
The changing profile of acute tubulointerstitial nephritis

Richard J. Baker¹ and Charles D. Pusey²

¹Renal Unit, St James University Hospital, Beckett Street, Leeds and ²Renal Section, Division of Medicine, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, UK

Keywords: acute renal failure; acute tubulointerstitial nephritis; steroids; tubulointerstitial nephritis and uveitis syndrome

‘Cellular and fluid exudation in the interstitial tissue...’ was described by Councilman in 1898 when he examined the kidneys of patients dying of scarlet fever and diptheria [1]. In particular he noted that the organs were sterile thus raising the possibility of an allergic-type phenomenon. This entity was termed acute tubulointerstitial nephritis (ATIN). The widespread introduction of percutaneous renal biopsy led to the discovery of similar findings in association with drug-related renal failure, in particular related to the use of penicillins and sulphonamides. Histological examination in ATIN reveals an infiltrate, which is largely composed of T cells, together with some macrophages and plasma cells. As there is some evidence for cutaneous delayed-type hypersensitivity and positive in vitro lymphocyte stimulation tests in response to suspected drugs, the aetiology is presumed to be immune-mediated [2]. This is illustrated by the rapid recrudescence of disease upon inadvertent rechallenge in drug-related ATIN, a clear manifestation of an immunological memory response [3–5].

Correspondence and offprint requests to: Dr Richard Baker, Renal Unit, St James University Hospital, Beckett Street, Leeds LS9 7TF, UK. Email: richard.baker@leedsth.nhs.uk

© 2003 European Renal Association-European Dialysis and Transplant Association

DOI: 10.1093/ndt/gfg464

The changing profile of acute tubulointerstitial nephritis

Richard J. Baker¹ and Charles D. Pusey²

¹Renal Unit, St James University Hospital, Beckett Street, Leeds and ²Renal Section, Division of Medicine, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, UK

Keywords: acute renal failure; acute tubulointerstitial nephritis; steroids; tubulointerstitial nephritis and uveitis syndrome

‘Cellular and fluid exudation in the interstitial tissue...’ was described by Councilman in 1898 when he examined the kidneys of patients dying of scarlet fever and diptheria [1]. In particular he noted that the organs were sterile thus raising the possibility of an allergic-type phenomenon. This entity was termed acute tubulointerstitial nephritis (ATIN). The widespread introduction of percutaneous renal biopsy led to the discovery of similar findings in association with drug-related renal failure, in particular related to the use of penicillins and sulphonamides. Histological examination in ATIN reveals an infiltrate, which is largely composed of T cells, together with some macrophages and plasma cells. As there is some evidence for cutaneous delayed-type hypersensitivity and positive in vitro lymphocyte stimulation tests in response to suspected drugs, the aetiology is presumed to be immune-mediated [2]. This is illustrated by the rapid recrudescence of disease upon inadvertent rechallenge in drug-related ATIN, a clear manifestation of an immunological memory response [3–5].

Correspondence and offprint requests to: Dr Richard Baker, Renal Unit, St James University Hospital, Beckett Street, Leeds LS9 7TF, UK. Email: richard.baker@leedsth.nhs.uk

© 2003 European Renal Association-European Dialysis and Transplant Association
Prevalence and clinical picture

Amongst asymptomatic Finnish army recruits, biopsied for either haematuria or proteinuria, the incidence of ATIN was 0.7 per 100 000 [6]. However, in a series of 109 patients from a large centre, biopsied for unexplained renal impairment with normal sized kidneys, ATIN accounted for 29 of 109 (27%) cases [7]. Thus, ATIN represents a significant cause of acute renal failure in hospital practice.

Many previous series comprise cases predominantly caused by beta-lactam antibiotics and sulphonamides, and in these series there is a high incidence of ‘allergic-type’ features, notably rash, fever, arthralgia and eosinophilia [3,8–14]. We have recently analysed our own experience of this condition with 33 cases over a 15-year period (1986–2001), alongside two of the largest contemporary series, and together they yield a total of 128 patients [15,16]. These series span a period from 1968 to 2001 and consist of 72 of 128 (56.3%) males with a mean age of 46.6 years (range 16–79). At presentation, rash was present in only 19 of 128 (14.8%), fever in 35 of 128 (27.3%) and eosinophilia in 14 of 60 (23.3%). The classic triad of fever, arthralgia and rash was present in only six of 60 (10%) patients for whom the information was available. This finding is in stark contrast to earlier series where allergic-type features dominated the clinical picture.

Diagnosis

A number of clinical tests have been proposed as possibly diagnostic for ATIN, including urinary eosinophilia and gallium scanning; however, none has withstood further scrutiny. While it is true that most patients will have low-level haematuria and subnephrotic range proteinuria, these tests are not specific enough for diagnosis, although they may suggest the need for biopsy. Enlarged renal bipolar length can be deemed supportive of the diagnosis of ATIN in the correct clinical context, but is not specific and firm diagnosis still depends upon renal biopsy.

Aetiology

In the three series reviewed, the aetiology was drug-related in 91 of 128 (71.1%), with antibiotics accounting for about a third of these cases. Twenty of 128 (15.6%) were infection-related, 10 of 128 (7.8%) were idiopathic, six of 128 (4.7%) due to the tubulo-interstitial nephritis and uveitis syndrome (TINU) and one of 128 (0.8%) due to sarcoidosis. Many drugs contributed the development of ATIN in these series and the need for ongoing vigilance is emphasized by recent reports of ATIN associated with COX-2 inhibitors, omeprazole and indinavir [17–20]. The overall picture that emerges is of a syndrome that is becoming both increasingly non-specific in clinical features and diverse in aetiology.

In four cases in our own series the causative agent was presumed to be Mycobacterium tuberculosis on clinical grounds, although organisms were not grown from renal tissue. In all four cases, renal disease developed prior to starting anti-tuberculous drug therapy and renal function improved after the commencement of therapy. This mechanism could possibly contribute to the observation that Asian patients, who have a higher risk of tuberculosis, have an increased incidence of end-stage renal disease secondary to chronic tubulointerstitial nephritis [21–23].

TINU syndrome

In our series there were six cases of the TINU syndrome, which was first reported in 1975 as an association between ATIN and anterior uveitis, sometimes associated with bone marrow granulomas [24,25]. Although associations with both chlamydia and mycoplasma infections have been suggested, the aetiology remains obscure [26]. The uveitis may occur several weeks before, or up to 3 months after, the ATIN. Amongst adults, females usually predominate (3:1). They generally suffer from weight loss and anaemia, and have a raised ESR. Prolonged steroid therapy usually leads to improvement in both renal function and uveitis, although the latter may relapse [27]. In our series, five out of six (83.3%) cases of TINU occurred in women with ages ranging from 25–50 years (mean 32). Three of the six (50%) cases had suffered from weight loss and in all cases the uveitis predated the presentation with ATIN. All six patients were treated with steroids and the renal outcome was good at 3 months (creatinine 88–184 μmol/l, median 142 μmol/l).

Outcome and prognostic factors

In most historical series, recovery of function has been observed in the great majority of cases. Reviewing the three modern series, only 82 of 128 (64.1%) made a full recovery (creatinine < 132 μmol/l), while 30 of 128 (23.4%) gained a partial recovery (creatinine > 132 μmol/l) and 16 of 128 (12.5%) remained on renal replacement therapy. This relatively poor outcome may reflect the different case-mix in recent series, with less patients having traditional allergic-type ATIN. Clearly it would be useful to have prognostic indicators for ATIN and it has been suggested previously that the long-term outcome is worse if renal failure lasts for > 3 weeks [10,13]; however, this is not useful prospectively. Two series have shown worse prognosis with increasing age [10,28], as in our patients, but there appears to be no correlation with peak creatinine concentration [8]. Attempts have also been made to gain prognostic
information from the renal biopsy. Only the degree of tubular atrophy predicted renal outcome in our series.

Some authors have reported that patchy cellular infiltration predicts a better outcome than diffuse disease [13,28]. However, recent studies have not supported a correlation between the degree of cellular infiltration or tubulitis and outcome [15,29]. The degree of interstitial fibrosis has been correlated to outcome [29,30], but in other studies there is no such relationship [31]. These conflicting observations may be due to the patchy nature of the disease and the random sampling on renal biopsy. The infiltrate is generally most prominent at the corticomedullary boundary, and the medulla is relatively spared [32]. This was recognized over 100 years ago by Councilman, who commented on the local nature of the histological changes [1].

Steroid treatment or not?

The role of steroids in the treatment in ATIN remains to be defined. In the absence of prospective randomized double blind trials, we are compelled to use evidence from small, uncontrolled series. A retrospective study of 20 patients with ATIN, by Laberke et al. [33], demonstrated that the seven patients who were treated with steroids had a significantly better renal outcome than those who were not treated. Pusey et al. [3] and Galpin et al. [8] also described benefits from steroids in small series of patients. More recently, Buyse et al. [15] described 27 patients with ATIN, 17 of whom improved spontaneously with conservative measures and drug discontinuation. The remaining 10 showed further deterioration of renal function in the 2 weeks following admission, and were then treated with steroids. In all these patients, renal function then improved, returning to normal in six. In our series, most patients were treated with high dose oral steroids (1 mg/kg) and there was a non-significant trend for deteriorating function to be reversed soon after the initiation of therapy. We currently advocate the early use of a short course of steroids, although some authors favour waiting for a week to see whether there is improvement with conservative measures (including drug withdrawal if appropriate) [34]. A multicentre prospective trial investigating the role of early steroid therapy in ATIN would be welcome. For patients resistant to steroids both cyclosporin and cyclophosphamide have been suggested, but there is no evidence in favour of the use of these agents or other newer immunosuppressants.

Conclusion

It is important to recognize that ATIN is a common cause of acute renal failure, especially when there is no obvious precipitant of ATN. Clinical features will often be absent or non-specific, and therefore early renal biopsy is recommended. Persisting vigilance is required to identify the emergence of new toxic compounds and infections that cause ATIN. Renal outcome will usually be good but in a significant minority, particularly the elderly, the outcome may be poor. There is suggestive evidence from a number of series that steroids lead to a more rapid and more complete recovery of renal function.

Conflict of interest statement. None declared.

References

Alcohol and red wine: impact on cardiovascular risk

Michael Böhm¹, Stephan Rosenkranz² and Ulrich Laufs¹

¹Medizinische Universitätsklinik und Poliklinik, Innere Medizin III, Kardiologie/Angiologie, Homburg/Saar and
²Klinik für Innere Medizin III, der Universität zu Köln, Köln, Germany

Keywords: alcohol; cardiovascular risk; coronary heart disease; French Paradox; myocardial infarction; platelet-derived growth factor receptor

Historical background

The potential beneficial effects of wine on health were reported by Paracelsus, Plinius and Galenus. Hippocrates of Kos (459–377 AD) suggested the application of wine as a tranquilizer, analgesic and also used its diuretic properties. In addition, the disinfection of the gastrointestinal mucosa as well as the treatment of wounds are well documented. Caesar recommended wine with meals in order to protect his soldiers from gastrointestinal infections. Specific actions of wine were reported by Galenus of Pergamon (ca. 130–200 BC), who used heavy red wine to protect from gastrointestinal infection and tannin-rich red wines to protect from gastrointestinal bleeding. Hildegard of Bingen (Germany, 1098–1179) applied a special wine recipe in order to ‘treat’ cardiovascular disease (‘Herzwein’). The problems of alcoholism were also recognized early and were documented by Pharaoh Rameses II, who complained about heavy alcohol consumption in the Egyptian population.

Effects of alcohol and wine on cardiovascular mortality

At present there are numerous epidemiological studies reporting the protective effects of moderate alcohol and wine intake [1–5]. Effects on lipids and haemostasis of different alcoholic beverages have been suggested to play a role [6–9]. A large database has been provided by the Health Professionals Follow-Up Study in 50 000 male individuals. The relative risk of developing symptomatic coronary heart disease was reduced by one-quarter following wine alcohol intake of 5–30 g/day [6,10]. ‘The French Paradox’ concerns the phe-