Anti GBM disease in patient with Membranous nephropathy

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Abstract:
Crescentic transformation of primary membranous nephropathy (MN) due to anti-Glomerular basement membrane antibody (anti-GBM antibody) is a rare cause of acute renal failure in patients with MN. This is a case report of 19-year-old gentleman who was initially diagnosed with Membranous nephropathy presented one year later with accelerated hypertension and rapidly progressive renal failure (RPRF). His serum anti-GBM antibody was positive. Renal biopsy revealed circumferential crescents in all glomeruli with linear IgG staining by immunofluorescence. Patient was treated with steroids, oral cyclophosphamide and plasmapheresis. Due to non-recovery of renal function he became dialysis dependant and died nine months later. Though anti-GBM antibody is a well known cause of RPRF in patients with MN less very few cases have been reported so far. This case is presented for its rarity.

Keyword: membranous nephropathy, rapidly progressive renal failure, rapidly progressive glomerulonephritis, Anti-GBM (Glomerular basement membrane) antibodies, ANCA (Anti-neutrophil cytoplasmic antibodies) Introduction Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. It is characterized by diffuse and uniform thickening of the glomerular capillary wall in light microscopy, finely granular immune deposits by immunofluorescence and subepithelial immune deposits by electron microscopy. MN can be primary or secondary. Primary MN can be due to auto-antibodies to M type Phospholipase A2 receptor, which is expressed in podocytes. Primary MN is a disease of adults occurring in the fourth to sixth decade of life and is more common in males, 2:1. Secondary MN may be due to autoimmune diseases, chronic infections, drugs or malignancy and can present in any age. The usual presentation is nephrotic syndrome, microscopic hematuria (30 – 40%) with or without hypertension. The renal function is usually normal, but can be impaired. The natural history is that 20% of patients with primary MN progress to ESRD over the course of 10 to 15 years.
Sometimes sudden worsening of renal function in MN can occur. It is commonly due to 1 intravascular volume depletion

2 drug induced acute interstitial nephritis

3 thrombosis of renal veins or rarely renal arteries 4. Rarely it can undergo crescentic transformation, with or without the development of Anti-GBM antibodies or ANCA.

Anti-glomerular basement membrane (Anti-GBM) disease is a rare autoimmune disorder characterized by crescentic glomerulonephritis and the presence of circulating Anti-GBM antibodies directed against 3 chain of NC domain of type IV collagen. MN can predispose to Anti-GBM disease by exposing the cryptic epitope. Conversely MN can develop in a patient with Anti-GBM disease. More often, when both are seen, they occur simultaneously. Case report In October 2011, 19 year old gentleman presented with pedal edema of 4 months duration. His blood pressure was 110/80 mm of Hg. Sr. Creatinine 0.8 mg/dl, Sr. Albumin 1 gm/dl and his 24-hour urine protein was 6 gms. HIV, anti-HCV and HBsAg was negative. His renal biopsy revealed MN. He was started on ACE inhibitors, diuretics and statins. He was not compliant with his medications and was soon lost to follow-up. One year later, in September 2012, he presented with blurring of vision, headache, oliguria and one episode of generalized tonic-clonic seizures. His BP was 240/140 mm of Hg. Examination revealed anasarca, right pleural effusion and bilateral papilledema. Investigations revealed 3+ proteinuria with 5-6 RBCs/HPF. Sr. Creatinine was 10.8 mg/dl. CT Brain was normal. CT Thorax revealed bilateral pleural effusion more on the right, with no evidence of alveolar hemorrhage. Doppler of renal vessels ruled out thrombosis. After adequate control of BP and initiation of hemodialysis, renal biopsy was done. Light microscopy revealed circumferential cellular crescents in all 14 glomeruli and fibrinoid necrosis in 2 glomeruli (Picture 1); Extensive Interstitial Fibrosis and Tubular Atrophy; Mild mesangial expansion and normal cellularity; numerous spikes and pin-hole lesions. Immunoflourescence showed linear 3+ positivity for IgG and 2+ positivity for C3 (Picture 2). His serology results were

1 ANA - Negative
2 ANCA - Negative
3 Anti GBM - 58.2 U/ml (Positive > 20 U/ml)
Thus, based on renal biopsy features and positive Anti-GBM antibody, a diagnosis of Anti-GBM disease was made in a patient with MN. There was no evidence of pulmonary hemorrhage. Intensive immunosuppressive therapy with pulse steroids, oral cyclophosphamide and plasmapheresis was initiated. Due to development of severe sepsis, immunosuppression was stopped. Due to non recovery of renal function, the patient was advised to undergo maintenance hemodialysis. Once again he was non compliant with treatment and he died 9 months later. Discussion Though it is well known, there have been very few case reports of co-existence of MN and anti-GBM disease. Only 17 cases have been reported till the end of 2010. Review of the reported cases showed the mean age of presentation was 46 years and more common in males. The mean Sr. creatinine was 8.8 mg/dl. Only 3 patients whose Sr. creatinine was low were benefitted by the immunosuppression. The rest were dialysis dependant or expired. In five of these, MN preceded the development of Anti-GBM disease and were elderly. In another five patients, who were younger, Anti-GBM preceded the diagnosis of MN. The remaining seven patients had simultaneous MN and Anti-GBM disease. The pathogenesis of MN in Anti-GBM disease is by in situ immune complex formation, increasing antigen synthesis by injured podocytes and facilitated by shedding and capping of immune complexes in sub-epithelial space. Anti-GBM develops in MN due to thickening of GBM and opening of the cryptic epitope. The co-existence of Anti-GBM and MN warrants early and aggressive immunosuppression as in isolated Anti-GBM disease and the outcomes are dismal if treatment is delayed or there is extensive renal injury. Conclusion The development of Anti-GBM disease in MN is very rare. A systematic approach to the sudden worsening of renal function in patients with MN is necessary including antiGBM antibody assay and renal biopsy.

References:
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