Review of Onconephrology Cases: An Insight from the Middle East
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Background: Onconephrology is a new subspecialty of nephrology and its data was sparse from the middle east. We have collected data of cancer patients admitted to a tertiary care center and referred to the department of Nephrology to recognize the most common preventable causes of AKI and their outcome in this patient population.

Methods: We conducted a retrospective observational study of 39 admitted cancer patients referred to the department of Nephrology between November 2020 and March 2021.

Results: In our study 69% were males, 31% were females. Tumors were prostate cancer (n=6), bladder cancer (n=5), RCC (n=5), HCC (n=4) and Colon cancer (n=3). Breast cancer (n=3), unknown primary (n=2), n=1 were SCC, tongue, ovary, thyroid, endometrial cancer and laryngeal cancer, additionally B cell lymphoma (n=1), and multiple myeloma (n=2). Background history of CKD was present in, 38% (n=15) of the cohort. CKD stage 3 was the most prevalent (n=10). 1 patient had ESRD and maintained on dialysis and 2 patients had undergone a kidney transplant. Recurrent AKIs were most common (n=6), followed by nephrectomy (n=4) and hypertension (n=4), other included diabetes mellitus, urinary tract obstruction, atrophic kidneys, and multiple myeloma.

Causes of AKI were Sepsis 30%, hypovolemia 12%, urinary tract infection 10.2%, drug-induced AKI 10% & Hypercalemia 7.6%. Less common causes were hemorrhagic shock and IV contrasted medication exposure. Only 35% of the study population was actively receiving oncotherapy at the time of admission. Amongst the cohort, 48% were oliguric and the rest were non-oliguric. A total of 16 patients, received renal replacement therapy during admission; CRRT was done in 10/16 patients, 5/16 patients received conventional hemodialysis and 1 patient received both modalities. Amongst the patients requiring CRRT, the survival rate was 21%, and for patients who received hemodialysis, the survival rate was 50%.41% of the patients died during the admission; 62% of the deaths were deemed secondary to underlying cancer and the remaining 38% were attributed to other causes; the most common being sepsis.

Conclusions: Our study reiterates the importance of prevention of AKI by early recognition and prompt management of risk factors. This study prompts the need for quality improvement initiatives aiming at improving the outcomes of such patients at all tertiary care centers.

Pseudohyperkalemia Leading to Pseudohyponatremia in Severe Leukocytosis
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Introduction: Electrolyte abnormalities are common in oncologic malignancies. However spurious derangements are rarer. Here we present a case of coexisting reverse pseudohyperkalemia and pseudohyponatremia in chronic lymphocytic leukemia.

Case Description: An 84 year old male was diagnosed with chronic lymphocytic leukemia at presentation with weight loss and fevers. Labs showed a WBC of 760 K/mcl, Plasma sodium was 133 Meq/L, plasma potassium 8.8 Meq/L, BUN 15mg/dl, Creatinine 2.8 mg/dl and a GFR of 20 ml/min. Urine analysis showed 100 mg/dl of protein, 300 mg/dl of glucose and small blood. Urine sodium of 82 meq/L and osmolality of 444 mosmol/kg with serum osmolality of 300 mosmol/kg. EKG did not show any hyperkalemic changes. He received insulin, dextrose and karexalate. Repeat plasma potassium was 10.7 Meq/L. Given high suspicion for reverse pseudohyperkalemia due to leukocytosis, serum labs were sent. Serum potassium was 4.2 Meq/L and serum sodium 134 Meq/L with a concurrent plasma Potassium of >9.0 Meq/L and plasma sodium of 127 Meq/L. The WBC count remained elevated at 693.2 K/mcl. The sodium is measured at our institution with direct ion-specific electrode method making derangements from hyperlipidemia and hyperproteinemia unlikely. Treatment was started with methylprednisolone and Rituximab for CLL. The WBC count trended down from 693 to 339.5 K/mcl. Serum potassium remained stable (3.7-4.9) as well as serum sodium (138-141) with concurrent plasma values decreasing in disparity from potassium >9Meq/L to 4.9 Meq/L and sodium 127 Meq/L to 139 Meq/L as the WBC count decreased.

Discussion: This case portrays a challenging case of reverse pseudohyperkalemia and pseudohyponatremia in severe leukocytosis. While the phenomenon of pseudohyperkalemia in leukemia/lymphomas is established, reverse pseudohyperkalemia where plasma potassium is falsly elevated compared to normal serum levels is less known. Furthermore, no mechanism has been established for pseudohyponatremia in plasma samples compared to serum samples in leukocytosis however it was postulated that sodium levels decreased from extracellular potassium release from the leukocytes. Hence in cases of reverse pseudohyperkalemia serum samples are preferred over plasma samples. Parameters need to be established to avoid treatment of spurious electrolyte disorders to avoid treatments resulting in hypokalemia and hyponatremia.

Light Chain Proximal Tubulopathy Without Fanconi Syndrome as the Sole Presenting Feature of Multiple Myeloma
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Introduction: Light chain proximal tubulopathy (LCPT) is a rare pattern of immunoglobulin-related renal injury that occurs in the setting of dysproteinemias. Classic disease associations for LCPT are multiple myeloma, monoclonal gammapathy of renal significance (MGRS), and other hemopathological malignancies. The key LCPT pathologic feature is the accumulation of monoclonal light chains within the cytoplasm of proximal tubule (PT) cells with resultant clinical PT defects, proteinuria, and renal dysfunction.

Case Description: A 64-year-old man with prostatic adenocarcinoma presented for evaluation of incidentally discovered proteinuria (3.852 g/d creatinine) and stage two chronic kidney disease. Initial evaluation was significant for a kappa/lambda ratio of 474.79, serum M-spike of 0.9 g/dL, and urine M-spike of 1.082 g/dL. Urine immunofixation electrophoresis revealed 94.1% Bence-Jones protein (1.629 g/dL) consistent with monoclonal IgG, kappa type. Other laboratory features of myeloma (hypercalemia, anemia) were absent. Renal biopsy revealed monoclonal kappa light chain crystal inclusions in the cytoplasm of PT epithelial cells. Glomeruli show no significant histologic or ultrastructural abnormalities. Despite the severe histopathologic dysfunction, no clinical features of Fanconi Syndrome were present, including a negative work up for renal tubular acidosis as well as no renal wasting of phosphorous, amino acids, glucose, uric acid, or potassium. PET scan revealed diffuse marrow infiltrating disease with multiple lytic osseous lesions, and the patient was referred to urology to begin chemotherapy.

Discussion: LCPT continues to be a rare pattern of kidney injury with significant variability in presentation based largely on the combination of the light chains. The toxicity of kappa light chains results from their ability to form crystals, which resist lysosomal proteolysis. Although our patient had extensive crystalline inclusions and significant evidence of tubular injury, no clinical evidence of proximal tubulopathy was evident with proteinuria as the sole presenting feature of diffuse myeloma. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

Monoclonal Gammapathy of Renal Significance: Not Reserved for the Elderly
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Introduction: Monoclonal gammapathy of renal significance (MGRS) is defined by renal involvement of monoclonal immunoglobulins in the absence of other organ involvement. MGRS include a wide variety of renal lesions. It is particularly important to distinguish MGRS from monoclonal gammapathy of undefined significance (MGUS), as early treatment improves renal survival.

Case Description: 36 years old with a history of pre-ecclampsia, stage II chronic kidney disease, and hypertension well controlled on valsartan 320 mg and metoprolol succinate 100 mg, presented 2 years postpartum with worsening hypertension and proteinuria. Initial urinalysis was positive for 3+ proteinuria and 2+ blood, with dysmorphic RBCs on sediment. Urine protein to creatinine ratio (UPC) was 1574 mg/g Cr. ANA and ANCRA were negative. Serum creatinine was normal. Her creatinine rose from 1.2mg/dL to 1.8mg/dL over the next two years, and proteinuria rose to 20%. Renal biopsy confirmed IgG kappa monoclonal immunoglobulin deposition disease, with large subepithelial deposits and moderate tubular injury, with 20% global and segmental glomerulosclerosis, 10% juxtaglomerular apparatus, and minimal mesangial and tubulocapillary sclerosis. Serum and urine immunofixation and serum free light chain ratio were normal. Bone marrow biopsy was also negative, confirming the diagnosis of MGRS. She was treated with dexamethasone and bortezomib for a year, followed by lenalidomide, with stabilization of her renal function and proteinuria for over 3 years. Her creatinine is 2.4mg/dl and UPC is 354mg/g Cr. She has been off therapy for 4 months with no change.

Discussion: There has been historical resistance to treat MGRS, as it does not meet criteria for a proliferative disorder and chemotherapy toxicity is of concern. However, it is associated with progression to CKD/ESRD without treatment. Treatment depends on renal pathology and clone type, and may include proteasome inhibitors, alkylating agents, or immunomodulators. Certain forms of MGRS, such as AL amyloidosis, may benefit from autologous hematopoietic stem cell transplantation due to its high rate of recurrence. It is important to recognize MGRS. This case highlights the need for renal biopsy in patients with worsening proteinuria and renal function out of proportion to hypertension, and the role of chemotherapy in MGRS to change the trajectory of disease.

Variable Expression of Eighteen Common Housekeeping Genes in Human Non-Cancerous Kidney Biopsies
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Background: Housekeeping, or reference genes (RGs) are by definition, loci with stable expression profiles that are widely used as internal controls to normalize mRNA levels. However, due to specific events, such as pathological changes, or technical problems, their expression may be altered, failing to fulfill critical normalization pre-requisites.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: To identify RG genes suitable as internal controls in human non-cancerous kidney tissue, we selected 18 RG candidates based on previous data and screened in 30 expression datasets (>800 patients), including our own, publicly available or provided by independent groups. Datasets included specimens from patients with hypertensive and diabetic nephropathy, Fabry disease, focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, and minimal change disease. We examined both microdissected and whole section-based datasets. Expression variability of 4 candidate genes (YWHAZ, SLC4A1AP, and ACTB) was further examined by qPCR in biopsies from patients with hypertensive nephropathy (n=11) and healthy controls (n=3).

Results: Only YWHAZ gene expression remained stable in all datasets whereas SLC4A1AP was stable in all but one Fabry dataset. All other RGs were differentially expressed in at least 2 datasets, and in 4.5 datasets on average. No differences in YWHAZ, SLC4A1AP, RPS13 and ACTB gene expression between hypertensive and control biopsies were detected by qPCR.

Conclusions: Although RGs suitable to all techniques and tissues are unlikely to exist, our data suggest that in non-cancerous kidney biopsies expression of YWHAZ and SLC4A1AP genes is stable and suitable for normalization purposes.

Comparison of Proteomic Methods in Evaluating Biomarker-AKI

Richard X. Liu,1 Heather Thiessen Philbrook,1 Vasan S. Ramachandran,2,3 Josef Coresh,2,4 Peter Ganz,2 Joseph V. Bonventреc,2,5 Paul L. Kimmel,6 Chirag R. Parikh,7 Johns Hopkins University School of Medicine, Baltimore, MD; 4Boston University School of Medicine, Boston, MA; 3Boston University School of Public Health, Boston, MA; 2Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 7Johns Hopkins University Welch Center for Prevention Epidemiology and Clinical Research, Baltimore, MD; 5Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, CA; 6Brigham and Women’s Hospital, Boston, MA; 1Harvard Medical School, Boston, MA; 8National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

Background: Although immunoassays are the most widely used protein measurement method, aptamer-based methods such as the SomaScan platform can quantify up to 7,000 proteins per sample, creating new opportunities for unbiased discovery.

Methods: In a subset of the TRIBE-AKI cohort, preop and postop plasma samples from 294 patients with previous immunoassay measurements were analyzed using the SomaScan platform. Inter-platform Spearman correlations (r) and AKI associations for 8 proteins preop and 12 postop. All significant immunoassay-AKI associations for 13 proteins preop and 24 postop, molarity, with Spearman correlation 0.64 preop and 0.53 postop. No strong associations exist, our data suggest that in non-cancerous kidney biopsies expression of YWHAZ and SLC4A1AP genes is stable and suitable for normalization purposes.

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Performance of Creatinine-Based Equations to Estimate Glomerular Filtration Rate in the Context of Drug Dosage Adaptation

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Background: The 1976 Cockroft-Gault (CG) creatinine-based equation is still used to estimate GFR (eGFR) for dose adaptation of drugs excreted by glomerular filtration although it estimates creatinine clearance. It was developed based on non-standardized creatinine assays and is not recommended by any nephrology guidelines. Incorrect eGFR may lead to hazardous over- or under-dosing. We aimed to compare the performance of CG with modern equations based on standardized creatinine assays.

Methods: In a cross-sectional analysis CG was validated against measured GFR (mGFR; using various tracer methods) in 15,479 participants and compared with the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), Lund-Malmö-Revisted (LMR), and European-Kidney-Function-Consortium (EKFC) equations. Validation focused on bias, imprecision and accuracy (percentage of estimates within ±30% of mGFR, P30), overall and stratified for mGFR, age and body mass index intervals at mGFR <60 mL/min, as well as classification in mGFR stages.

Results: The CG equation performed worse than the other equations, overall and in mGFR, age and BMI subgroups in terms of bias (systematic overestimation), imprecision and accuracy (P30 overall for CG/MDRD/CKD-EPI/LMR/EKFC 73.6%/81.0%/82.4%/87.5%/86.9%) except for patients ≥65 years where bias and P30 were similar to MDRD and CKD-EPI, but worse than LMR and EKFC. At BMI ≥18.5-25kg/m², all equations performed similarly and at BMI≥18.5kg/m² CG and LMR had the best results though all equations had poor P30-accuracy (CG/LMR 85.7%/57.2%). At BMI≥25kg/m², bias of CG increased with increasing BMI (+19.3mL/min at BMI≥40kg/m²). The four more recent equations also classified mGFR stages better than CG.

Conclusions: The CG equation exhibited worse performance than CG overall and in analyses stratified for GFR, age, and BMI. CG was inferior to correctly classify the patients in the mGFR staging compared to more recent creatinine-based equations.

Human Kidney Mimetic Tissue Using Endogenous Lipids and Metabolites as Standards for Quantification and Quality Control

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Background: Mass spectrometry imagine (MSI) determines the spatial localization of minimal species directly from the sample and has been herald in tissue analysis. However, majority of studies have not been quantitative and reproducible. The presentation of a quantified tissue distribution has distinct benefits over the common approach of quantifying the tissue homogeneous especially if tissue distribution is heterogeneous, making overcoming this limitation a top priority.

Methods: An improved mimetic tissue mold has been developed. Briefly, human kidney tissue was cut into small pieces and spiked with a normalization standard (lyso-PAF), an antioxidant, and a phospholipase A2 (PLA2) inhibitor to protect endogenous lipids and metabolites from the most common degradation. Lipidomic and metabolomic analyses of this mimetic tissue were performed, and the absolute amounts of various compounds were measured and used as standards for side by side MSI analysis of any tissue sample of interest. Since stabilizers are used, the quantitative data of the mimetic tissue are reliable and can be used as quality control (QC) tracers to tissue samples during storage and shipment.

Results: Mimetic tissue molds were prepared by spiking stable isotope labeled compounds at different concentrations layer by layer for validation. Initial validation experiments found that: a) MSI can detect the concentration differences with acceptable linearity, accuracy, and repeatability; b) Spiking of high concentrations affects the endogenous signals; c) It’s not practicable to spike each compound for its quantification due to signal suppression, high material and labor consumption; d) Using endogenous amounts as reference standards is a suitable approach. To use the homogenized mimetic tissue as a spatial quantitative and QC standard, the endogenous amounts of lipids and metabolites were measured with bulkomics. More than 200 lipids, 25 amino acids, and numerous organic acids were quantified.

Conclusions: Quantifying endogenous lipids and metabolites using bulk methods as MSI quantification standards is innovative in the field. The similarity of tissue matrix and targeting compounds between mimetic and sample tissues can provide more meaningful and reliable results.

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