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Acute interstitial nephritis

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Acute interstitial nephritis (AIN) represents a frequent cause of acute kidney injury, accounting for 15–27% of renal biopsies performed because of this condition. By and large, drug-induced AIN is currently the commonest etiology of AIN, with antimicrobials and nonsteroidal anti-inflammatory drugs being the most frequent offending agents. Pathogenesis is based on an immunologic reaction against endogenous nephritogenic antigens or exogenous antigens processed by tubular cells, with cell-mediated immunity having a major pathogenic role. The characteristic interstitial infiltrates, mostly composed of lymphocytes, macrophages, eosinophils, and plasma cells, experience a rapid transformation into areas of interstitial fibrosis. A significant proportion of AIN has nowadays an oligosymptomatic presentation, although the presence of specific extrarenal symptoms such as fever, skin rash, arthralgias, and peripheral eosinophilia has an important role to orientate clinical diagnosis. Identification and removal of the offending drug are the mainstay of the treatment, but recent studies strongly suggest that early steroid administration (within 7 days after diagnosis) improves the recovery of renal function, decreasing the risk of chronic renal impairment. Delayed steroid treatment, when interstitial fibrosis has taken place, would have a less pronounced or nule therapeutic benefit.

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DEFINITION AND ETIOLOGY

Acute interstitial nephritis (AIN) is characterized by the presence of inflammatory infiltrates and edema within the interstitium, usually associated with an acute deterioration in renal function. AIN represented 1–3% of all renal biopsies in some studies.[1,2] However, when the analysis was restricted to patients with acute kidney failure, AIN accounted for 15–27% of lesions.[3,4] These studies suggest that AIN is a common cause of acute renal dysfunction, but its true incidence might even be underestimated by several reasons. First, a significant number of patients in whom AIN is suspected on clinical grounds is not submitted to a confirmatory renal biopsy because empirical treatment is preferred, particularly in elderly and frail patients. Second, milder forms of AIN can be underdetected, either because of the absence or vagueness of clinical symptoms or because acute renal failure is attributed to other causes of renal injury.

As shown in Table 1, the main causes of AIN can be grouped as drug induced, infection related, idiopathic forms (which would include tubulointerstitial nephritis and uveitis syndrome (TINU) and anti-tubular basement membrane (anti-TBM) disease), and AIN associated with sarcoidosis and other systemic diseases (systemic lupus erythematosus, Sjögren, malignancies). Tubulointerstitial lesions that frequently accompany primary glomerulonephritis are usually not included within AIN. Regarding the frequency of these different etiologies, drug-induced AIN currently accounts for more than two-thirds of the cases, infection-related AIN for 15%, idiopathic forms for 10%, and TINU for 4%, the remaining ones being associated with systemic disorders.[5–7] However, the prevalence of drug-induced AIN could have even increased in the last years: according to our own experience (data not published), drugs were responsible for more than 90% of biopsy-proven AIN occurring during the period 2000–2008.

A large and expanding number of drugs has been implicated in causing AIN and it can be stated that any drug can theoretically induce an episode of AIN. However, the majority of cases have been caused by antimicrobial agents and nonsteroidal anti-inflammatory drugs (NSAIDs). Table 1 lists those drugs most commonly involved in AIN.

PATHOGENESIS

It is generally accepted that the initial event unleashing an AIN episode is the expression of endogenous nephritogenic antigens or exogenous antigens processed by tubular cells.

Table 1 | Etiology of biopsy-proven AIN

Drugs (>75% of AIN)	Antibiotics: ampicillin, cephalosporins, ciprofloxacin, cloxacillin, methicillin, penicillin, rifampicin, sulfonamides, vancomycin. NSAIDs Other: allopurinol, acyclovir, famotidine, furosemide, omeprazole, phenytoin
Infections (5–10%)	Bacteria: *Brucella*, *Campylobacter*, *Escherichia coli*, *Legionella*, *Salmonella*, *Streptococcus*, *Staphylococcus*, *Yersinia* Viruses: cytomegalovirus, Epstein–Barr, hantavirus, human immunodeficiency virus, polyomavirus Other: *Leptospira*, *Mycobacterium tuberculosis*, *Mycoplasma*, *Rickettsia*, *Schistosoma*, *Toxoplasma*
Idiopathic (5–10%)	Anti-TBM TINU
Associated with systemic diseases (10–15%)	Sarcoidosis, Sjögren, systemic lupus erythematosus

Abbreviations: AIN, acute interstitial nephritis; NSAID, nonsteroidal anti-inflammatory drug; TBM, tubular basement membrane; TINU, tubulointerstitial nephritis and uveitis syndrome.
Most commonly involved causative agents.

Immunization of rabbits or rats with Tamm–Horsfall protein or megalin (a protein localized in the brush border of proximal tubular cells) induced an AIN,[8] thus suggesting a possible pathogenic role of these proteins as endogenous antigens in the development of some human AIN. Other endogenous antigens implicated in AIN have been identified as components of TBM, such as the tubulointerstitial nephritis antigen, a glycoprotein important for TBM integrity and whose molecular composition has been cloned and sequenced.[9] Tubulointerstitial nephritis antigen is likely to be the target for some human cases of anti-TBM AIN, an uncommon entity in which circulating anti-TBM antibodies that react specifically with proximal TBM are found. The mechanisms involved in the appearance of such antibodies, as well as the proportion of human idiopathic AIN that are caused by this pathogenic mechanism, remain unknown. Anti-TBM AIN is occasionally manifested in association with membranous nephropathy.[10]

The above-referred antigens are likely to be responsible for most idiopathic types of AIN. The pathogenesis of the more common drug-induced AIN is also believed to have an immunologic basis, as indicated by the relatively common appearance of extrarenal manifestations of hypersensitivity, its dose-independent character, and the recurrence of AIN after re-exposure to the offending drug.[11] Medications and specific microbial antigens could elicit an immune reaction after their interstitial deposition (planted antigens). Conversely, tubular cells have the capacity to hydrolyze and process exogenous proteins. In this regard, medications can bind to a normal component of TBM, behaving as a hapten, or can mimic an antigen normally present within the TBM, inducing an immune response directed against this antigen (reviewed by Rossert[11]). Although evidence is not so strong, some microbial antigens could also induce AIN through these mechanisms.

The fact that only a minority of patients treated with a particular drug or suffering an infectious process develop AIN indicates that the expression of nephritogenic antigens at renal tubulointerstitium is likely counterbalanced by complex protective mechanisms, mainly involving suppressor T cells.[12] When these protective mechanisms are surpassed (likely on the basis of a genetically determined susceptibility) and AIN ensues, both experimental studies and cumulative evidence in humans indicate that cell-mediated immunity has the major pathogenic role.[12,13] Target antigen, or one cross-reactive with it, is presented to T cells. Activated T-helper cells induce the differentiation of other effector T cells, such as those mediating delayed-type hypersensitivity and cytotoxicity. With the exception of anti-TBM disease and some cases of drug-induced AIN (mainly those related to methicillin), immunofluorescence studies in renal biopsies of patients with AIN are generally negative, indicating the absence of antibody-mediated immunity that has a marginal, if any, pathogenic role.

The inflammatory cellular infiltrates that characterize AIN, mainly composed of T lymphocytes and macrophages, are a powerful source of cytokines that increase the production of extracellular matrix and the number of interstitial fibroblasts, and induce an amplification process recruiting more inflammatory cells and eosinophils into the interstitium.[12,13] Particularly decisive for the final outcome of renal function is the rapid transformation of these inflammatory lesions into destructive fibrogenesis, a process that can be detected after only 7 days of interstitial inflammation.[14] Interstitial fibrosis is marked by the loss of renal tubules and the accumulation of fibroblasts and extracellular matrix proteins (collagens, fibronectin, laminin). There is a number of profibrotic cytokines and growth factors actively synthetized by inflammatory cells that have a crucial role in the progression of interstitial fibrosis, such as transforming growth factor-β, platelet-derived growth factor-BB, endothelin-1, epidermal growth factor, and fibroblast growth factor-2. These mediators are also an important stimulus for local epithelial-to-mesenchymal transition that affects tubular epithelium after injury.[14] Fibroblasts derived from epithelial-to-mesenchymal transition have a crucial role in tubulointerstitial fibrosis.[15] However, some recent studies have cast doubts about the implication of epithelial-to-mesenchymal transition in renal fibrosis.[16]

PATHOLOGY

The characteristic inflammatory cell infiltrates of AIN (Figure 1) can be diffuse or patchy. Interstitial edema is a typical finding, whereas glomeruli and vessels are distinctly normal. Interstitial infiltrates are mostly composed of lymphocytes (CD4+ T cells being the most abundant type), macrophages, eosinophils, and plasma cells. Interstitial granulomas can be observed in some cases of drug-induced AIN, but the possibility of sarcoidosis, tuberculosis, and some other infections must be kept in mind when they are found.

Results of immunofluorescence studies are negative in most of patients, although granular or linear deposits of IgG