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GATA3 Is a Useful Immunohistochemical Marker to Differentiate Variants of Renal Tubular Lesions from Different Segments of Renal Tubules

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Introduction/Objective: TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) is a rare systemic inflammatory disorder. First reported in 2010, the majority of cases are from Japan, where it is currently regarded as a subtype of HHV8-negative Multicentric Castleman Disease.

Methods/Case Report: We report a case of TAFRO occurring in a 17-year old from Puerto Rico. She originally presented with abdominal pain, vomiting, and fever, and was also found to have splenomegaly, elevated sedimentation rate and C-reactive protein. Over the course of the next several days she developed respiratory distress, requiring ventilatory support, and anuric renal failure. Renal biopsy demonstrated evidence of thrombotic microangiopathy, which was interpreted as atypical hemolytic syndrome, requiring dialysis and treated with eculizumab. Because other diagnostic considerations at the time also included hemophagocytic lymphohistiocytosis and catastrophic antiphospholipid syndrome, bone marrow examination was performed which demonstrated increased megakaryocytes, without fibrosis or hemophagocytosis. Over the next two months, she developed anasarca with ascites, pleural effusion, pericardial effusion, multiple enlarged axillary and cervical lymph nodes, and persistence of splenomegaly. Biopsy of a left cervical lymph node demonstrated features suggestive of Castleman's disease, plasma cell variant. The constellation of symptoms, laboratory investigations and biopsy diagnoses support the diagnosis of TAFRO syndrome. The patient received rituximab, high dose steroids, and hemodialysis with clinical improvement. At 16 months follow up, the patient is in remission.

Results (if a Case Study enter NA): NA

Conclusion: From a pathology standpoint, the case provides biopsy findings of three distinct organ systems all with relatively unusual findings that together are characteristic of TAFRO syndrome. It highlights the risk of accepting "biopsy proven" diagnoses such as atypical hemolytic uremic syndrome that also require significant laboratory and clinical correlation for true confirmation, and points out the importance and opportunity for pathologists to see the forest along with the trees in order to recognize rare diseases such as TAFRO.

Quality improvement Initiative to eliminate silver precipitate during Periodic Acid Silver Methenamine Stain (PAMS) automated protocol of renal biopsies at McGill University Health Centre

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Introduction/Objective: Annually, about 400 renal biopsies are processed at the McGill University Health Centre

(MUHC) pathology laboratory located in Montreal, Canada. One of the stains used to visualize the glomerular basement membrane is Periodic Acid Silver Methenamine Stain (PAMS). In August 2020, a strong, granular precipitate of silver was noted during PAMS automated staining resulting in uninterpretable results and delay in the diagnosis. Based on a sample analysis, this problem affected 21 % of kidney biopsies.

Methods/Case Report: A cause-and-effect workflow was developed for systematic assessment of potential causes of the granular precipitate including pre-analytical and analytical factors. Some of the pre-analytical factors included length of time spent in transport before fixation and patient factors that predisposed precipitate formation. Analytical factors were categorized as fixation problems (temperature, pH, duration), embedding problems (parafilm temperature, cooling method, type of parafilm), slide preparation (temperature, water bath pH, dehydration and further processing steps), microtome parameters (microtome calibration, thickness, laboratory technologist expertise), automatic staining parameters (cartridge age, hematoxylin counterstain duration, wash-out period etc.) and coverslip placement (adhesive type, temperature, drying).

Results (if a Case Study enter NA): Following our systematic approach, the cause of granular precipitate was identified as the timing of hematoxylin counterstain. A portion of renal biopsy tissue was taken from parafilm blocks of previously reported cases of patients with membranous glomerulonephritis to further test the hypothesis by introduction of various incubation times with the hematoxylin counterstain.

Conclusion: Best PAMS staining was attained when no hematoxylin counterstain was employed (instead, neutral red counterstain for 70 seconds was used). PAMS staining with hematoxylin counter stain for no more than 60 seconds was found to be acceptable for the interpretation of glomerular pathology.

GATA3 Is a Useful Immunohistochemical Marker to Differentiate Variants of Renal Tubular Lesions from Different Segments of Renal Tubules

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Introduction/Objective: GATA3 is found in glomerular mesangial cells, and the distal tubules & collecting ducts in metanephros and eventual kidneys, but not associated with the proximal tubules and loops of Henle. We hypothesize that GATA3 can be used as a marker to identify the origin of tubular differentiation in most renal tumors.

Methods/Case Report: Ten negative controls and 43 renal mass lesions (RCC, papillary, clear cell papillary, and chromophobe carcinomas, oncocytoma, and polycystic

kidney disease). GATA3 nuclear stain was graded as negative (absent stain), equivocal and positive (< 5 and > 5% cells, respectively). Details of their GATA3 nuclear expression was analyzed for identifying their tubular segmental origins.

Results (if a Case Study enter NA): In 10 normal renal parenchyma, GATA3 was positive in mesangial cells, distal tubules, and collecting ducts, but was negative in the proximal tubules and loop of Henle. The cystic lining of glomerulocystic renal disease was stained negatively for GATA3 (proximal tubular origin), whereas pediatric and adult variants of polycystic kidney diseases was positive for GATA3 staining (distal tubular origin). 1/10 ten clear cell RCC and papillary RCC showed focal positive GATA3 stain. GATA3 showed weakly positive staining in some oncocytomas (4/11) and some chromophobe RCC (4/11), indicating that they might be derived from the junctional segment between the loop of Henle and the distal tubules. By contrast, all clear cell papillary RCC (distal tubule origin) were diffusely positive.

Conclusion: Our results indicate that GATA3 is a useful immunohistochemical marker to determine the developmental origin in the specific renal tubular segment for the majority of renal mass lesions. Thus, it may be useful for routine differential diagnosis of these lesions.

Case Report. Cryoglobulin Hyaline-thrombi Associated Acute Jejunitis in A Patient with Type 2 Cryoglobulinemic Glomerulonephritis.

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Introduction/Objective: Only one prior case report indicates that mixed positive cryoglobulin in serum can be associated with intestinal vasculitis (Annals of Internal Medicine, 1974).

Methods/Case Report: We report a 63-year old man with history of positive serum cryoglobulin and hepatitis-C 4 years ago and membranoproliferative pattern of glomerulonephritis with possible cryoglobulin type of deposits by electron microscopy on renal biopsy. After treatment, his hepatitis C became negative. But he was recently found to have monoclonal IgM-kappa and positive cryoglobulin in his serum, and the concurrent renal biopsy showed membranoproliferative pattern of glomerulopathy with many hyaline-thrombi (eosinophilic vascular occlusions with no lamination, inflammatory cells or nuclear debris) in the glomerular capillary loops (Figure, left panel). Both immunofluorescent and electron microscopy confirmed a mixed IgG polyclonal and IgM monoclonal type 2 cryoglobulinemic glomerulonephritis. The patient also developed abdominal pain and underwent intestinal endoscopy with biopsy. His jejunal biopsy

revealed neutrophil infiltration into glands and surface epithelium, with superficial sloughed epithelial cells, consistent with acute jejunitis with features of ischemic etiology. In addition, hyaline-thrombi were identified in the submucosal vessels with surrounding vasculitis (Figure, right panel); the central part of thrombi was morphologically similar to that found in glomerular capillary loops. Therefore, we conclude that cryoglobulin associated hyaline-thrombi were the most likely etiology to cause the acute ischemic jejunitis in this patient.

Results (if a Case Study enter NA): NA

Conclusion: NA

Recurrent Focal Segmental Glomerulosclerosis Progressing to Collapsing Glomerulopathy in Renal Graft of an Autopsy study.

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Introduction/Objective: Collapsing glomerulopathy (CGN) mainly occurs in patients of African descent because a majority of these patients have APOL-1 gene mutations that results in damage of terminally differentiated podocytes, diffuse fusion of foot processes, and podocyte hyperplasia. Idiopathic FSGS is associated with high rates of recurrent FSGS in renal transplants and can be seen in patients with APOL-1 gene mutations as well, but recurrent FSGS progressing to CGN is not reported. Here we report an autopsy case with renal transplant showing recurrent FSGS progressing to CGN.

Methods/Case Report: Our patient was a 32 year old African American man who had a native renal biopsy which showed primary FSGS (with no infectious history) 8 years ago. Last year he received a renal transplantation (complex donor kidney from a deceased 25 year old man with pre-mortem serum creatinine (sCr) at 0.7 mg/dl). His initial post-transplant sCr level was as low as 1.17 mg/dl. However, in 4 months his sCr went up and he began to have higher levels of proteinuria. Sequential biopsies indicated that the patient developed a recurrent FSGS that progressed to show features of CGN. In his autopsy kidney graft, approximately 50% of glomeruli show collapsed loops with various degrees of hyperplastic podocytes, confirmed by positive CD133 staining (a progenitor cell marker). In addition, the hyperplastic podocytes lost WT-1 expression and were positive for Ki-67 staining. Distal tubules showed obvious cystic dilation. Overall findings were consistent with a severe form of CGN.

Results (if a Case Study enter NA): NA

Conclusion: The clinical presentation of recurrent FSGS progressing to collapsing FSGS in our patient suggests that CGN and idiopathic FSGS may share a common pathophysiologic mechanism of disease.