of other drugs.[9,10]

The duration of treatment with the offending antibiotic had varied from 2 days to 2 months before diagnosis was made.[8,11] NSAIDs may lead to this nephrotic syndrome 2 weeks to 18 months after initiation of therapy; the condition resolves 1 month to 1 year after withdrawal of the drug. The efficacy of steroids in treating the syndrome is unproven.

Sulfasalazine and the combination of pyrimethamine and sulfadoxine have not previously been associated with AIN, but in view of the previous experience with other sulfonamide derivatives, it is not surprising that they have been implicated as possibly causing AIN in two of our patients.

Less common etiologies of AIN are systemic infections not directly invading the kidney, including group A streptococci,[11] toxoplasmosis,[12] Legionnaire's disease, malaria, leptospirosis, salmonellosis, Epstein-Barr virus,[13] and typhoid fever.[14] Similar infections are suspected etiologies in two of our patients (a typhoid-like illness in patient 1, and a systemic viral illness in patient 12).

In the present study, seven patients had underlying renal disease. Most other studies exclude such patients,[3,11,15,16] or include very few.[10,17,18] Clinically, these patients appeared to have a primary tubulointerstitial process superimposed on their underlying disease because their interstitial-nephritis-induced renal failure proved to be reversible. Similar cases may often be missed if the renal failure from the interstitial process is assumed to be secondary to the underlying glomerulopathy. Many glomerular diseases develop a significant secondary tubulointerstitial component through a poorly understood tubuloglomerular feedback mechanism, but biopsy alone cannot distinguish whether an interstitial infiltrate is secondary to glomerulopathy or the result of primary AIN. Therefore, it is important to actively consider primary AIN in these patients by checking for drugs that may be implicated in producing AIN and withdrawing them to see whether the AIN resolves.

Pathology and pathogenesis

Immunofluorescent studies are seldom positive in AIN, although sometimes linear deposits of IgG and complement may be noted along the tubular basement membrane.[13] In this study, positive immunofluorescence was rarely found. In experimental models, even when the initial assault involves a humoral component with binding of anti-tubular basement membrane antibodies, the interstitial injury is still a cell-mediated process.[19] Direct allergic type I reactions are also plausible in cases of drug hypersensitivity AIN, especially when fever, rash, eosinophilia, elevated IgE levels, and interstitial plasma cells and eosinophils are present.[19]

Four of our patients had non-necrotizing granulomas. Epithelioid granulomas in the kidney have been noted rarely in AIN,[13,20,21] but bone marrow granulomas have been described previously.[22–24] Our patients did not undergo bone marrow aspiration. Another striking finding was uveitis in three patients. A number of reports of AIN and uveitis of unknown cause appear in the literature as well.[16,21,23–25] In some of these reports, bone marrow granulomas were also described.[21,23,24] This syndrome of AIN with bone marrow granulomas and uveitis lends credence to the hypothesis that a systemic immune disorder not yet understood is responsible for AIN in these patients.

Clinical and laboratory features

Pathologically, fusion of the foot processes and interstitial infiltrate are seen.[5] Other clinical and laboratory features are relatively nonspecific and may include fatigue, arthralgias, fever, hematuria, proteinuria (usually non-nephrotic), eosinophilia, and eosinophiluria. In hypersensitivity or acute allergic interstitial nephritis, fewer than one third of patients exhibit the full triad of fever, rash, and eosinophilia.[8] The sole patient in this study who had the triad did not have any history of drug ingestion that could have precipitated the disease. The flank pain and kidney enlargement reported in AIN are probably due to distension of the renal capsule by interstitial edema.[13]

Renal failure in AIN is usually non-oliguric. However, three of the patients in this study were oliguric, and up to 35% of patients with AIN may require dialysis.[15,17]

Metabolic acidosis, renal tubular acidosis, hyperkalemia, and decreased concentrating ability may occur due to tubular dysfunction. Glycosuria and aminoaciduria in AIN due to tubular damage have also been described.[26,27] These features were rare in our patients. Eosinophiluria greater than 5% supports a diagnosis of AIN but is neither specific nor highly sensitive for it.[28,29]

Treatment and prognosis

In treating suspected cases of drug-induced AIN,

prompt discontinuation of the offending drug is most important, for if its use is continued, renal insufficiency may progress until it becomes irreversible. Surveillance for this entity is important, even in patients with underlying chronic renal failure who have suffered a recent worsening of their renal function. Thus, much may be gained by suspecting drug-induced AIN early in the course of acute renal failure.

The effectiveness of steroids in treating AIN is controversial. The study by Galpin et al[18] suggested that patients treated with prednisone recovered significantly faster than those treated with discontinuation of methicillin alone. A case has been reported of tolmetin-induced AIN which was reversible with discontinuation of the drug and utilization of prednisone,[30] and there is some evidence that prednisone can halt renal insufficiency even while the offending drug is continued. A case of cimetidine-induced AIN was reported in which renal failure abated with the addition of prednisone.[31] When prednisone was stopped, renal function deteriorated again on cimetidine. It again resolved with discontinuation of the cimetidine. In our study group, patient 7 may represent a similar situation since his renal function improved with prednisone even before the offending diuretic was discontinued. However, fully controlled studies have not been done and many authorities feel that the use of steroids in AIN is not substantiated by the current studies.[11,19] In this regard, note that the three patients in our study who did not receive steroids recovered remarkably well.

Factors thought to contribute to poor prognosis in AIN are diffuse infiltration of the interstitium, prolonged renal failure (longer than 6 weeks), and adult age at onset of the disease. However, most cases are reversible, regardless of the initial severity of the disease. With prompt diagnosis and treatment, very few patients with AIN will require permanent dialysis, though some patients may require dialysis temporarily, as a supportive measure.[15]

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