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Onco-nephrology: Time to Intravasate

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EDITORIAL

Onco-nephrology: Time to Intravasate

I was recently confronted by the case of a patient with immunoglobulin E myeloma who had mild, acute kidney injury (AKI). Recalling that there is significant mortality associated with AKI in oncology, I was concerned. If the situation worsened precipitously, embarking on a potentially prolonged course of renal replacement therapy might prove even more precipitous. Nonetheless, the question to answer was immediately apparent: "Did this patient require a kidney biopsy?" There was neither a profound degree of proteinuria nor a discernible trend in declining kidney function, but the patient was manifesting MGRS—indicative of a monoclonal gammopathy of renal significance—when monoclonal gammopathy of undetermined significance is no longer undetermined or insignificant, as coined by the International Kidney and Monoclonal Gammopathy Research Group.[1–3] In addition, this new nomenclature does not require the presence of malignancy, and it distinguishes monoclonal gammopathies that have injured the kidneys from those that have not. Parenchymal injury is not attributable to proliferation but to the downstream effects of immunoglobulin deposition/precipitation. By definition, a diagnosis of MGRS signifies that a "dangerous" B cell clone is present that does not meet the criteria for lymphoma or myeloma (Table 1). With no readily available urinary biomarkers to assist me, my most available resources were the literature, a seasoned hemato-oncologist, and a skilled renal pathologist. Collectively, we and the patient developed a plan of kidney biopsy and the manner of procession, which would be contingent on the histopathology encountered. In brief, this case simply underscored the escalating number of etiologies of AKI that are associated with patients with cancer.

The foremost cause of cancer-related AKI, predating the advent of the Papanicolau smear, was cervical cancer with asymptomatic urinary outlet obstruction. The prognosis of this combination was abysmal, with a 6-month survival of 30%.[4] Most cases presented far too late and eventuated in death from uremia. This form of obstructive uropathy led to the formulation of a differential diagnosis of fibrosclerosing tumors that induced secondary retroperitoneal fibrosis, such as carcinoid tumors; breast, pancreatic, and colon cancers; para-aortic lymphomas; and metastatic lymph nodal tumors. Cancer-related AKI was otherwise relegated essentially to chemotherapy-induced tumor lysis syndrome; chemotherapy-induced AKI such as occurs with cisplatin, potentially attenuated by prophylactic bicarbonate infusion; humoral hypercalcemia of malignancy; myeloma kidney and related disorders attributable to plasma cell dyscrasias[3]; the administration of high-osmolal, iodinated contrast in volume-depleted individuals undergoing diagnostic evaluation of their cancers; and tumor infiltration of the kidney—a rare occurrence that implies near-total replacement of the kidney parenchyma by the encroaching malignant tissue.[5]

Thus, making the appropriate diagnosis was once a relatively unencumbered process. However, this is no longer so because the pathomechanisms of AKI in patients with cancer are myriad and are attributable to the circumstances surrounding the malignancy and its consequences. In addition, nephrology-related complications often arise from the cancer treatments themselves, especially with the newer agents. Epidermal growth factor receptor interruption-related provocation of hypomagnesemia by cetuximab[6]; proteinuria and hypertension from angiogenesis inhibitors (small-molecule tyrosine kinase inhibitors that target the intracellular tyrosine kinase domain of the vascular endothelial growth factor receptor)[7]; cisplatin-induced renal tubular acidosis, the combined result of multiple platinum-induced injury and cell death pathways[8]; mitomycin-C- or gemcitabine-induced hemolytic uremic syndrome[9]; antineoplastic, anthracycline-derivative-related, caspase-induced, topoisomerase II-inhibited cardiomyopathy with accompanying cardiorenal syndrome[10]; and dose-related renal

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Table 1. Monoclonal Gammopathy of Renal Significance Classification Scheme by Ultrastructural Immunoglobulin Deposition

Organized Deposit Type		*Nonorganized Deposit Type*	
Pathomediator	Classification	Pathomediator	Classification
LC	AL	Monoclonal Ig	MIDD, Randall type
HC	AH	Monoclonal Immunoglobulin	PGNMID, non-Randall type
LC, HC	ALH	LC	Nonamyloid, proximal tubulopathy, Fanconi syndrome
Microtubules	Cryoglobulinemia, types 1 and 2	—	—
Microtubules	ITG	—	—

Abbreviations: AL, light-chain amyloidosis; AH, heavy-chain amyloidosis; ALH, light- and heavy-chain amyloidosis; HC, Ig heavy chain; Ig, immunoglobulin; LC, Ig light chain; ITG, immunotactoid glomerulopathy; MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis with monoclonal immunoglobulin deposits.

parenchymal toxicity from the chloroethylnitrosureas and methotrexate represent just a small proportion of these complications.[11] Even the seemingly mild pathophysiologically insult of androgen deprivation therapy is associated with the adverse outcome of AKI per a recent nested case-control analysis. This observation was more notable when combination androgen deprivation therapy was used.[12]

The aforementioned arise from the cancer-killing agents; however, the AKI that is associated with autologous, hematopoietic, stem cell transplantations originates directly from the transplanted organ itself. Free iron generates oxidative stress, and the reaction is agnostic to the source of iron. The anaphylactoid reactions encountered during intravenous iron infusions likely represent the penalties incumbent with free, catalytic iron in plasma. Fortunately, clinical AKI is generally not provoked by therapeutic, parenteral iron. However, the bone marrow houses iron, and lots of it, and the frequency of hematopoietic stem cell transplantation-related AKI is as high as 40%.[13]

On the other hand, kidney therapies applied to oncology patients may produce injury and complications. For example, patients with tumor lysis syndrome treated by continuous renal replacement therapy to optimize urate clearance will be rendered hypophosphatemic and hypokalemic, a particularly foreboding combination that could promote respiratory failure in an already critically ill individual.[14] High-dose xanthine dehydrogenase inhibition may result in life-threatening multiorgan dysfunction from untoward hypersensitivity reactions. Even aggressive volume repletion therapies are fraught with the hazard of volume overload in susceptible individuals, such as for those with hypercalcemia or those with lower than anticipated estimated glomerular filtration rates due to malignancy accompanied by cachexia and inanition.[15] In fact, volume depletion from malignancy treatment-associated malnutrition with AKI is considered the most common form of the paraneoplastic syndromes.[16]

Thus, it appears undoubtable that the increase in AKI, due to advances in medical progress and the resulting increased survivorship, has entailed the requirement of a substantial increase in base knowledge by nephrologists to adequately care for cancer sufferers. How can this be accomplished? In some interdisciplinary centers of cancer treatment excellence, dedicated internists or close collaborations with nephrologists are prerequisites to programmatic and operational success, but generally this is not the case.

Intravasation, the process by which tumor cells enter the circulation before extravasation, is the forerunner to metastatic disease. On a limited basis, intravasation into oncology floors is perhaps the best way for nephrologists and nephrologists-to-be to acquire the essentials for optimal recognition and treatment of the kidney problems incurred by oncology patients. After acquisition of the knowledge, it must be more widely spread, purposefully metastasized to one's particular practitioner group. Sadly, despite the mutual benefits to oncologists and nephrologists, this idealized scenario is unlikely to occur. Nonetheless, the ultimate decision is decidedly yours. Spending additional, dedicated time with oncology patients and oncologists will only benefit patients. Furthermore, it engages the nephrologist at several pivotal points of care: early establishment of the diagnosis; timely interventions where applicable; and, in cases of medical futility, leverage for the withdrawal of therapy.

Therefore, to partially bridge the gap in our knowledge of onconephrology, the guest editors, Drs. Mark A. Perazella, Jeffrey S. Berns, and Mitchell H. Rosner, have provided an engaging forum relevant to the multitude of kidney problems encountered by patients with cancer. Their colloquy features 12 papers that provide a vital touchstone for those participants in the expanding space of onconephrology. After reviewing this month's issue, perhaps you will find the time to engage your oncology colleagues and their patients to an even greater extent than you are doing now. It is time to intravasate.

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