

TINU, another syndrome in search of the meaning of (its) life

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For a real, thorough and up-to-date review on this topic, please see reference (1) and forget this disparaging essay.

A paediatrician can base his academic career on publishing case reports of unfortunate patients with rare genetic or congenital syndromes that no one else will see again; a true freak show.

Not me. I don't like case reports and I think their contribution to the way we practice medicine is close to zero.

So why was I invited to write this view point on a supposedly rare disease, tubulointerstitial nephritis associated with uveitis (TINU syndrome), an entity mostly published by paediatric nephrologists and ophthalmologists in the form of case reports? Well, my group published a case report², and this journal has published 4 case reports of TINU syndrome within the last 12 months²⁻⁴. A real epidemic.

Two cases were diagnosed in adults and two in children, in all of whom other possible causes of tubulointerstitial disease were convincingly excluded, and a good case made for this new entity. Looking closely at the 4 cases, however, shows that their presentation, chronologic relationship with uveitis, severity, proposed treatment and response were all quite different and we wonder if they are all the same disease or just a random association of symptoms. Why, then, are they all lumped together?

We don't know much about their parent disease, tubulointerstitial nephritis (TIN) or acute interstitial nephritis (AIN) to begin with, but we certainly don't

know anything about TINU syndrome and we haven't become more knowledgeable reading through recent reports.

We are particularly confused about the pathogenesis underlying TINU syndrome. Activation and proliferation of T-lymphocytes has been implicated, but so has suppression of cell-mediated immunity with reported anergy, or, more recently, concomitant deposits of autoantibodies in proximal and distal tubular epithelial cells, along with IgG deposits in uveal cells (ciliary body and iris)⁵⁻⁷.

There are no identifiable risk factors or definite familial, genetic (no consistent HLA type association) or geographic clustering, despite a handful of speculative suggestions based on one case report apiece.

Clinically, we frequently find, as in any other AIN, associated systemic, non-specific symptoms such as fever, weight loss, malaise, anorexia, fatigue, flank pain, arthralgias, but then again, they may be absent. Uveitis, predominantly anterior (in 80% of the cases), but not always, usually presents up to 14 months after the onset of TIN, but on the other hand it may also precede (in 35% of the cases) renal signs by a couple of months⁸.

The renal manifestations are typical of AIN, which by the way are not typical at all, going from totally asymptomatic to a full-blown nephritic syndrome. Physiologically, we may find either proximal tubular defects, in the form of a partial or complete Fanconi syndrome, or distal tubular defects, interfering with the concentration or acidification mechanisms⁹.

There are no specific laboratory or histology findings to differentiate TINU syndrome from other TIN, and the differential diagnosis of the association of an AIN plus ocular symptoms, from entities such as sarcoidosis, Sjogren's syndrome, Behcet's disease, nephronophthisis, Fabry's disease, hyperoxaluria or cystinosis, may prove very difficult in the absence of the characteristic involvement of other organs¹.

What about treatment? As usual in so many other renal diseases that we cannot understand, when in doubt give steroids in empiric dose, schedule and duration. It is reminiscent of the equine medicine we learned from western movies: if a broken jaw – shoot, if a broken leg – shoot, if traumatic evisceration – shoot, if not eating – shoot, but in the rare cases where the heroine begs the hero for mercy, some fortunate horses would recover and share the happy ending, riding off into the sunset. We behave like those cowboys and steroids are our bullets, as there is not one single controlled trial clarifying the best treatment of AIN.

The prognosis of nephritis has an independent course from uveitis; many cases resolve spontaneously¹⁰, a few cases may recur, while others progress, requiring transient dialysis. Persistent renal dysfunction has been reported in 11% of all patients. The rate of recovery of AIN due to other inciting factors is also not clear.

For patients with biopsy-confirmed AIN who do not have significant chronic damage, there is a level C recommendation for therapy with corticosteroids. Therapy may also be instituted in patients with a strongly suggestive history of drug-induced AIN in whom a biopsy cannot be performed. The overall prognosis depends, as expected, on how far fibrosis developed before we treated or not.

However, the sad truth is that we don't know who will progress and if early treatment prevents chronic status: in the process we may be treating patients who wouldn't necessarily need it.

Medical science never ceases to amaze me; so far we have not shown any clinical relevance in identifying

this “new” syndrome and I just hope my patients never suspect the present state of my knowledge of this matter.

The Editor-in-Chief of our journal has certainly made 2008 “TINU awareness year”, doing a good job reminding us that if we suspect or diagnose an AIN/TIN and our patient has other systemic symptoms, bear it in mind. Then if a broken jaw...

Conflict of interest statement. None declared.

References

- 1 Izzedine H. Tubulointerstitial nephritis and uveitis syndrome (TINU): a step forward to understanding an elusive oculorenal syndrome. *Nephrol Dial Transplant* 2008;23:1095-1097
- 2 Mateus A, Ramos A, Ponce P. Tubulo-interstitial nephritis and uveitis syndrome. *Port J Nephrol Hypert* 2007;21:49-52
- 3 Bento V, Castro I, Batista J, Mesquita J. TINU Syndrome - two clinical cases of tubulointerstitial nephritis and uveitis. *Port J Nephrol Hypert* 2008;22:263-266
- 4 Possante M, Martins AP, Ramires L, Gusmão L. Tubulo interstitial nephritis and uveitis (TINU) syndrome revisited: a *propos* a case report. *Port J Nephrol Hypert* 2008;22 (4): (in press)
- 5 Gafter U, Kalechman Y, Zevin D, *et al.* Tubulointerstitial nephritis and uveitis: association with suppressed cellular immunity. *Nephrol Dial Transplant* 1993;8:821-826
- 6 Yoshioka K, Takemura T, Kanasaki M, *et al.* Acute interstitial nephritis and uveitis syndrome: activated immune cell infiltration in the kidney. *Pediatr Nephrol* 1991;5:232-234
- 7 Abed L, Merouani A, Hadad E, Benoit G, Oligny LL, Sartelet H. Presence of autoantibodies against tubular and uveal cells in a patient with tubulointerstitial nephritis and uveitis (TINU) syndrome. *Nephrol Dial Transplant* 2008;23:1452-1455
- 8 Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. *Surv Ophthalmol* 2001;46:195-208
- 9 Igarashi T, Kawato H, Kamoshita S, Nosaka K, Seiya K, Hayakawa H. Acute tubulointerstitial nephritis with uveitis syndrome presenting as multiple tubular dysfunction including Fanconi's syndrome. *Pediatr Nephrol* 1992;6:547-549
- 10 Takemura T, Okada M, Hino S, *et al.* Course and outcome of tubulointerstitial nephritis with uveitis syndrome. *Am J Kidney Dis* 1999;34:1016-1021

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