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GEMCITABINE INDUCED ATYPICAL HEMOLYTIC SYNDROME TREATED WITH ECULIZUMAB: 2 CASES:

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Gemcitabine induced thrombotic microangiopathy (GITMA) is rare but its outcomes are poor. We report 2 cases of GITMA successfully treated with Eculizumab. First patient: a 69 yo white male with stage IIA pancreatic cancer treated with surgery and chemotherapy including Gemcitabine (G). After 6 months G was discontinued due to worsening anemia (Hb of 5.6 g/dL), plateltes $16x10^9$/L and progressive elevation of serum creatinine (Scr) 4.3mg/dL with the suspicion of GITMA The ADAMTS-13 activity, ANA, C3 and C4 were normal. Kidney biopsy was consistent with chronic drug induced TMA. Patient was managed with high dose steroids and 5 sessions of TPE without improvement. IV Eculizumab was then added and led to normalization of LDH and platelet count (169 X 10^9/L), Scr improved to 1.9mg/dL and Hb to 12g/dL. Genetic studies showed Thrombomodulin mutation. Second patient: a 65 yo white female with anal cancer treated with surgery and chemotherapy for 6 months. G was discontinued due to hemolytic anemia (schistocytes, Hb 6g/dL, LDH 465U/L), low platelets ($51x10^9$/L and worsening renal function (Scr 3.2 mg/dL). The ADAMTS-13 activity and complement levels were normal. Kidney biopsy demonstrated chronic TMA. There was no response to high dose steroids and 5 sessions of TPE. Patient required hemodialysis (HD). Eculizumab was started with improvement in hemolytic anemia (Hb of 8.9g/dL), platelets (175 $x10^9$/L), normalization of LDH, but the patient remained on HD . Genetic studies revealed heterozygous complement factor H mutation.GITMA is poorly responsive to steroids and TPE. G is likely causing GITMA in susceptible individuals and routine screening for aHUS mutations might be warranted. Both our patients had mutations increasing risk of aHUS. Therefore, eculizumab should be considered as a 1st line Rx for GITMA until fast complement factors mutation screening tests are available.

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ACUTE KIDNEY INJURY DUE TO CHRONIC LYMPHOCYTIC LEUKEMIA INFILTRATION OF KIDNEY ALLOGRAFT

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Chronic lymphocytic leukemia is a malignant hematological disorder characterized by proliferation with an accumulation of small B-lymphocytes. We report a case with AKI associated with extensive infiltration by CLL without any evidence of acute rejection of a deceased donor renal allograft.

A 71 year old man with end stage kidney disease due to diabetic nephropathy received a deceased donor renal allograft in March 2011. His Serum creatinine (Scr) remained stable at 1.1 mg/dL. His immunosuppression included tacrolimus and mycophenolate mofetil. In July, 2013, he developed leukocytosis with smudge cells and was diagnosed with CLL, Stage 0. In Sep, 2015, he was admitted with progressive diffuse lymphadenopathy and pleural effusions associated with respiratory distress. Flow analysis of pleural fluid was consistent with pleural involvement with CLL. Lymph node and bone marrow histopathology were also consistent with CLL. This was complicated with acute kidney injury with a rising Scr to 2.5 mg/dL. The differential diagnoses included acute tubular necrosis, acute interstitial nephritis, calcineurin inhibitor toxicity, or acute rejection. The kidney biopsy showed diffuse infiltration of the interstitium with lymphoproliferative cells. The immunohistochemical stains showed lymphocytes positive for + CD 19, CD 20, CD 23, CD 5 and negative for CD 10, FMC 7 which was consistent with CLL. Ki-67, EBV, CMV, HHV-6 all were negative. Mycophenolate mofetil was discontinued. He remained on tacrolimus. In view of worsening kidney function, he was treated with R-CHOP (Cytoxan, doxorubicin, vincristine, rituximab). His Scr improved and stabilized at 1.0 mg/dL. He was discharged home.

In conclusion, a potential complication of CLL involvement of kidney allograft should be recognized and timely therapy can result in improvement of kidney function.

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C3 GLOMERULONEPHRITIS WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

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We report the case of a 79 year-old male with chronic kidney disease (baseline Cr 1.7 mg/dL), "Connective Tissue Disorder", HTN, and DM presenting with microangiopathic hemolytic anemia, pyuria (urine culture negative), and kidney function at baseline. Plasmapheresis was stopped after one session, as suspicion for TTP was low (ADAMTS13 63%). Cr rose to 2.8 mg/dL, and new nephrotic-range proteinuria (3.8 g/g) and hematuria (8 RBCs/hpf) were seen. Low serum C3 (78 mg/dL) and normal C4 were noted. Kidney biopsy demonstrated diffuse staining for C3 (2-3+) and no staining for Ig on immunofluorescence, with electron microscopy showing subepithelial hump-like deposits, subendothelial deposits, and no intramembranous dense deposits. An elevated complement Factor H autoantibody (71 U/mL, reference $\leq$ 22 U/mL) was also found. SPEP showed a monoclonal gammopathy (IgG M-spike 0.2 g/dL) with no evidence of malignancy on bone marrow biopsy, suggesting MGUS. After 5d of IV methylprednisolone (1 mg/kg) and transient Cr improvement, renal function worsened (Cr 4.2 mg/dL). Thus he was started on weekly eculizumab, a monoclonal antibody that prevents formation of the terminal complement complex C5b-9, with improved Cr to 2.2 mg/dL 4 weeks later.

Though alternative complement pathway dysregulation plays a role in both atypical hemolytic uremic syndrome and C3 glomerulonephritis, and the two processes have been reported to coexist, his kidney biopsy findings did not suggest thrombotic microangiopathy. Thus, this case raises the possibility of a monoclonal immunoglobulin (autoantibody to Factor H) leading to C3 glomerulonephritis, which has been previously described. However, to our knowledge, this would be the first report of a patient with C3 glomerulonephritis associated with MGUS seeing clinical improvement on eculizumab. Our assessment was limited, as an anti-Factor H assay on the patient's monoclonal Ig was not performed.

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VISCERAL ADIPOSITY, NUTRITION, AND THE RISK OF CHRONIC KIDNEY DISEASE IN AFRICAN AMERICANS: THE JACKSON HEART STUDY

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African Americans are at high risk for chronic kidney disease (CKD). Obesity, which is prevalent in African Americans, may increase this risk. We investigated whether poor nutrition modifies the association of obesity with incident CKD in African American adults.

We estimated kidney function by the CKD-EPI creatinine equation at baseline and follow-up (median 8 y), visceral adiposity (VA) at an interim study visit by abdominal CT (median 4.6 y post-baseline), and nutrition at baseline by Food Frequency Questionnaire then categorized by American Heart Association guidelines as poor vs. intermediate or ideal. We defined incident CKD as new eGFR <60 mL/min/1.73m^2 with >25% decline, or new urine albumin-to-creatinine ratio >30 mg/g.

Our analysis included those with data on VA and without baseline CKD (n=1481). Baseline eGFR was 97.6 ± 16.8 mL/min/1.73m^2, median VA volume was 745.5 cm^3 (IQR 526.5-1013.9 cm^3), and poor nutrition was observed in 859 participants (58%). After full adjustment, higher VA was associated with higher risk of incident CKD (n=177 events, p=0.0023), although the effect was U-shaped and depended on nutrition (p-interaction=0.01). Among those with poor nutrition, odds of incident CKD were higher among those in the highest quartile (Q4) of VA compared to the reference quartile (OR 2.66; 95% CI 1.36-5.20 for Q4 vs. Q2), but there was no association if nutrition was intermediate or ideal (p=0.9).

The obesity-associated risk of incident CKD was higher in adult African Americans exhibiting poor nutrition. Our analysis was limited by assessment of visceral adiposity post-baseline.