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Reply

Dear Editor,

We have read the comment by Sakallıoğlu on our article¹ describing two cases with tubulointerstitial nephritis (TIN), one of them also having uveitis (TINU)². We appreciate the author's contribution to the concept of drug-induced TIN. The author states that our second case could not be defined as TIN or TINU due to lack of either histopathological analysis, or renal failure or uveitis. First of all, we considered this patient a probable case of TIN (not TINU) associated with medications. Secondly, this patient had transient mild renal functional impairment characterized by low glomerular filtration rate (in the range of 90-100 mL/min/1.73 m²) along with signs of tubular dysfunction (mild proteinuria, glucosuria). Acute TIN accounts for 10–25% of reported cases of acute renal failure in adults and up to 7% of such cases in children. On the other hand, it has been reported that in both children and adults acute TIN may be underreported because many patients with acute renal failure recover spontaneously after removal of the suspected offending agent, and definitive diagnosis based on a renal biopsy is not routinely established³. Thus, in the presence of medication history and eosinophilia, we considered this patient a probable case of TIN.

The author also states that the diagnosis of TIN or TINU may be verified by measuring urinary β 2-microglobulin or Krebs von den Lunge-6 glycoprotein levels². Monitoring of sensitive urinary markers of tubulointerstitial damage, such as neutrophil gelatinase-associated lipocalin, liver type fatty acid-binding protein and kidney injury molecule-1, has been suggested as a non-invasive means of evaluating early renal damage and evolution of TIN^{4,5}. However, it has been stated that more investigations are required prior to translation of these approaches to clinical practice⁶. As such, serum Krebs von den Lunge-6 level has been

reported to be a potential laboratory parameter for the diagnosis and follow-up of patients with TINU syndrome⁷. However, there is only one study in the literature (published in 2006) on this subject, and it is unwise to designate this approach a clinical confirmatory test.

The author suggests that the time between usage of the drug and emergence of TINU seems too long in both cases to hold the drugs responsible for TINU². In patients with drug-induced acute TIN, the mean delay between the starting of the offending drug and the appearance of renal manifestations is 10 days, although the latent period may be as little as 1 day after some antibiotics or as long as several months in the case of NSAIDs⁶. Thus, it is wise to consider the possibility that TIN in our patients could be associated with codeine and/or paracetamol, as both patients used the offending drug within one month prior to the development of TIN.

Acute tubulointerstitial nephritis-related renal failure can be asymptomatic or accompanied by various clinical or laboratory findings, that, when present, are very valuable to orient the diagnosis. The specific clinical findings in drug-induced TIN, such as low grade fever, maculopapular skin rash and arthralgia, are related to an allergic-type reaction. The presence of eosinophilia (35% of patients) is considered another expression of this allergic-type reaction⁶. Both of our patients had significant eosinophilia, which is a valuable indicator of drug-induced TIN. Although our patients did not have fever or rash, recent series have shown that only a minority of patients (<10-15%) showed the classic triad of fever, rash and eosinophilia⁶. Thus, we still consider our first patient a TINU case and our second patient a probable TIN case associated with codeine and paracetamol.

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