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EDITORIAL

Shiga toxin-induced tubular injury in hemolytic uremic syndrome

To conform with a proposed new terminology for the shiga-like toxin (Stx) family [1], we use the term Shiga toxin-associated hemolytic uremic syndrome (Stx HUS) for cases caused by Stx-producing bacteria [2]; however, diarrhea-associated HUS (D+ HUS) and Stx HUS are still used interchangeably. Stx HUS is a well-defined clinicopathologic entity in which acute renal injury is usually the major component. Stx HUS is a complication of Stx-producing *E. coli*, usually but not always, serotype 0157:H7 and *Shigella dysenteriae* type 1. Patients with Stx HUS may have normal urine output. More often they may be anuric or oliguric and some may have non-oliguric renal failure [3]. There is abundant clinical, pathophysiologic and histopathologic evidence for glomerular endothelial cell injury in Stx HUS. Renal tubular injury has been considered to be secondary to glomerular and arteriolar injury in Stx HUS. However, evidence for direct renal tubular cell damage in Stx HUS is increasing [4–7].

In HUS caused by *Shigella dysenteriae* type I, there are glomerular injury and fibrin thrombi. However, in 1978 Raghupathy et al noted that there were also histopathologic changes of acute tubular necrosis manifested by tubular epithelial shedding, casts, interstitial edema, interstitial inflammation at the cortico-medullary junction and mononuclear cells in the vasa rectae [8]. It is of historical interest that the title of what may have been the first reported case of HUS, in 1954, was *Acute Tubular Necrosis with Anaemia* [9]. The four-year-old patient presented with vomiting and watery diarrhea with blood and mucus complicated by acute hemolytic anemia, thrombocytopenia, acute renal failure and seizures [9].

Evidence for primary renal tubular cell damage in Stx HUS has been derived mainly from *in vitro* and *in vivo* studies in animals [4–7]. Takeda et al showed that human adenocarcinoma cells of renal tubular origin were highly sensitive to Stx1 and Stx2 [4]. They also found significantly increased urine concentrations of N-acetyl glucosaminidase and β_2 microglobulin in patients with Stx HUS [4]. This pointed to renal tubular injury but did not provide convincing evidence for a direct effect of Stx on the tubules. Induction of medullary renal tubular injury by Stx in an isolated perfused rat kidney model was more compelling evidence for a direct effect of Stx on the renal tubule [5].

Hughes et al have studied the effects of Stx1 on human proximal tubule cells *in vitro* and have provided additional compelling evidence to support the hypothesis that Stx directly injures these cells [10]. Their findings complement those of others [4–7]. Human renal tubular cells undergo apoptosis *in vivo* following D+ HUS and in an *in vivo* mouse model of *E. coli*-associated HUS [6]. Apoptosis was also shown in human adenocarcinoma-derived renal tubular epithelial cells [7]. In these models the effect of Stx is enhanced by tumor necrosis factor-α (TNF-α) [6,7]. Hughes et al have found that Stx1 binds to receptors and injures the proximal renal tubular cells [10]. Incubation with interleukin-1 (IL-1) enhanced the cytotoxic effect of Stx1 and lipopolysaccharide increased cell sensitivity to Stx without altering Stx binding. Neither IL-6 nor TNF-α had any effects. A similar cascade of effects has been found in human renal endothelial cells. Learning how Stx is able to pass through the glomerular capillary wall in order to reach the tubular epithelial cells will add considerably to understanding the biology of Stx-induced renal injury.

These findings suggest that the oligo-anuria that occurs in many of these patients, and the non-oliguric renal failure that occur in some [3] may not be the result of glomerular and vascular injury alone. These observations may help to differentiate Stx HUS more precisely from other types of HUS such as malignancy-associated HUS, inherited HUS, and atypical D− HUS, and from thrombotic thrombocytopenic purpura. Taken together, these studies add considerably to our understanding of the pathogenesis of acute renal injury in Stx HUS. These findings do not, as yet, change the treatment or prognosis of this entity.

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