Original Research Article

Paradigm shift in Membranous nephropathy

Abstract:

The present study discusses about Paradigm shift in Membranous nephropathy.Recently, using laser microdissection of glomeruli and mass spectrometry analysis of the proteins in the biopsies of patients with MN, Sethi et al. discovered another antigen, exostosin, associated with autoimmune etiologies of the disease. Human embryonic kidneys showed the presence of NELL-1 in the extracellular component and possible deposition in the glomerular basement membrane.In patients tested, the glomerular basement membrane and subepithelium stained positively for NELL-1.In biopsies of patients with a diversegroup of glomerular diseases and in those with primary MN, NELL-1 was not present who were PLA2R or THSD7A positive. It can be safely concluded that pts. With NELL1 deposit do not seem to be at a higher risk for malignancies.

Keywords: Paradigm shift, Membranous nephropathy,malignancies,embryonic kidneys

Introduction-

Membranous nephropathy (MN), a common cause of nephrotic syndrome in adults, may be either primary or associated with a number of etiologies each with unique antigens and antibody complexes localizing in a subepithelial location of the glomeruli(1). Beck et al. discovering a phospholipase A2 receptor (PLA2R) antigen in the deposits along with immunoglobulin has paved the way for recent clinical and bench research in primary MN. As of now, we know that 70% to 80% of primary MN is related to PLA2R while 1% to 5% are associated with THSD7A.(1) THSD7A (thrombospondin type 1 domain containing 7A) is a large transmembrane glycoprotein that is expressed by podocytes and has IgG4 predominant immune response similar to PLA2R. However, the correlation between the THSD7A antigen and disease activity isn't proven yet.THSD7A is more commonly associated with certain malignant tumors and is more common in females.

Recently, using laser microdissection of glomeruli and mass spectrometry analysis of the proteins in the biopsies of patients with MN, Sethi et al. discovered another antigen, exostosin, associated with autoimmune etiologies of the disease(2). Sethi et al. described a new antigen, NELL-1 (neural epidermal growth factor like 1 protein),and labeled it as a distinct cause of primary MN(3). The finding of anti-PLA2R antibodies in the serum and/or the finding of PLA2R antigen in a patient's kidney biopsy helps confirm that the patient's MN is primary. These are already standard techniques at many institutions. Sethi et al. described a novel antigen, NELL-1, in PLA2R- and THSD7A-negative cases of "primary" MN.NELL-1 encodes a 90-kDa proteinof 810 amino acids and is known to be highly expressed in osteoblasts. NELL-1 is overexpressed in patients with craniosynostosis.(3)Human embryonic kidneys showed the presence of NELL-1 in the extracellular component and possible deposition in the glomerular basement membrane.In patients tested, the glomerular basement membrane and subepithelium stained positively for NELL-1.In biopsies of patients with a diversegroup of glomerular diseases and in those with primary MN, NELL-1 was not present who were PLA2R or THSD7A positive. However, unlike PLA2R-positive MN, where malignant tumors are infrequently found and thought to be coincidental, the relationship between NELL-1 and malignant tumors is yet unknown(4). Tumors were not detected in the discovery or pilot cohort. It is unknown whether these patients with malignancies had a coincidental finding of NELL-1 and a tumor or whether NELL-1 positivity was found in the tumor cells like in some cases of THSD7A. Therefore, whether NELL-1 is truly a primary MN etiology or in some populations related to a malignant tumor remains to be determined.

Method: A study was conducted in the department of nephrology, at Sawai Man Singh medical college Jaipur wherein a data of 440 patients with renal pathology was collected.

- Study design: retrospective observational study
- Inclusion criterion:
    - Data collected from January 2023 to December 2023
    - Renal biopsy suggestive of membranous nephropathy

- Exclusion criterion:
    - Lupus nephritis
    - History of malignancy
    - feature suggestive of disease causing secondary MN
    - Patient not consenting for the study

A thorough history was taken of the enrolled patients along with their informed consent. The patients creatinine was measured at presentation and regularly at subsequent visits along with dipstick from proteinuria. Renal biopsy was performed using 20G renal biopsy gun with the help of ultrasound by a nephrologist and samples were subsequently sent for light microscopy and immunofluorescence. All patients underwent routine investigations and were tested for viral markers including HIV, HEPATITIS B, HEPATITIS C. Quantitative serum pla2r levels were also done in patients without deposition of PLA2R and THSD7A. all the patients underwent thorough workup for malignancy including chest xray, ultrasonography of abdomen, complete blood count, stool routine and microscopy, pap smear as per indication.

Result: Out of 440 patient biopsied, 52 came out to be having MN with female preponderance of 29 patients.

Table1:Agedistributionofstudiedpatients

<20yrs	20-29yrs	30-39yrs	40-49yrs	50-59yrs	>60yrs	total
0	3	8	17	18	6	52

Of these 52 patients 7(13.5%) were seen associated with NELL1 deposition in glomeruli with negative PLA2R levels in serum.

Table2:Agedistributionofpatients with NELL1 deposit

<20yrs	20-29yrs	30-39yrs	30-39yrs	40-49yrs	50-59yrs	>60yrs	total
0	0	1	0	1	1	4	7

Table3:GFRdistributionofstudiedpatients

GFR(ml/min/m^2)	number
>60	32
45-59	12

30-44	8
15-29	0
<15	0

The THSD7A was found positive in 3 patients while no deposition was found in 2 patients. All the 7 patients with NELL1 glomerular deposition

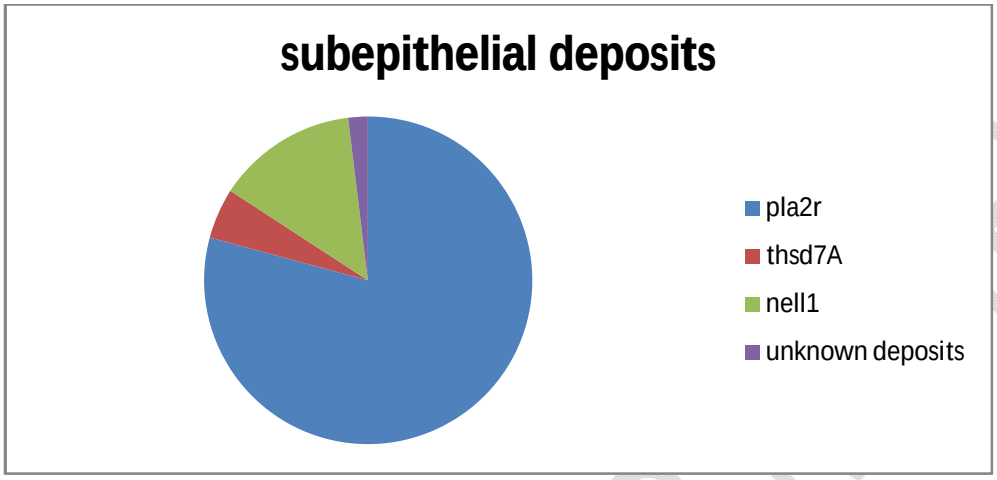

Figure 1: distribution as per type of deposit.

also had elevated IgG1 levels amongst the 7 patients 5 were female while the remaining were male. The pts. Were followed up for the subsequent year but no signs suggestive of malignancy was found. 2 pts. With Nell 1 positivity had deranged renal functions with creat 2.4 and 2.8 subsequently. All the patients were treated with inj. Rituximab but complete remission was achieved in only 4 patients. Among the 52 pts. With MN , 3 pts. With pla2R positivity were found to have malignancy. Two patients had carcinoma of colon while one had small cell lung carcinoma.

Discussion:

Membranous nephropathy (MN) is a unique glomerular lesion that is the most common cause of idiopathic nephrotic syndrome in nondiabetic adults. About 80% of cases are renal limited (primary MN, PMN) and 20% are associated with other systemic diseases or exposures (secondary MN)(5) Most PMN is mediated by antibodies to the M-type phospholipase A2 receptor (anti-PLA2R) (85%), thrombospondin type 1 domain containing 7A (THSD7A) (3%–5%), or by other as yet unidentified mechanisms (10%)(6,7).

The study corresponded with the no. of pla2R positive pts. (76%) and the no. of pts positive with THSD7A (5%) but the no. of unidentified mechanism was 3%. One of the factor contributing to low incidence of unidentified mechanism could be testing for NELL 1 deposition which was missing in the previous studies. As mentioned by Sanjeev Sethi (8) four novel types of MN: exotosin 1 (EXT1)– and exotosin 2 (EXT2)–associated MN, NELL1-associated MN, Sema3B-associated MN, and PCDH7(protocadherin 7)-associated MN. Each of these represents a distinct disease entity, with different

clinical and pathologic findings. However, when the clinical test to detect the other novel agents will become available it will further reduce the percentage of unidentified mechanisms

While most cases of NELL1 MN likely fall into idiopathic/primary MN(9), it is of the authors opinion that NELL1 MN to be categorized as secondary MN as all secondary diseases have been described in association with NELL1 in various previous studies. (9) moreover, the standard immunosuppressive usedin MN are found to be less effective in NELL1 MN.

CONCLUSION:

Based on the findings of study it can be concluded that patients with NELL1 deposit belong to an older age group as compared to overall patients of MN. Patients with NELL1 deposit cannot be differentiated from patients of primary MN nor on the basis of clinical features and nor on the GFR deposit or amount of proteinuria. The pts. With NELL 1 deposit also appear to be treatment resistant, however further subsequent research are required for the treatment strategies. Moreover, it can be safely concluded that pts. With NELL1 deposit do not seem to be at a higher risk for malignancies.

Limitations of study: the study was a single centre study with patients evaluated from last 1 year only. With such a small sample size, the extrapolation of results to the general would be deafening. The association of NELL1 MN with malignancy needs long follow up and regular evaluation. Response and relapse of NELL1 MN associated with traditional treatment of MN needs to be further instigated before any conclusion can be drawn.

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