Abstract:
Membranous Nephropathy (MGN) could be either idiopathic (primary) or secondary to systemic autoimmune disease, chronic infections, malignancy or therapeutic drugs. We present a 24 year old Asian lady, diagnosed to have Wilsons disease and started on D-Penicillamine. Eighteen months later she presented with nephrotic proteinuria, benign urinary sediment, normal blood pressure and normal serum creatinine. A renal biopsy was done which revealed Membranous Nephropathy. The serum M type Phospholipase A2 receptor antibody was negative. Though D-Penicillamine induced MGN is a well known entity, we are reporting this case because of its rarity.

Keyword: Wilsons disease, D-Penicillamine, secondary Membranous nephropathy, Phospholipase A2 receptor antibody.

Introduction:
One of the leading causes of primary nephrotic syndrome in adults is MGN.[1,2] Primary MGN is an auto-immune disease with auto-antibodies to M type Phospholipase A$_2$ receptor (MPLA$_2$R) [3] which is a cell surface transmembrane receptor expressed on podocytes, in majority of cases. Primary MGN accounts for 75-80% of total cases of MGN and the rest is due to secondary MGN. Primary MGN is more common in the fourth to sixth decades and has a male preponderance (M: F = 2:1). Secondary MGN can occur at any age group, Hepatitis B associated MGN is more common in childhood [4] and does not have sex preponderance. Secondary MGN is due to autoimmune diseases, chronic infections, malignancy, therapeutic agents or denovo MGN in renal allograft. Drug induced secondary MGN is more commonly reported after the use of Non-steroidal anti-inflammatory drugs[5,6] and cyclooxygenase-2 (COX-2) inhibitors, mercury containing skin lightening agents[7], gold and D-Penicillamine.

Case Report:
Herein we present a 24 year old lady, non diabetic and non hypertensive. She is the first of the three siblings born out of a second degree consanguineous parentage. She was
evaluated for primary infertility in 2009 after two years of marriage. In June 2011, she developed severe anemia, jaundice (Serum Bilirubin 2.6 mg/dl, SGOT 102 IU/L, SGPT 99 IU/L). She was diagnosed to have Wilson’s disease as the serum ceruloplasmin was low, 14.4 mg/dl (20-60 mg/dl) and 24 hours urine copper was high. She received D-Penicillamine 1 gm/day (June 2011) in divided doses. She was asymptomatic thereafter. In February 2013, she noticed facial puffiness, pedal edema and frothy urine. No h/o hematuria, oliguria, lithuria, bone pain or bony deformities. She was advised to discontinue D-Penicillamine by the Gastroenterologist. She was notormensive and routine urine examination showed 3+ proteinuria, 3+ blood. Urine culture was sterile. 24 hours urine protein was 10.9 gms. Hemoglobin 12.2 gms/dl, platelet count, PT and APTT was normal. She had normal serum creatinine (0.8 mg/dl) elevated total cholesterol and triglycerides. Her Tubular function tests and Liver Function tests were unremarkable. Ultrasonography of abdomen revealed normal sized kidneys with preserved cortico-medullary differentiation. Renal biopsy by light microscopy showed 6 glomeruli, none are globally sclerotic, with normal cellularity, no mesangial proliferation and patent capillary loops. Tubulointerstitium and vessels were unremarkable. Basement membrane mottled and show pinhole lesions on Methenamine-Silver stains. Immunofluorescence revealed 3 glomeruli with IgG 3+ and C3 2+ in capillary walls. A diagnosis of Membranous Nephropathy was made. Serum auto-antibodies to M type Phospholipase A2 receptor (MPLA2R) was tested using indirect immunofluorescence, which was negative in 1:10 dilution, reiterating the fact that it is secondary Membranous Nephropathy probably due to D-Penicillamine [8]. The prevalence of MPLA2R antibodies in patients with primary MGN is 68.5 % [9]. There is still 30 % false-negativity with serum MPLA2R antibodies in primary MGN. Tissue staining for MPLA2R has sensitivity of 75 % and specificity of 83 % [10]. The same could not be done in our patient for technical reasons.

Discussion:
The most common therapeutic agents implicated in secondary MGN are NSAIDS, mercury containing skin lightening agents [7], D-Penicillamine, Gold salts, Bucillamine, anti-Tumor Necrosis Factor agents, Etanercept, Infliximab and Adalimumab. Therapeutic agents induced MGN can occur at any age and usually develops within 6 to 12 months of exposure to the offending agent, but the onset may be delayed for 3 to 4 years [11]. Our patient developed MGN after 18 months of exposure to D-Penicillamine. D-Penicillamine though no longer in widespread use in Western part of the World, it is still being used in India for Rheumatoid Arthritis and Wilson’s disease. The spectrum of D-Penicillamine induced nephropathy are – MGN (80 %), Tubulo-interstitial disease, Minimal Change Disease, Crescentic glomerulonephritis, Good-Pasture’s syndrome and Renal limited vasculitis [12]. The protein excretion may continue to rise for several months after the cessation of D-Penicillamine and the mean time to resolution of the proteinuria is 9 to 12 months, in some cases it may take upto 2 to 3 years. The mean dose of D-Penicillamine was 1.09 gm/day and the mean duration of treatment until diagnosis of Nephrotic Syndrome was 11.9 (± S.D 18.8) months. Peak level of proteinuria 10.79 gm/day. In the overwhelming majority proteinuria disappeared within 7 months after stoppage of D-Penicillamine. Patients treated with corticosteroids had a faster
response \[^{13}\]. Our patient is on regular follow-up. There is partial remission of proteinuria after 5 months. We are hopefully awaiting complete resolution of proteinuria in the ensuing months.

<table>
<thead>
<tr>
<th>SECONDARY MN</th>
<th>PRIMARY MN</th>
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<tr>
<td>Presence of Mesangial hypercellularity suggests an underlying systemic disease.</td>
<td>Rare</td>
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<tr>
<td>Tubuloreticular inclusions (which may be found in association with viral or SLE-associated MGN)</td>
<td>Rare</td>
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<tr>
<td>Immune-complex deposits throughout the glomerulus suggests secondary MGN</td>
<td>Only in sub epithelial zone</td>
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<tr>
<td>Intense C1q staining (which correlates with SLE-associated disease)</td>
<td>Rare</td>
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Membranous neohropathy after use of UK-manufactured skin creams containing mercury. JM. 2011; 104:893-896.


10 Christopher P. Larsen, Modern Pathology 2013, 26, 709-715.

