

A Potential New Marker of Post-HCT Kidney Injury

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SHL Frost

Acute kidney injury (AKI) and chronic kidney disease (CKD) are common complications after hematopoietic cell transplantation (HCT). They manifest either as an abrupt loss of renal function or a more gradual deterioration of the kidneys, and can be detected through increased levels of serum creatinine or protein in the urine. The exact mechanisms for HCT-associated renal failure are unknown, but it may be connected to the general inflammatory state the body is subject to after pre-transplant conditioning and post-transplant complications such as graft-versus-host-disease (GVHD). This association between GVHD and loss of kidney function sparked the interest of Drs. Sangeeta Hingorani, Ted Gooley and colleagues in the Clinical Research Division, who set out to investigate the underlying causality. Their results were e-published in *Clinical Journal of the American Society of Nephrology* in November 2014.

"Until recently, the prevailing thoughts on the etiology of the kidney injury that occurred after hematopoietic cell transplant has been that the injury is secondary to the calcineurin inhibitors used to prevent and treat GVHD and TBI [total body irradiation] used as part of the conditioning regimen," Dr. Hingorani said, adding that GVHD has lately been identified as a risk factor for renal injury. Given the association of GVHD and kidney disease and the documented correlation between skin GVHD and serum elafin levels, the investigators decided to assess the potential use of urinary elafin levels as a marker of kidney inflammation or injury. This low-molecular weight protein is produced by epithelial cells as a response to tissue injury and inflammation, and by stimulation through cytokines TNF- α and IL1- β . The two cytokines have been associated with both acute GVHD and inflammatory renal disease.

Urine samples were prospectively collected from 205 patients that underwent their first HCT between 2003 and 2010; half of the transplants were of unrelated donor origin, the rest were allogeneic (32%), or autologous (18%). All patients received conditioning regimens tailored according to their respective transplants. In addition, everyone who received stem cells from genetically non-identical donors were administered prophylaxis against GVHD. Urine collection was performed weekly for the first 100 days, then monthly during the first year after transplant.

The results showed that patients with micro- or macroalbuminuria had higher mean urinary elafin levels, as did patients with AKI. Moreover, higher average urinary elafin levels were recorded during the first 100 days after HCT in patients who developed CKD at one year after transplant, compared

with those who did not. The association between elevated urinary elafin levels and GVHD was also confirmed. Interestingly, each 500-pg/mL increase in urinary elafin within the first 100 days after transplant increased the risks of overall mortality and nonrelapse mortality by 7% and 9%, respectively. To determine if elafin was present in the kidneys, kidney biopsy specimens were collected from a separate cohort of 26 HCT patients, of which 20 had documented albuminuria. Positive immunohistochemical staining of elafin was subsequently demonstrated in distal and collecting duct tubules.

"This study suggests that the injury is tubular and is in response to the inflammatory milieu of GVHD or related to direct injury by cytokines or T cells," said Dr. Hingorani. She further hypothesized that urinary elafin may be a local epithelial response to inflammation, and may serve as a marker of renal tubular injury and ongoing inflammation leading to chronic kidney disease.

However, clinical measurement of urinary elafin is not yet readily available as a test for renal injury. "More research is needed to determine if patients with macroalbuminuria at day 80 post-HCT also have elevated urinary elafin levels and potentially biopsy them to determine the pathology of the renal injury." According to Dr. Hingorani, ongoing randomized trials in Europe are currently assessing the use of elafin infusions to decrease the inflammatory response of cardiac tissue to ischemia-reperfusion injury in patients undergoing cardiopulmonary bypass. "There may be a potential therapeutic application of elafin in patients with kidney injury to prevent ongoing injury and progression to CKD but this will require more research."

Further studies are also needed to determine if elafin is produced in the kidneys as a response to injury, or if the increased levels are due to filtration and reabsorption of circulating protein that is produced elsewhere. To shed light on that issue, Dr. Hingorani and colleagues will investigate other known markers of acute and chronic kidney injury, such as NGAL and KIM-1, and have submitted an R01 grant application to enable further studies in this patient population. "Our goal is to better understand the mechanisms of injury so that we can intervene early and prevent both acute kidney injury and progression to CKD."

Regardless of what they find, the current article highlights an intriguing problem and encourages further challenge of old assumptions. "I think this study changes the way we think about the potential causes of kidney injury in patients post-HCT," concluded Dr. Hingorani.

[Hingorani S, Finn LS, Pao E, Lawler R, Schoch G, McDonald GB, Najafian B, Sandmaier B, Gooley T.](#) 2015. Urinary elafin and kidney injury in hematopoietic cell transplant recipients. *Clin J Am Soc Nephrol.* 10(1):12-20.

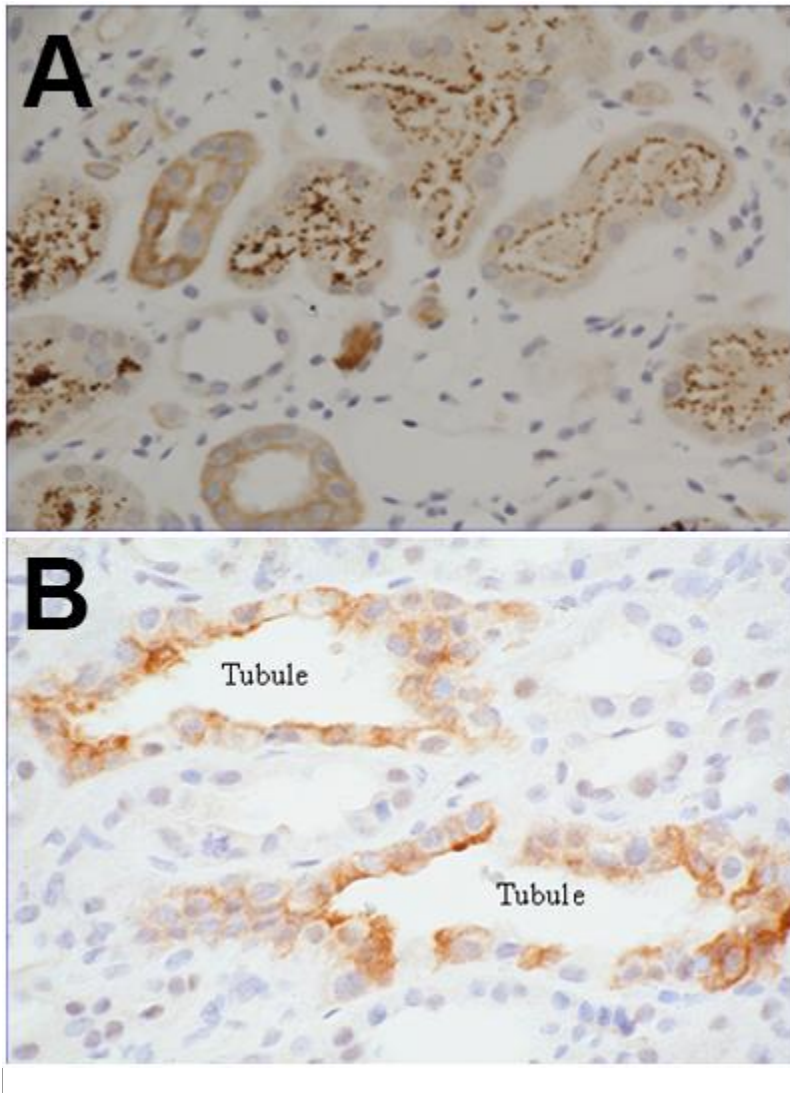


Image provided by Dr. Sangeeta Hingorani

Staining of elafin in the tubular epithelium in renal tissue from a patient with macroalbuminuria and elevated creatinine after HCT. The patterns of staining changed based on the extent of the injury. A) Original magnification, x200; B) original magnification, x400.