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NEPHROLOGY FORUM

Drug-induced acute interstitial nephritis

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CASE PRESENTATIONS

Patient 1. A 68-year-old man was referred to another hospital because of fever and a cutaneous infection of the right elbow. On admission, his temperature was 39.5°C; heart rate, 120 beats/min; and blood pressure, 110/75 mm Hg. The hemoglobin was 15 g/dL. The white blood cell count was 20,000/mm^3, with 88% polymorphonuclear leukocytes, 7% lymphocytes, and 5% monocytes. Serum creatinine was 80 μmol/L (0.9 mg/dL), and blood urea was 5 mmol/L. Seven blood cultures were positive for *Staphylococcus aureus*, and treatment with methicillin (12 g/day) was initiated. After 12 days of treatment, the fever resumed, his renal function deteriorated, and he was transferred to the renal unit of Hôpital Tenon.

On admission, his temperature was 39°C. The physical examination was normal except for the cutaneous lesion of the right elbow. The serum creatinine was 320 μmol/L (3.6 mg/dL); blood urea was 27 mmol/L. Urinalysis disclosed macroscopic hematuria and 200 white cells/mm^3. Proteinuria was 1 g/day. The white blood cell count was 12,000/mm^3, with 12% eosinophils. Renal biopsy disclosed an infiltration of the interstitium by numerous lymphocytes and macrophages that was associated with severe tubular lesions. Glomeruli and blood vessels were normal. Immunofluorescent studies showed linear deposits of IgG along the tubular basement membranes. Methicillin was replaced by pristinamycin. Hematuria, pyuria, and proteinuria quickly resolved, and his renal function progressively returned to baseline values.

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Patient 2. A 42-year-old man was referred to a department of respiratory medicine because of persistent cough, anorexia, and asthenia. He was a heavy smoker but had no pertinent medical history and was taking no medication. His temperature was 38°C, and his blood pressure was 110/70 mm Hg. He had lost 5 kg over the previous two months, and he weighed 46 kg. Physical examination was normal. Hemoglobin was 10.5 g/dL. The white blood cell count was 12,000/mm^3, with 80% polymorphonuclear leukocytes, 1% eosinophils, 10% lymphocytes, and 9% monocytes. The serum creatinine was 55 μmol/L (0.6 mg/dL); and blood urea was 2 mmol/L. Liver function tests were normal. Tests for HIV infection were negative. A chest radiograph was suggestive of pulmonary tuberculosis, and this diagnosis was confirmed by the identification of numerous acid-fast bacilli in sputum smears. The patient was given rifampicin (600 mg/day), isoniazid (250 mg/day), and pyrazinamide (1500 mg/day). Three weeks later, he had gained 3 kg and was feeling less tired. Routine laboratory tests were unchanged; in particular, the serum creatinine was still 55 μmol/L (0.6 mg/dL). Four weeks later, the patient had gained two more kg and his general status seemed to be improving, but laboratory tests showed that the serum creatinine was 150 μmol/L (1.7 mg/dL) and the blood urea 10 mmol/L. The patient was referred to our renal unit.

On admission, he had no complaints. His blood pressure was 105/70 mm Hg; heart rate, 80 beats/min; and temperature, 37°C. Physical examination was normal. The serum creatinine was 200 μmol/L (2.4 mg/dL), and blood urea was 12 mmol/L. Urinalysis revealed less than one white blood cell/mm^3, and less than one red blood cell/mm^3. Proteinuria was 0.5 g/day. A stain for urinary eosinophils was negative. Hemoglobin was 11 g/dL, and the white blood cell count was 10,700/mm^3, with 72% polymorphonuclear leukocytes, 7% eosinophils, 12% lymphocytes, and 9% monocytes. Eosinophilia subsequently increased to 1,000/mm^3. Renal sonography was normal. Rifampicin administration was stopped. Renal biopsy disclosed extensive inflammatory infiltrates within the interstitium that were composed of lymphocytes and macrophages; granulomas were not seen. The inflammatory infiltrates were associated with interstitial edema, focal tubular lesions ranging from mild to severe, and in some places slight fibrosis. All 22 glomeruli were normal. Immunofluorescent examination of the biopsy specimen revealed no immune deposits. No anti-rifampicin antibody could be detected. After stopping rifampicin, his renal function progressively improved, but two years after this episode, the serum creatinine remains 130 μmol/L (1.5 mg/dL), which corresponds to a calculated creatinine clearance of 50 mL/min.

DISCUSSION

Dr. Jérôme Rossert (*Department of Nephrology and INSERM U489, Hôpital Tenon; and Professor of Nephrology, University of Paris VI, Paris, France*): The two patients presented today, but who were seen more than 20 years apart, both had acute interstitial nephritis (AIN). Acute interstitial nephritis is a rather uncommon disease that has occurred at a relatively stable rate over the years. In three large series published between 1988 and 1998, AIN represented 2% to 3% of all renal biopsies [1–3]. Nevertheless, the clinical presentation of drug-induced AIN has changed since the time when methicillin-induced AIN was prototypical of this entity. After briefly discussing the pathophysiology of drug-induced AIN, and in particular the links between AIN and interstitial fibrosis, I will review the clinical spectrum of drug-induced AIN, the diagnostic tools that can be used besides renal biopsy, and the prognosis and treatment of this disease.

Pathophysiology

Four arguments strongly suggest that drug-induced AIN is secondary to immune reactions in humans. First, AIN occurs only in a small percentage of individuals taking the drug. Second, AIN is not dose-dependent. Third, drug-induced AIN is associated with extrarenal manifestations of hypersensitivity. Four, AIN usually recurs after accidental re-exposure to the drug or to a closely related agent. It is thus tempting to draw a parallel between drug-induced AIN and immune-mediated experimental AIN, and to use these experimental models to understand the pathophysiology of drug-induced AIN.

Two main categories of antigens can induce experimental AIN: (*1*) endogenous renal antigens, which can be either non-collagenous components of the tubular basement membrane (TBM) or proteins synthesized by tubular cells but which are not part of the TBM, and (*2*) non-renal antigens [reviewed in 4, 5]. The ability of renal antigens to induce AIN has been extensively studied since the first description of this model in 1971 [6]. Immunization of some strains of guinea pigs (such as strain XIII), of rats (such as Brown-Norway rats), or of mice (such as SJL mice) with heterologous TBM can induce AIN [reviewed in 4, 5]. Similarly, animals immunized with endogenous renal proteins that are not part of the TBM can develop AIN. Immunization of rabbits or rats with Tamm-Horsfall protein, or injection of rats with antisera to Tamm-Horsfall protein can induce AIN [reviewed in 4]. Immunization of Lewis rats with megalin induces a membranous nephropathy, which has been associated with tubular lesions and interstitial inflammatory infiltrates [reviewed in 4]. These models suggest that drugs responsible for AIN induce an immune reaction directed against endogenous renal antigens. The drug or one of its metabolites could serve as a hapten and modify the immunogenicity of native renal proteins (Fig. 1A), or it could mimic renal antigens and induce an immune reaction that also will be directed against components of the TBM (Fig. 1B).

Experimental AIN also can be induced by promoting immune reactions against extrarenal proteins that have become trapped within the kidney ("planted" antigen). The lesion can be induced by injecting rabbits daily with bovine serum albumin, or by injecting aggregated bovine gamma globulins under the renal capsule of pre-sensitized rats or guinea pigs [reviewed in 4]. In the former case, the AIN is associated with a glomerulonephritis and is characterized by granular deposits of immunoglobulins, C3, and antigen along the TBM, in the interstitium, and in the basal area of interstitial capillaries. In the latter case, aggregated bovine gamma globulins induce delayed-type hypersensitivity reactions within the interstitium. These two animal models could correspond to human AIN induced by drugs that trigger an immune reaction and become deposited within the interstitium. The drug could first be trapped in the interstitium and then become the target of an immune reaction, as exemplified by the second model (Fig. 1C). It could also form circulating immune complexes, which then deposit in the interstitium, as might be the case in the first model (Fig. 1D).

Studies of experimental models of AIN have shown that their induction can involve either cell-mediated immunity or antibody-mediated immunity, and that in some cases the same antigen can even trigger either type of immune response depending on the species [reviewed in 4, 5]. For example, immunization of strain XIII guinea pigs with heterologous TBM induces an AIN associated with linear deposits of IgG along the TBM and mediated by antibodies. The lesion can be transferred with antibodies but not with immune cells, and guinea pigs are protected from the disease by "decomplementation" or by injection of anti-idiotypic antibodies [7–9]. In contrast, immunization of SJL mice with heterologous TBM induces a purely cell-mediated AIN. This AIN can be induced by injection of a T-cell clone that mediates delayed-type hypersensitivity but it cannot be transferred by anti-TBM antibodies [10, 11].

In humans, most drug-induced AIN probably involves cell-mediated immunity, as renal biopsies usually do not disclose any immune deposits. This hypothesis is reinforced by the fact that interstitial infiltrates usually contain a considerable percentage of T-cells and that they sometimes form granulomas. Nevertheless, deposition of anti-TBM antibodies or immune complexes can be observed occasionally on renal biopsies, as in the methicillin-induced AIN in today's first patient. In these cases, antibody-mediated immunity might play a role in the induction of the disease.

Analyses of human renal biopsy tissue and of kidneys taken from animals with experimental AIN have shown

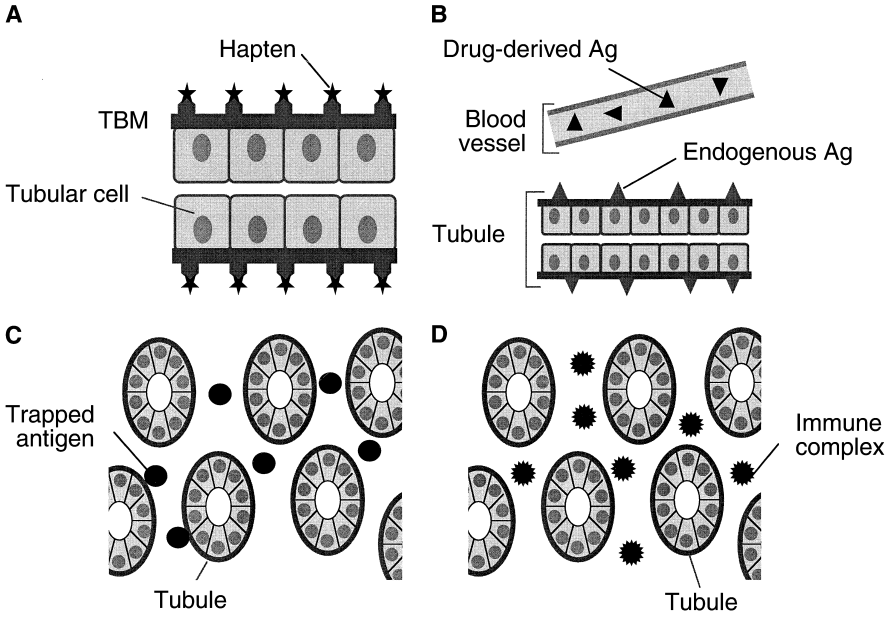

Fig. 1. Mechanisms whereby a drug (or one of its metabolites) can induce acute interstitial nephritis (AIN). (*A*) The drug can bind to a normal component of the tubular basement membrane (TBM) and act as a hapten. (*B*) The drug can mimic an antigen normally present within the TBM or the interstitium and induce an immune response that will also be directed against this antigen. (*C*) The drug can bind to the TBM or deposit within the interstitium and act as a planted ("trapped") antigen. (*D*) The drug can elicit the production of antibodies and become deposited in the interstitium as circulating immune complexes.

that acute interstitial inflammatory reactions are associated with damage to tubular cells. These tubular lesions probably play a key role in the pathogenesis of acute renal failure associated with AIN. The lesions are multifactorial and are due to direct interactions between inflammatory cells and tubular epithelial cells, to the release of soluble molecules by inflammatory cells, or to activation of the complement cascade. Nevertheless, tubular cells are not only a target for inflammatory lesions, they also can actively interact with infiltrating cells to increase interstitial inflammation. Analyses of renal biopsies, studies of kidneys from animals with experimental nephritides, and co-culture experiments have shown that in response to an insult tubular cells can become activated and produce pro-inflammatory molecules such as cytokines, growth factors, adhesion molecules, or chemokines [reviewed in 12, 13]. For example, analyses of renal biopsies from patients with AIN or from Brown-Norway rats immunized with heterologous TBM have disclosed an overexpression of chemokines by tubular cells [14, 15], and co-culture experiments have shown that, in vitro, T-cells can induce chemokine production by tubular epithelial cells [16]. Similarly, in a mouse model of spontaneous acute interstitial nephritis, tubular cells overexpress the *osteopontin* gene, which encodes an adhesion molecule [17].

In some cases, acute interstitial inflammatory reactions induce an accumulation of extracellular matrix that leads to permanent impairment of renal function. Experimental studies and analyses of renal biopsies have shown that macrophages, lymphocytes, and activated tubular cells can produce many cytokines that can induce a proliferation of fibroblastic cells, and/or increase the production of extracellular matrix by these cells in vitro [reviewed in 2, 18]. For example, inflammatory cells can produce transforming growth factor-β (TGF-β), interleukin (IL)-1, IL-4, and lipid peroxidation products, which increase the production of extracellular matrix proteins by fibroblastic cells in vitro. Similarly, tubular cells can synthesize TGF-β, insulin-like growth factor-1 (IGF-1), endothelin-1 (ET-1), and lipid peroxidation products, which stimulate the production of extracellular matrix components by fibroblastic cells in vitro. Nevertheless, in vivo only three of these molecules induce fibrotic reactions within the renal interstitium: TGF-β, ET-1, and platelet-derived growth factor-BB (PDGF-BB).

A potent anti-inflammatory molecule, TGF-β1 is probably the most important profibrotic factor identified so far. It is produced by many cells, including monocytes/macrophages, lymphocytes, fibroblasts, endothelial cells, and tubular cells. After being activated, TGF-β1 binds to its receptors and acts mostly by inducing the phosphorylation of Smad proteins [reviewed in 19]. The profibrotic properties of TGF-β1 are explained by its ability to be chemotactic for fibroblasts, to induce a proliferation of fibroblastic cells, to increase the transcription of genes encoding proteins of the extracellular matrix and the stability of the corresponding mRNAs, to inhibit the production of metalloproteinases, and to increase the production of tissue inhibitors of metalloproteinases (TIMPs), which are their natural inhibitors [reviewed in 20]. Nevertheless, some of these profibrotic properties might be indirect and mediated by increased production of a cysteine-rich protein called connective tissue growth factor [21]. The ability of TGF-β1 to induce renal interstitial fibrosis has been shown by an analysis of the phenotype of trans-

genic mice, which produce high levels of active TGF-β1. Transgenic mice, which express a cDNA encoding mature TGF-β1 under the control of the albumin enhancer/promoter, have elevated circulating levels of TGF-β1, and progressively develop fibrosis of different organs, including liver and kidney [22]. Analysis of the corresponding kidneys shows that they display glomerular immune deposits, glomerulosclerosis, and interstitial fibrosis [23]. Similarly, transgenic mice that harbor a cDNA encoding active TGF-β1 under the control of rat phosphoenolpyruvate carboxykinase regulatory sequences develop renal interstitial fibrosis, glomerulosclerosis, and fibrosis of the liver and adipose tissue [24].

In vivo, ET-1 also can induce renal interstitial fibrosis. The predominant isoform of endothelin, ET-1 is produced by endothelial cells, vascular smooth muscle cells, and tubular cells [reviewed in 25]. Its production can be induced by a variety of stimuli, including hypoxia, angiotensin II, and TGF-β. In vivo, the profibrotic properties of endothelin have been demonstrated by the analysis of transgenic animals overexpressing either ET-1 or ET-2, and by the beneficial effects of endothelin inhibitors in various experimental models of fibrosis involving organs such as kidney, liver, or lung. For example, Hocher et al generated transgenic mice using a 16 kb fragment of human genomic DNA that contained the ET-1 gene, about 8 kb of 5′ flanking sequence, and 1.5 kb of 3′ flanking sequence [26]. These mice overexpress ET-1 predominantly in lung, brain, and kidney, are normotensive, and progressively develop glomerulosclerosis, renal interstitial fibrosis, and pulmonary fibrosis [26, 27]. Although few in vitro studies are available to explain the profibrotic properties of ET-1, this molecule has been shown to be mitogenic and to stimulate collagen synthesis by some fibroblastic cell lines, as well as by vascular smooth muscle cells, hepatic stellate cells, and osteoblastic cells [28–32]. Nevertheless, ET-1's mode of action is still elusive. In particular, the mechanism of its ability to directly modulate the transcription of collagen genes and/or the stability of the corresponding mRNAs remains unknown.

The third molecule that induces fibrosis in the renal interstitium, PDGF-BB, is a potent growth factor. It induces renal interstitial fibrosis in vivo: continuous infusion of PDGF-BB to rats induces not only a proliferation of interstitial myofibroblastic cells, but also an accumulation of extracellular matrix within the renal interstitium [33]. Nevertheless, the profibrotic effects of PDGF-BB are probably indirect and mediated by an overproduction of TGF-β1 [34].

In recent years, much attention has focused on angiotensin II as a profibrotic molecule, because of beneficial effects of angiotensin I converting enzyme inhibitors on the progression of chronic renal diseases [reviewed in 35]. Nevertheless, data suggest that the effects of angiotensin II on extracellular matrix production are indirect, mediated through an increased production of growth factors such as TGF-β or PDGF, and of other molecules such as thrombospondin-l [reviewed in 35].

Clinical presentation

Methicillin-induced AIN has long been considered prototypical of drug-induced AIN. About 100 cases of methicillin-induced AIN have been described in the English literature, and analysis of these case reports shows that the corresponding clinical picture was quite monomorphic (Fig. 2) [reviewed in 36–38]. Renal symptoms typically developed about two weeks after the patients started taking methicillin. Hematuria was present in 90% of cases. It was macroscopic in about 80% of cases and was never associated with red blood cell casts. Pyuria was almost always present and often was associated with leukocyte casts. Renal failure, which occurred in only 50% of adults and 15% of children, was oliguric in 20% of the cases. Approximately 33% of the patients with abnormal renal function required dialysis. The most common extrarenal symptom was fever, which was present in about 80% of patients, could be as high as 40°C, and usually lasted 7 to 10 days after discontinuation of methicillin. A generalized cutaneous rash was observed in only 25% of patients, and arthralgias were uncommon. Eosinophilia was present in about 80% of patients, ranging from 500 to 5000/mm^3. After the methicillin was discontinued, hematuria and pyuria usually resolved within a few days, but renal failure, when present, could last much longer and its mean duration was 1.5 months. Nevertheless, complete recovery of renal function was the rule, and serum creatinine returned to normal levels in about 90% of reported patients.

Besides methicillin, many other drugs can induce AIN (Table 1), but the clinical presentation of AIN induced by these drugs is often incomplete and less suggestive of the diagnosis, as illustrated by the second patient presented today. To try to get a global view of this entity, we reviewed more than 150 case reports, as well as our own unpublished cases (Fig. 2). This analysis showed that renal manifestations develop within three weeks after starting the inciting drug in about 80% of patients, with an average delay of about ten days. The clinical presentation most suggestive of the diagnosis is that of a sudden impairment of renal function associated with mild proteinuria and abnormal urinalysis in a patient with flank pain, normal blood pressure, and no edema. Nevertheless, such a clinical picture is observed in less than one-fourth of cases. Analysis of the different manifestations showed that renal failure is almost constant, and that dialysis is required in about one-half of patients. The presentation is usually that of parenchymal renal failure, but patients with a low fractional excretion of sodium occasionally have been reported. Hematuria and

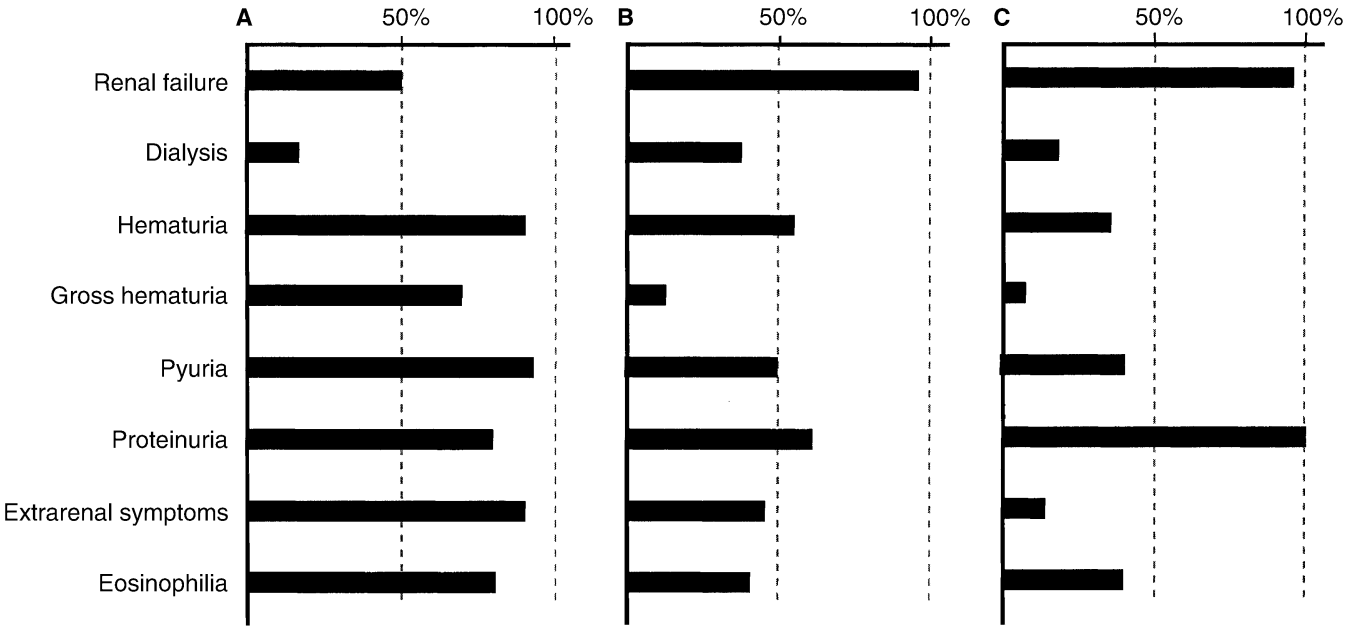

Fig. 2. Approximated frequency with which clinical manifestations occur during the course of methicillin-induced AIN (*A*), AIN induced by drugs other than methicillin (*B*), or AIN induced by NSAIDs and associated with a nephrotic syndrome (*C*). Proteinuria was considered positive when it was at least 0.5 g/L or + by dipstick. Data are derived from case reports and from analysis of our own cases.

pyuria are each present in only about 50% of patients. Flank pain, reflecting distension of the renal capsule, is also observed in about the same percentage of cases, and it can be the main complaint on admission. Ultrasonography usually discloses an increased cortical echogenicity (comparable to or higher than that of the liver), but as far as we know, the diagnostic value of this finding has not been assessed [39]. Extrarenal symptoms and signs reflecting a hypersensitivity reaction typically include low-grade fever, maculopapular rash, mild arthralgias, and eosinophilia, but each of these manifestations is present in fewer than 50% of patients, and all of them are present together in fewer than 5% of patients. With some drugs, such as rifampicin or allopurinol, other manifestations of hypersensitivity such as hemolysis or hepatitis can be present. Nevertheless, it should be emphasized that signs of hypersensitivity are not specific to AIN and they also can be observed in patients with acute renal failure not related to AIN. In a study of 81 patients with acute renal failure who had a renal biopsy, signs of hypersensitivity were found in 14% of patients with drug-induced acute tubular necrosis [40].The clinical and biologic manifestations of AIN might have some specificity, depending on the drug involved, and I would like to emphasize the particularities of AIN induced by nonsteroidal anti-inflammatory drugs (NSAIDs) and by rifampicin. Analysis of more than 80 case reports showed that NSAID-induced AIN is associated with a nephrotic syndrome in more than 70% of patients and that it usually is diagnosed in patients who have taken the drug for a few months (mean delay, 6 months). Furthermore, AIN induced by NSAID and associated with a nephrotic syndrome usually occurs in patients over 50, possibly because NSAIDs are consumed more often by elderly people. Besides these particularities, the presentation is quite similar to that of other types of drug-induced AIN (Fig. 2). The main differences are that hematuria is almost never macroscopic and extrarenal symptoms are present in only about 10% of these patients.

Not all NSAIDs have the same propensity to induce a nephrotic syndrome. Fenoprofen accounts for almost 50% of the reported cases, and other NSAIDs have only been involved in a few cases. Besides NSAIDs, a few cases of AIN associated with a nephrotic syndrome have been reported after administration of ampicillin, rifampicin, lithium, interferon, diphenylhydantoin, or D-penicillamine [41–45].

The association between rifampicin administration and AIN is common; more than 100 patients with rifampicin-induced AIN have been reported [reviewed in 46, 47]. Analysis of these cases shows that they fall into two quite different categories, patients treated over the short term with rifampicin, and those whose AIN occurs subsequent to intermittent or earlier use of the drug.

In five reported cases [46], and in today's second patient, AIN developed in patients who had been continuously treated with rifampin for one to ten weeks. The patients had mild to severe acute renal failure, and two patients had nephrotic-range proteinuria. Extrarenal symptoms were present in only one patient. In all cases,

Table 1. Drugs responsible for acute interstitial nephritis (AIN)

Antimicrobial agents	NSAIDs including salicylates	Diuretics
Acyclovir	Alclofenac	Chlorthalidone
AMPICILLIN[ab]	Azapropazone	Ethacrynic acid
Amoxicillin	ASPIRIN	FUROSEMIDE[b]
Aztreonam	Benoxaprofen	Hydrochlorothiazide[b]
Carbenicillin	Diclofenac	Indapamide
Cefaclor	Diflunisal[b]	Tienilic acid[b]
Cefamandole	Fenclofenac	Triamterene[b]
Cefazolin	FENOPROFEN	
Cephalexin	Flurbiprofen	Others
Cephaloridine	IBUPROFEN	
Cephalothin	INDOMETHACIN	
Cephapirin	Ketoprofen	ALLOPURINOL[b]
Cephradine	Mefenamic acid	Alpha-methyldopa
Cefixitin	Meloxicam	Azathioprine
Cefotetan	Mesalazine (5-ASA)	Bethanidine[b]
Cefotaxime	NAPROXEN	Bismuth salts
CIPROFLOXACIN	Niflumic acid	Captopril[b]
Cloxacillin	Phenazone	Carbimazole[b]
Colistin	PHENYLBUTAZONE	Chlorpropamide[b]
Cotrimoxazole[b]	PIROXICAM	Cyclosporine
Erythromycin	Pirprofen	CIMETIDINE
Ethambutol	Sulfasalazine	Clofibrate
Foscarnet	Sulindac	Clozapine
Gentamicin	Suprofen	Cyamethazine[b]
Indinavir	TOLEMETIN	D-penicillamine
Interferon	ZOMEPIRAC	Fenofibrate[b]
Isoniazid		Gold salts
Lincomycin	Analgesics	Griseofulvin
METHICILLIN[b]		Interferon
Mezlocillin	Aminopyrine	Interleukin-2
Minocycline	Antipyrine	OMEPRAZOLE
Nafcillin	Antrafenin	PHENINDIONE[b]
Nitrofurantoin[b]	Clometacin[b]	Phenothiazine
Norfloxacin	Floctafenin[b]	Phenylpropanolamine
Oxacillin[b]	Glafenin[b]	Probenecid
PENICILLIN G[b]	Metamizol	Propranolol
Piperacillin	Noramidopyrine	Propylthiouracil
Piromidic acid		Ranitidine
Polymyxin acid[b]	Anticonvulsants	Streptokinase
Quinine		Sulphinpyrazone
RIFAMPICIN[b]	Carbamazepine	Warfarin
Spiramycine[b]	Diazepam	
SULFONAMIDES	Phenobarbital	
Teicoplanin	PHENYTOIN[b]	
Tetracycline	Valproate sodium	
Vancomycin		

[a] Drugs most commonly involved are shown in capital letters
[b] Drugs that can induce granulomatous AIN

renal biopsy disclosed severe interstitial inflammatory infiltrates with a few tubular lesions. No patient had anti-rifampicin antibody. Renal function completely recovered in four patients after discontinuing the drug, but in two patients, the serum creatinine did not return to baseline values.

The vast majority of cases of rifampicin-induced AIN comprise patients receiving intermittent therapy or patients previously exposed to the drug [46, 47]. In these instances, symptoms occur abruptly and usually are accompanied by fever, chills, digestive manifestations (nausea, vomiting, diarrhea, abdominal pain), flank pain, and myalgias. Laboratory tests disclose thrombocytopenia and hemolysis in about one-fourth to one-third of patients, and anti-rifampicin antibodies are present in most cases. Renal biopsy usually shows substantial tubular lesions in addition to inflammatory infiltrates, but immunofluorescence staining does not reveal immune deposits. This pattern suggests that anti-rifampicin antibodies are not responsible for the renal lesions and that cell-mediated immunity plays a key role in the induction of this nephropathy.

Noninvasive diagnostic procedures

The clinical diagnosis of drug-induced AIN is quite often difficult. Two diagnostic procedures have been proposed to allow an accurate diagnosis without performing a renal biopsy: determination of eosinophiluria and gal-

Table 2. Diagnostic value of eosinophiluria

Number of patients	65	92	183	199	539
Patients with AIN					
Eosinophiluria	8	10	5	6	29
No eosinophiluria	1	1	3	9	14
Patients without AIN					
Eosinophiluria	27	12	15	10	64
No eosinophiluria	29	69	160	174	432
Reference	[48]	[49]	[50]	[51]	[48–51]

lium scanning. Galpin et al reported that at least 10% of urinary white cells were eosinophils in nine patients with methicillin-induced AIN, and this was not the case in 43 patients with renal diseases different from AIN [38]. Thus, measuring the percentage of eosinophils among urinary white cells could be helpful in making the diagnosis of AIN. Two stains have been used to detect urinary eosinophils: the classic Wright's stain and Hansel's stain, which are both eosin-methylene blue combinations. The latter appears to be much more sensitive, and in two series including a total of 19 patients with AIN, eosinophiluria was demonstrated by Hansel's stain in 15 patients (79%) and by Wright's stain in only four patients (21%) [49, 50]. Eosinophiluria is considered positive when more than 1% of white cells are stained.

Four large series have studied the usefulness of eosinophiluria for the diagnosis of AIN (Table 2) [48–51]. Because of the heterogeneity of these series, and because some cases of AIN were not confirmed by a renal biopsy but only by a retrospective analysis of the patient's file, it is difficult to draw a definite conclusion about the usefulness of eosinophiluria. Nevertheless, eosinophiluria seems to have a rather low sensitivity, and if one considers all four series, only 29 of 43 patients with AIN (67%) had eosinophiluria (Table 2). On the other hand, eosinophiluria could be relatively specific for AIN. Of 436 patients without AIN, 372 (85%) had no eosinophiluria (Table 2), and if only the 210 patients with acute renal failure are considered, the specificity of the test is similar, as 138 patients had no eosinophiluria out of 167 patients not having AIN (83%). Among patients with eosinophiluria but no AIN, renal failure can be due to diseases such as acute tubular necrosis, glomerulonephritis, atherothromboembolic renal disease, or even pre-renal azotemia [48–52]. Furthermore, in the first three series, eosinophiluria was found in 28% of 93 patients with urinary tract infection [48–50]. Urinary schistosomiasis is also associated with eosinophiluria, and in a series of 58 patients with urinary schistosomiasis, all had eosinophiluria [53].

Wood et al reported two decades ago a marked renal uptake of gallium (^{67}Ga) in three patients with AIN [54] and suggested that ^{67}Ga renal scanning could be a useful tool for the diagnosis of AIN. Isolated case reports have supported this hypothesis by showing a substantial renal uptake of ^{67}Ga in patients with AIN, but as far as we know, only one large series has been reported [55]. In this study, 44 patients with biopsy-proven renal disease, 18 patients with clinically diagnosed renal disease, and 46 patients without renal disease had renal gallium scanning. All 11 patients with biopsy-proven AIN had an intense renal ^{67}Ga uptake at 48 hours, but 9 patients without AIN also had positive renal scanning. These patients had glomerulonephritis, pyelonephritis, chronic interstitial nephritis, or even no renal disease. Thus, from this series, renal scanning appears to be a very sensitive method for identifying AIN but to have a lower specificity. Nevertheless, the sensitivity of gallium scanning has been challenged by at least two groups. In a small series of 16 patients with acute renal failure and drug-induced AIN, only 11 (69%) had positive gallium scanning [56]. In another small series of 12 patients with interstitial nephritis, only 7 (58%) had positive renal ^{67}Ga scanning, but in this series patients with a negative scan probably had a chronic interstitial nephritis rather than AIN, and none of them had drug-induced renal disease [57]. The relative lack of specificity of gallium scanning is supported by case reports describing patients with renal uptake of ^{67}Ga who had diseases such as cancer, pyelonephritis, minimal change disease, or acute renal failure associated with IgA nephropathy (personal observations) [55, 58].

Clinical presentation of AIN being quite polymorphic, and noninvasive diagnostic procedures having clear limitations, renal biopsy is often essential for the diagnosis. Its importance has been illustrated by a series of 32 patients with acute renal failure [2]. In this series, 7 patients (22%) had AIN but another diagnosis had been suspected before the biopsy. In contrast, in 25 patients thought to have AIN, biopsy confirmed the diagnosis in only 11 (44%). Let me very briefly review the well known histologic features of AIN.

The hallmark of AIN is the presence of inflammatory infiltrates within the interstitium. These infiltrative lesions can be diffuse, but often they are patchy, predominating in the deep cortex and in the outer medulla. They are composed mostly of T-cells and of monocytes/macrophages; plasma cells, eosinophils, and a few neutrophilic granulocytes also can be present. Among T-cells present within the interstitium, the relative number of CD4+ T-cells and CD8+ T-cells appears to be quite variable from one patient to another [59–63]. The relative representation of T-cells is probably influenced by the noxious drug, but also by other factors such as the genetic background of the patient. Infiltrating cells sometimes form granulomas, which are usually sparse, non-necrotic, with a few giant cells, and associated with non-granulomatous interstitial infiltrates. In some cases, T-lymphocytes infiltrate across the TBM and between tubular cells, causing what is known as tubulitis.

Interstitial infiltrates are always associated with an

interstitial edema separating the tubules. They also can occur with focal tubular lesions, which range from mild cellular alterations to extensive necrosis of epithelial cells, and which sometimes disrupt the TBM. These tubular lesions usually predominate where the inflammatory infiltrates are most extensive. Vessels and glomeruli appear normal, and even in AIN associated with a nephrotic syndrome, the structure of the glomeruli is preserved on light microscopy, and only on electron microscopy can fusion of foot processes be seen.

In the vast majority of cases, renal biopsies from patients with AIN do not show immune deposits. Nevertheless, linear staining of the TBM for IgG occasionally can be seen, mostly in patients taking methicillin, an NSAID, phenylhydantoin, or allopurinol. Immune deposits indicate the presence of antibodies directed against membrane antigens or against drug metabolites bound to the TBM.

Course and treatment

Based on the course of methicillin-induced AIN, drug-induced AIN has long been considered a relatively benign nephropathy, and complete recovery of renal function was supposed to be the rule if the inciting agent was removed. Nevertheless, even in the case of methicillin-induced AIN, although hematuria, leukocyturia, and extrarenal manifestations usually disappeared within two weeks, complete recovery of renal function often was delayed, with a mean recovery time of about 1.5 months. Analysis of published cases of AIN induced by drugs other than methicillin and review of our own cases show that nowadays the course of drug-induced AIN is far from always being benign, and that the serum creatinine level remains elevated in about 40% of patients (Fig. 3A).

It would be clinically important if we could identify patients with drug-induced AIN who are at high risk of incomplete recovery. Unfortunately, few prognostic factors are available. One could have assumed that the severity of renal failure was correlated with the prognosis, but analysis of different series suggests that maximal serum creatinine levels have little prognostic value (Fig. 3B). Most histologic data also appear not to predict outcome. In a series of 30 patients with AIN, renal prognosis was less favorable when interstitial infiltrates were diffuse and not patchy; at the end of follow-up, mean serum creatinine was higher than 175 μmol/L (2.0 mg/dL) in 10 of 18 patients with diffuse infiltrates (55%), whereas it was below 100 μmol/L (1.1 mg/dL) in 9 of 12 patients with patchy infiltrates (75%) [64]. Nevertheless, in two other studies including 27 and 14 patients respectively, no correlation could be established between the extent of interstitial infiltrates and either the long-term outcome or the duration of renal failure [2, 65]. Other authors have suggested that the presence of granulomas in the renal interstitium indicates poor prognosis, but this also has not been established. A small series suggests that the severity of tubulitis is not predictive of the outcome [63]. In this last series, as in a larger one [66], the main prognostic factor was the severity of the interstitial fibrosis, but this factor was not of prognostic value in a third series of 10 patients [62]. It is possible that these discrepancies regarding the prognostic value of histologic lesions arise from the fact that renal biopsies were performed at different times after the onset of AIN.

The best prognostic factors might be the duration of acute renal failure and/or renal function a few weeks after the diagnosis. In a series of 30 patients, mean serum creatinine values at the end of follow-up were about 120 μmol/L (1.4 mg/dL) when acute renal failure lasted less than two weeks, and about 300 μmol/L (3.4 mg/dL) when it lasted more than three weeks [64]. In another series of 14 patients, serum creatinine values at the end of follow-up closely correlated with renal function 6 to 8 weeks after the diagnosis [65].

Removing the drug responsible for AIN is probably the most important aspect of treatment, and administration of the inciting agent should be stopped as soon as possible. The possibility that AIN evolves toward chronic renal failure prompted different researchers to treat patients not only by removing the inciting drug, but also by administering a brief course of corticosteroids. Therapeutic regimens have been variable, but most patients received an initial dose of 1 mg/kg/day prednis(ol)one, which was then tapered over a few weeks. Analysis of seven series comparing patients who received corticosteroids with others who did not indicated that corticosteroids did not decrease the risk of chronic renal failure [2, 38, 56, 66–69]. In 52 patients who received corticosteroids, serum creatinine levels remained above 200 μmol/L (2.3 mg/dL) in 17% of cases and decreased below 110 μmol/L (1.3 mg/dL) in only 58%. Similarly, in 48 patients who did not receive corticosteroids, serum creatinine levels remained above 200 μmol/L (2.3 mg/dL) in 19% and decreased below 110 μmol/L (1.3 mg/dL) in only 52%. Nevertheless, I should stress that all seven series are small, non-randomized, and retrospective, and that renal failure tended to be more severe in patients receiving corticosteroids than in those not treated with corticosteroids [mean maximum serum creatinine values, 818 μmol/L (9.3 mg/dL) vs. 570 μmol/L (6.5 mg/dL), respectively]. In contrast, a brief course of corticosteroids can hasten the recovery of renal function [2, 69]. For example, in ten patients whose renal function did not improve within 5 to 20 days after the inciting drug was stopped, administration of pulse methylprednisolone for three days or of prednisolone (40 to 60 mg/day for three to four weeks) quickly induced a dramatic decrease of serum creatinine values [2]. One can thus suggest administering a short course of prednis(ol)one in patients whose renal function fails to improve within one week after stopping the inciting drug, provided that the diagnosis of AIN has been

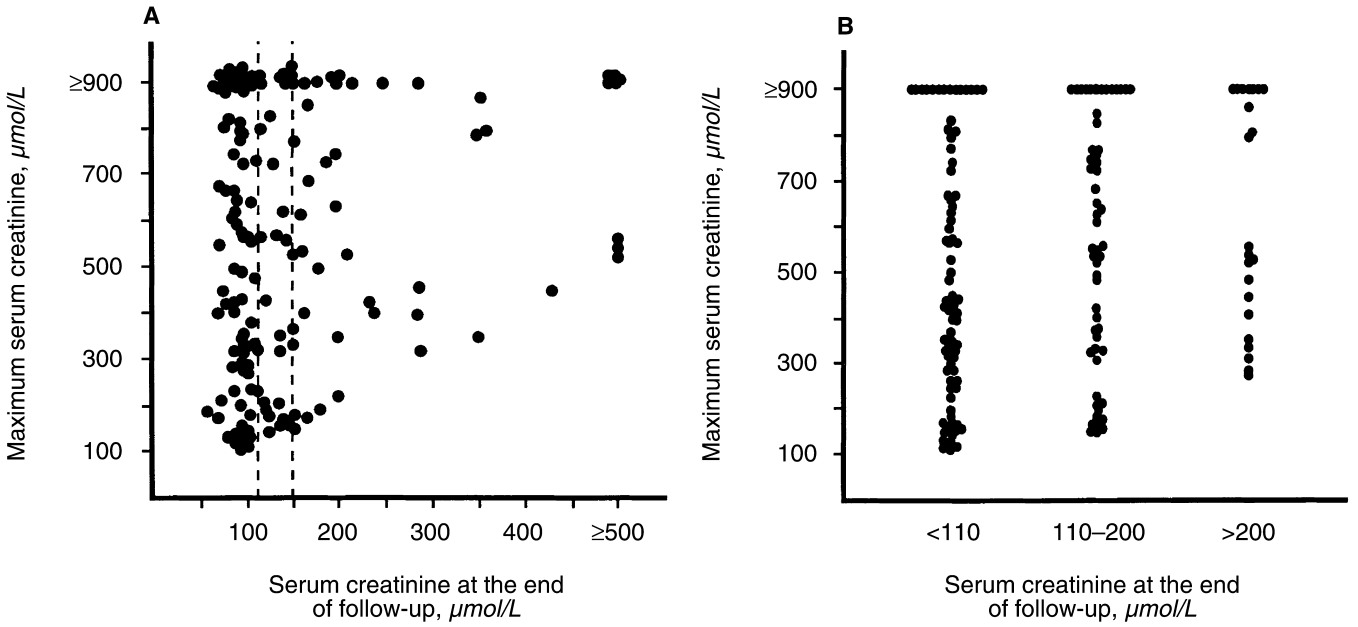

Fig. 3. Evolution of renal function in patients with drug-induced AIN, as a function of maximum serum creatinine levels. (*A*) Correlation between maximum serum creatinine values and serum creatinine values at the end of follow-up. Only 68% and 49% of patients had serum creatinine levels below 150 μmol/L (1.7 mg/dL) and 110 μmol/L (1.2 mg/dL) at the end of follow-up, respectively. (*B*) Patients were arbitrarily divided into three groups depending on serum creatinine levels at the end of follow-up: patients with serum creatinine below 110 μmol/L (1.2 mg/dL); patients with serum creatinine between 110 and 200 μmol/L (1.2 and 2.2 mg/dL), and patients with serum creatinine above 200 μmol/L (2.2 mg/dL). Maximum serum creatinine levels did not differ among these three groups. S, serum.

confirmed by renal biopsy. Our tendency is also to use corticosteroids in patients whose nephropathy has evolved for more than two to three weeks. It is of note that in patients with NSAID-induced AIN, corticosteroids do not seem to modify the course of the nephrotic syndrome.

In conclusion, the clinical spectrum of drug-induced AIN has largely changed since the time when methicillin was the most frequent culprit. Clinicians now have to face two problems. The first is the diagnosis of drug-induced AIN in patients with isolated acute renal failure. Renal biopsy remains an essential tool in most cases, even though the presence of eosinophiluria may be helpful. The second is the prevention of interstitial fibrosis. Corticosteroids are the only drugs available so far, but they seem to be more effective in accelerating the recovery of renal function than in preventing interstitial fibrosis. In the coming years, a better understanding of the mechanisms responsible for the interstitial infiltration by inflammatory cells, and for the increased production of extracellular matrix within the interstitium, should help define new therapeutic agents.

QUESTIONS AND ANSWERS

Dr. Nicolaos E. Madias (*Executive Academic Dean, Tufts University School of Medicine, Boston, Massachusetts, USA*): Thank you very much, Dr. Rossert, for a wonderful presentation. You presented a number of molecules of the TBM that can function as antigens in tubulointerstitial nephritis. Could you tell us more about some of them in terms of their structure, expression, and whether their nephritogenic domains have similarities?

Dr. Rossert: Different groups have tried to precisely identify molecules of the TBM that are recognized by anti-TBM antibodies and that can induce AIN. In 1991, Eric Neilson and colleagues cloned a cDNA encoding a peptide that is recognized by anti-3M-1 antibodies, that is, antibodies recognizing a 48 kD protein involved in the pathogenesis of experimental AIN; this peptide is present within cortical TBM and appears to harbor a major nephritogenic epitope [70], but the proteins containing this peptide are still unknown. In 1992, Kazuo Yoshioka and coworkers purified and partially sequenced a protein called gp54 [71]. Recognized by sera from patients with anti-TBM nephritis, it can induce experimental AIN, and it is present selectively in the basement membrane of proximal tubules. In 1995, Todd Nelson et al cloned a cDNA encoding a third protein, called TIN-Ag/TIN1, which is a 58 kD glycoprotein that is recognized by sera from patients with anti-TBM AIN [72]. This protein, which is expressed mainly in the renal cortex, interacts with type IV collagen and laminin and promotes cell adhesion. Recently, an alternative spliced form of *TIN-Ag*, called TIN2, was described in humans [73]. Interestingly, the antisera used to characterize TIN-Ag/TIN1 also can immunoprecipitate 3M-1 and gp54; this

finding suggests that different nephritogenic proteins are present within the TBM and have similar nephritogenic epitopes. Nevertheless, the peptide cloned by Eric Neilson and thought to represent a major nephritogenic domain of 3M-1 is not present in TIN-Ag/TIN1.

Dr. Madias: You mentioned that in a significant number of patients, the AIN evolves towards chronicity and interstitial fibrosis. We could probably learn a fair amount about the mechanisms of this process by studying the normal repair process. Can you tell us a little bit about the biology of repair in AIN?

Dr. Rossert: Two different aspects comprise this reparation process: one is the resolution of the interstitial inflammatory reaction, and the other is the repair of the damaged tubules. Resolution of inflammatory reactions is a complex process that is far from being limited to a decreased production of pro-inflammatory factors. It also involves a progressive resistance of cells to pro-inflammatory mediators, an inactivation of these mediators by soluble molecules, and the production of anti-inflammatory factors [reviewed in 74]. These anti-inflammatory factors include cytokines such as IL-4, IL-6, IL-10, IL-11, IL-13, and TGF-β, but also by-products of heme catabolism, neuropeptides such as somatostatin, and products of arachidonic acid metabolism. Anti-inflammatory arachidonic acid derivatives include cyclopentenone prostaglandins and lipoxygenase derivatives. Cyclopentenone prostaglandins, such as PGD2 or 15 deoxy$\Delta^{12\text{-}14}$PGJ2, exert their anti-inflammatory effects by decreasing the production of nitric oxide, of cytokines such as TNF-α, and of chemoattractants such as monocyte chemoattractant protein-1 (MCP-1). Lipoxygenase derivatives, such as 15-HETE and lipoxins, have anti-inflammatory properties that are mediated through an inhibition of the influx of polymorphonuclear cells and through their ability to bind to PPAR-γ, which is a member of the nuclear receptor superfamily, respectively. The repair of tubular lesions probably occurs through a proliferation of tubular cells that did not undergo apoptosis or necrosis. As Robert Safirstein recently highlighted [75], if a pathway involving mitogen-activated protein kinases (MAPK) such as stress-activated protein kinases and p38 MAPK is antiproliferative and cytoreductive, another MAPK pathway promotes cell survival and proliferation through the activation of extracellular regulated kinases and the expression of p21, which is a cyclin-dependent kinase inhibitor. This latter pathway is activated by growth factors such as EGF or TGF-α, and it might play an important role in the repair process of tubular lesions.

Dr. Madias: Dr. Rossert, can we inhibit CTGF?

Dr. Rossert: Connective tissue growth factor (CTGF) could be a very important molecule to target to inhibit TGF-β-induced fibrotic processes, but so far we do not have a good tool for inhibiting CTGF in vivo. Nevertheless, since in vitro cyclic AMP can inhibit the production of CTGF induced by TGF-β, one possibility would be to modulate the cellular levels of cyclic AMP [21].

Dr. John Feehally (*Department of Nephrology, Leicester General Hospital, Leicester, UK*): How characteristic are eosinophils in the kidney as a feature of interstitial infiltrates, and do you believe that they have any special role in the pathophysiology of AIN?

Dr. Rossert: Eosinophils can be present within the interstitial inflammatory infiltrates, but they do not seem to be characteristic of drug-induced AIN. In a series of 12 children with AIN, 7 of 8 patients with drug-induced AIN had renal eosinophilia but 3 of 4 children with AIN not induced by a drug also had renal eosinophilia [76]. Similarly, eosinophils can be present within interstitial infiltrates during the course of acute rejection. It is tempting to speculate that the presence of eosinophils is secondary to an infiltration by TH2 cells and to the production of cytokines such as IL-5. Regarding the pathogenetic role of eosinophils, they produce toxic cationic molecules that probably participate in tubular damage, and they also synthesize pro-inflammatory lipid mediators, which can contribute to the inflammatory process [reviewed in 77]. The prognostic value of renal eosinophilia has not been carefully studied in patients with drug-induced AIN, but in patients with acute renal allograft rejection, renal eosinophilia has been associated with an increased risk of graft loss [78].

Dr. Madias: Do the subsets of lymphocytes identified on biopsy have any special significance pathophysiologically or prognostically?

Dr. Rossert: Different series have studied the percentage of CD4+ and of CD8+ T-cells present within the interstitial infiltrates. When these series are analyzed together, the percentages of CD4+ and of CD8+ T-cells vary considerably from one biopsy to the other. While it was initially suggested that these percentages depend on the drug involved, other factors are obviously also quite important, one of them probably being the time of the biopsy and another one the genetic background of the patient. It would be tempting to try to associate the presence of CD8+ T-cells with more severe tubular damage, and the presence of CD4+ T-cells with the presence of higher numbers of monocytes/macrophages, but so far this is purely speculative. Similarly, to date no data have suggested that the prognosis of drug-induced AIN correlates with the subsets of T-cells present within the interstitial infiltrates, but detailed analyses of infiltrating T-cells have only been performed in small series of renal biopsies.

Dr. Bruno Moulin (*Department of Nephrology, Hôpitaux Universitaires, Strasbourg, France*): Jérôme, you mentioned the subset of AIN with granulomas on renal biopsy. Could you comment on the mechanisms responsible for this type of AIN, and do you know whether it is more responsive to corticosteroids?

Dr. Rossert: Granulomatous AINs are secondary to delayed-type hypersensitivity reactions, and thus to cell-mediated immune responses involving TH1 cells. There are no data suggesting that patients with granulomas have a different prognosis, or that they respond differently to treatment with corticosteroids, but once more, you have to keep in mind that available data are only coming from small series.

Dr. Ghulam Malik (*Security Forces Hospital, Riyadh, Saudi Arabia*): We know that nonsteroidal anti-inflammatory drugs can cause hemodynamically-mediated acute renal failure, and that they also can cause AIN. How do we differentiate between these two entities?

Dr. Rossert: Prostaglandins play a significant role in the maintenance of renal blood flow only in the setting of decreased actual or effective circulating volume. Thus, for patients taking an NSAID, hemodynamically-mediated acute renal failure occurs mostly with an associated disease such as congestive heart failure, cirrhosis, or chronic renal insufficiency, or in the presence of hypovolemia. Furthermore, this acute renal failure is not associated with proteinuria, hematuria, or extrarenal symptoms, but these signs are present in about one-third to two-thirds of patients with NSAID-induced AIN. Finally, although hemodynamically-mediated acute renal failure can be responsible for acute tubular necrosis when ischemia is severe and persistent, most cases improve rapidly after the drug is discontinued, whereas resolution of AIN is a relatively more prolonged process. Only when renal function does not improve rapidly after the drug is discontinued can one perform a renal biopsy to distinguish between NSAID-induced acute tubular necrosis and NSAID-induced AIN.

Dr. Hemant Mehta (*Lilavati Hospital and Research Centre, Bandra Reclamation, Mumbai, India*): Are Cox-2-selective inhibitors safe from a renal point of view, and have they been responsible for AIN?

Dr. Rossert: While Cox-1 is constitutively expressed in most cells and tissues, Cox-2 is expressed only in activated cells. Cox-2-selective inhibitors thus could have fewer side effects than do conventional NSAIDs, which inhibit both Cox-1 and Cox-2. Regarding the kidney, most available clinical data suggest that Cox-2 is involved in the regulation of sodium reabsorption, but its role in maintaining renal hemodynamics, and thus renal function, is more controversial. Until further studies become available, clinicians should probably remember the early enthusiasm for sulindac, and assume that Cox-2-selective inhibitors carry the same risk of impairing renal function as conventional NSAIDs [79]. Regarding the risk of AIN, I am not aware of any paper describing a case of AIN induced by a Cox-2-selective inhibitor, but once more, we must be careful because sometimes such rare side effects are described only when large numbers of patients have received the drug.

Dr. Mehta: Rifampicin causes AIN when given continuously or intermittently. Do the mechanisms of AIN differ in these two settings? In which case will anti-rifampicin antibodies be found, and when do they appear?

Dr. Rossert: As de Vriese et al recently pointed out, with few exceptions, rifampicin given continuously is responsible for AINs that are not associated with anti-rifampicin antibodies or with extrarenal symptoms such as hemolytic anemia or thrombocytopenia [46]. By contrast, intermittent regimens are responsible for acute renal failure associated with anti-rifampicin antibodies, with gastrointestinal symptoms, and in about one-third of the patients with hemolytic anemia and/or thrombocytopenia. Furthermore, in the latter instance, renal biopsy typically shows significant tubular lesions associated with mild interstitial infiltrates, while in the former, biopsy shows mostly substantial inflammatory interstitial infiltrates. Thus, the mechanisms responsible for acute renal failure might not be the same in both cases, and a key difference could be the presence of anti-rifampicin antibodies. Since rifampicin appears to bind the I antigen, which is expressed by red blood cells and by platelets, but also by tubular epithelial cells, one hypothesis is that rifampicin binds to tubular cells, and that anti-rifampicin antibodies participate in the induction of tubular lesions [46]. Nevertheless, one should keep in mind that patients can have anti-rifampicin antibodies and no renal lesion. Regarding the delay between treatment initiation and appearance of anti-rifampicin antibodies, there has been no systematic study, but a review of the published cases shows that the delay between treatment initiation and occurrence of an acute renal failure is highly variable, ranging from three weeks to about one year [46].

Dr. Malik: When should we perform a renal biopsy in patients suspect of having AIN?

Dr. Rossert: The answer to this question depends largely on the clinical presentation of the patient. When acute renal failure occurs one to two weeks after starting a new treatment in a patient with no concomitant disease that could affect renal function, and the acute renal failure is associated with extrarenal symptoms of hypersensitivity and with eosinophiluria, it is probably not necessary to perform a renal biopsy. Nevertheless, the clinical presentation is much less suggestive in most patients, and it is quite difficult to make an accurate diagnosis without performing a renal biopsy. In a series of 32 patients, less than 50% of the subjects with clinically suspected AIN actually had AIN [2]. Most of the others had acute tubular necrosis, and two had extracapillary glomerulonephritis. Our own policy is to perform a renal biopsy in patients with clinically suspected AIN before starting treatment with corticosteroids (that is, when renal function does not improve within one week after the eliciting drug is discontinued, or when patients are referred while the nephropathy has been evolving for more than two

to three weeks), when the drug suspected of having induced the AIN is important for treating the patient (either at the time of acute renal failure or in the future), or when differential diagnoses include renal disease that could necessitate a specific treatment.

Dr. Doris M. W. Kinuthia (*Aga Ichan Hospital, Nairobi, Kenya*): When you decide to give corticosteroids to a patient with drug-induced AIN, which regimen do you use?

Dr. Rossert: We start with 1 mg/kg/day of prednisone, and after about one week we rapidly taper the dose to stop the treatment after about one month.

Dr. Georgi Abraham (*Sri Ramachchandra University Hospital, Chennai, India*): Angiotensin II might be responsible for interstitial fibrosis. Could ACE inhibitors be used to retard the progression of interstitial nephritis?

Dr. Rossert: Experimental data show that angiotensin II can increase the synthesis of extracellular matrix through different pathways, and in particular by increasing the production of TGF-β. Nevertheless, the involvement of angiotensin II in the development of interstitial fibrosis probably is quite variable depending on the underlying disease. For example, while ACE inhibitors slow the progression of chronic renal failure in patients with glomerulonephritis and proteinuria exceeding 1 g/day, no strong data suggest that ACE inhibitors slow the progression of renal failure in patients without proteinuria. Post-hoc analysis of the AIPRI study even suggests that patients with nephrosclerosis or interstitial nephritis did not benefit from treatment with an ACE inhibitor [80]. Thus, today it is difficult to advocate the use of ACE inhibitors in patients with persistently elevated serum creatinine after an episode of AIN.

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