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A STUDY ON CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY – A SINGLE CENTRE EXPERIENCE

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **" A STUDY ON CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY – A SINGLE CENTRE EXPERIENCE"** is a bonafide work done by **Dr. NIKHIL V JAIN,** registration number : 200120100520 at Madras Medical College, Chennai in partial fulfilment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under our guidance and supervision during the academic year 2020-2023.

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I, **Dr. NIKHIL V JAIN,** solemnly declare that this dissertation entitled " **A STUDY ON CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY – A SINGLE CENTRE EXPERIENCE"** was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during 2020-2023 under the guidance and supervision of my chief **Prof. Dr. T.S. SANTHI, M.D.**

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ABBREVIATIONS

ACEI	–	Angiotensin – converting enzyme inhibitors
ARB	–	Angiotensin receptor blockers
BSA	-	Bovine Serum Albumin
CKD	–	Chronic Kidney Disease
CTLD	-	C-type lectin domains
EM	–	Electron Micrograph
ESRD	–	End stage Renal Disease
GBM	–	Glomerular Basement Membrane
GPI	–	glycosylphosphatidylinositol
GWAS	–	Genome Wide Association Studies
HLA	–	Human Leucocyte Antigen
IST	–	Immunosuppresive Therapy
KDIGO	–	Kidney Disease Improving Global Outcomes
MN	–	Membranous Nephropathy
M-PLA$_2$R	–	M-type Phospholipase A$_2$ Receptor
NELL1	–	Neural Epidermal Growth Factor Like-1
NEP	–	Neural Endopeptidase
NTNG1	–	Netrin G-1
PCDH7	–	Protocadherin 7
Sema3B	–	Semaphorin 3B
THSD7A	–	Thrombospondin type 1 Domain containing-7A

ABSTRACT

BACKGROUND –

Membranous nephropathy is among the most common causes of nephrotic syndrome in adults who are not diabetic. Among primary and secondary membranous nephropathy, primary membranous nephropathy is more common. The aim is to study the outcome of various immunosuppressive therapies in patient with primary membranous nephropathy and also to study the adverse events following immunosuppressive therapy.

MATERIALS AND METHODS –

The patients with primary membranous nephropathy were included in the study based on inclusion and exclusion criteria. Their demographic profile were recorded and analysed. Also, the clinical and biochemical parameters were recorded. Based on the risk stratification patient were initiated on conservative line of treatment or immunosuppressive therapy and their response to treatment and complications if any were studied.

RESULTS AND CONCLUSION –

A total of 31 patients were included in the study. 48.4% ,41.9% and 9.7% of the population were low risk, moderate risk and high risk population respectively. Out of 31 patients, 28 patients were on conservative management and 3 patients were started on modified Ponticelli regimen since they were under high risk groups. After 6 months of conservative management 16.1%

(5/31) had spontaneous remission. A total of 26 patients had received modified Ponticelli regimen. At end of 12 months after completion of modified Ponticelli regimen, 69.2 % (18/26) had complete remission, 3.8% (1/26) had partial remission, 26.9% (7/26) had no remission. The 8 patients who had persistent proteinuria were initiated on tacrolimus. After 12 months of the treatment 1 patient had complete remission, 2 patient had partial remission. The modified Ponticelli regimen was tolerated well by the patients.

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INTRODUCTION

The most common cause of nephrotic syndrome in adults who are non diabetics is Membranous Nephropathy (MN). Membranous nehropathy can primary or secondary. Amomg the two, primary membranous nephropathy is more common. Primany membranous nephropathy is a disease which is now considered as autoimmune in origin and kidney specific. The M-PLA_2R antibodies is the most common antibody responsible for disease activity and accounts for 70%. The PLA_2R antibodies are mainly IgG4 subclass. On renal biopsy, the immune deposits were found to have PLA_2R AND IgG4 along side. The secondary causes of membranous nephropathy include hepatitis B and hepatitis C virus infection, malignancies, autoimmune diseases like systemic lupus erythematosus, rheumatoid arthritis, etc and drugs. Patients with pimary membranous nephropathy are categorized into low, moderate, high or very high risk based on proteinuria and renal function test. Low and moderate risk patients and treated conservatively and monitored for 6 months. Immunosppressive therapy is initiated if they don't resond to the conservative management. High and very high risk groups are initiated on immunosuppressive therapy. One third of patient with primary MN goes in for spontaneous remission. 14% of patients have progressive renal failure[78].

The incidence of recurrent MN in renal transplant recipients who had a history of MN in the native kidneys is between 10 and 45 percent[47-57]

AIMS OF THE STUDY

- To study the outcomes of various immunosuppressive therapies in patients with primary membranous nephropathy

- To study the adverse event of immunosuppressive therapies

REVIEW OF LITERATURE

The most frequent cause of nephrotic syndrome in adults who are not diabetics is Membranous Nephropathy (MN). An estimated 8–10 instances per million people are affected by it.. The pathophysiology and treatment have just recently become more clear, despite the fact that immunofluorescence and electron microscopy first recognised it as an unique clinic-pathological entity in the 1940s. Thrombospondin type 1 domain-containing 7A antibodies and M-type phospholipase A2 receptor (PLA2R) antibodies have opened up new avenues for research into the pathophysiology of disease. The first serologic marker with promising data is anti-PLA2R antibody.

In 1957, Jones recognised membranous glomerulonephritis as a separate pathologic entity based on Bell's proposed name and the different structural changes to the glomerular basement membrane (GBM) and thickening of the capillary walls with periodic acid-Schiff-silver methenamine stain[1,2]. Later it was shown that these distinctive histological changes were caused by immune complex deposits accumulating between the podocytes and subepithelial component of GBM. The nephrotic syndrome is a clinical outcome of these deposits interfering with normal podocyte barrier function. Due to the absence of considerable glomerular inflammation, the term membranous glomerulonephritis has been mainly superseded by membranous nephropathy (MN). Primary MN is

defined as MN that develops in patients when there are no known reasons and so is the case 75 – 80 % of patients with membranous nephropathy [3]. Malignancy (lung, kidney, stomach, and colon), systemic lupus erythematosus, medication responses (non-steroidal anti-inflammatory medicines, gold, and penicillamine), infection, and other disorders account for about 20% to 25% of MN cases (hepatitis B, C). Primary and secondary MN have significantly different immunohistochemistry and clinical trajectories[4,].

EPIDEMIOLOGY

MN can affect people of all sexes and ethnicities. But beyond age 40, primary MN is more prevalent in Caucasian males. Nephrotic syndrome in non-diabetic individuals is most frequently caused by MN, with an estimated prevalence of 8–10 cases per million. A single nucleotide polymorphism in HLA-DQA1, a member of HLA class II in Caucasians, which may predispose to autoimmunity, was linked to associations in a genome-wide association analysis conducted by a European consortium[5].

GENETICS

Familial MN is rare and is seen in younger individuals. Single nucleotide polymorphisms in non-coding areas of the PLA2R gene have also been discovered by GWAS research. Strong evidence points to an interaction between

the HLA and PLA2R genes as homozygosity for high-risk alleles in both the HLA and PLA2R genes increases the odds ratio for PMN almost eightfold in white patients and tenfold in Chinese patients and is associated with higher levels of antibody production. DRB1*1501/DRB1*0301 and DRB3*02:02 [8,9] are two additional independent HLA risk alleles that have recently been discovered in Chinese patients through two GWAS studies, and these findings raise the possibility that DRB1 may be more crucial in generating the HLA signal in that population than DQA1. Ninety-nine percent of PLA2R-positive patients have at least one of these HLA risk alleles, and having one HLA risk allele increases the odds ratio for developing PMN by almost a hundredfold. However, risk alleles found thus far are widespread in the general population, and research to date is also consistent with an environmental trigger as opposed to a specific coding variant in PLA2R genes conferring a propensity for autoimmune disease.

ANTIGENS IN PRIMARY MEMBRANOUS NEPHROPATHY

- **PHOSPHOLIPASE A2 RECEPTOR**

A transmembrane glycoprotein called PLA2R belongs to the family of mannose receptors. It has a tandem repetition of eight C-type lectin domains, a cysteine-rich (Ricin B) domain, and a fibronectin II domain (CTLD 1–8). Three domains - Cys-R, CTLD1, and CTLD7—have been found to include

anti-PLA2R-reactive epitopes that are conformation-dependent [10]. The discovery that patients with anti-PLA2R directed at the Cys-R epitope, which is recognised by 100% of anti-PLA2R antibodies, may have less severe disease and undergo more spontaneous remissions than those with antibodies primarily reactive with the CDL1 and CDL7 domains, and that epitope spreading beyond the Cys-R domain may confer a worse prognosis, suggests the possibility that these various epitopes could be of clinical significance.

- **THROMBOSPONDIN TYPE-1 DOMAIN CONTAINING 7A**

THSD7A is also a transmembrane receptor on podocytes. It might be the antigen responsible in 3% of primary MN and 10% of patients who are negative for anti PLA2R antibodies[11]. In a study of 154 patients anti PLA2R negative idiopathic MN only 15 paients had antibodies specific for THSD7A. There may be association of THSD7A in membranous nephropathy caused by malignancy. Some cases of MN associated with cancer may also have THSD7A aetiology[12]. THSD7A expression was found by immunohistochemistry on tumour cells but not on normal gallbladder tissue in one case report of a patient with anti-PLA2R-negative MN and concurrently diagnosed adenoneuroendocrine carcinoma of the gallbladder. In addition, the patient had high plasma levels of anti-THSD7A antibodies, which the investigators hypothesised were produced

against THSD7A that tumour cells had inappropriately expressed. Chemotherapy caused THSD7A antibodies to vanish from the plasma within two weeks and significantly reduced proteinuria. In other research, patients with THSD7A-associated MN were reported to have a greater malignancy rate (between 20 and 50%). There have been a few reported cases of primary MN with dual serological and/or tissue positive for THSD7A and PLA2R[13]. The immunological cause of this finding is unknown, and individuals with dual positive have the same clinical characteristics as other primary MN cases.

Additionally, PLA2R and THSD7A are both tissue and serologically negative in 15 to 20% of instances of probable primary MN, suggesting that there are additional, as yet unidentified antigens in primary MN.

- **NEURAL EPIDERMAL GROWTH FACTOR - LIKE-1**

About 16 percent of cases of primary MN with PLA2R negativity may be caused by the antigen NELL1[14]. In one of the studies, all the controls, including 23 cases of PLA2R-associated MN and 88 cases without MN, were negative for NELL1. This protein was first discovered by laser microdissection and mass spectrometry of glomeruli in 6 of 35 cases of PLA2R-negative primary MN. While no staining was seen in individuals with PLA2R-associated MN or other glomerular disorders, immunohistochemistry for NELL1 revealed positive

staining and colocalization with IgG along the GBM in all six cases of NELL1-positive MN as well as 23 of 91 additional cases of PLA2R-negative primary MN.

All five of the NELL1 positive MN patients for whom blood was available had circulating anti-NELL1 antibodies, but none of the control patients had PLA2R-associated MN, minimal change illness, or immunoglobulin A (IgA) nephropathy. The mass spectrometry results and the limited characterisation of the circulating anti-NELL1 antibodies point to the possibility that IgG1 rather than IgG4 may be the main IgG subclass in this illness. These results suggest that the presence of NELL1 may characterize a certain type of primary MN. To ascertain this significance of proteins in the pathogenesis of MN, more research is necessary. According to one study, up to one-third of people with NELL1-associated MN also had another cancer[15].

- **SEMAPHORIN 3B -**

It has been found that Semaphorin 3B (Sema3B) is the target antigen in a particular type of PLA2R-negative primary MN that seems to affect predominantly children and young adults[16]. In 3 of 160 cases of PLA2R-negative primary MN, sema3B was first discovered by laser microdissection and mass spectrometry of the glomeruli; the protein was not found in 23 cases of PLA2R-associated MN or 88 controls without MN. In all three cases of Sema3B-

associated MN and 8 of 118 additional cases of PLA2R-negative primary MN from three validation cohorts, immunohistochemistry for Sema3B revealed positive staining and colocalization with IgG along the GBM; staining was negative in patients with PLA2R-associated MN and other glomerular disorders. Four out of the five Sema3B-associated MN patients with available sera had circulating antibodies against Sema3B, whereas neither healthy individuals nor patients with other glomerular illnesses did. Eight of the 11 cases (73%) of Sema3B-associated MN involved kids under the age of 18, compared to three (27%), who were adults. Of the eight paediatric patients, five experienced the onset of MN at or before the age of two years. There is a chance that the disease has an inherited component because two of the children patients were siblings and a third patient had a father who had MN.

- **PROTOCADHERIN -**

In a subset (14 instances) of MN patients whose kidney biopsy was negative for all other known antigens, protocadherin 7 (PCDH7) was discovered as a distinct target antigen [17]. In this sample, the median age was 66 years, and six patients had Sjögren's syndrome/SLE, sarcoidosis, or cancer as potential secondary connections. Reduced levels of complement factor 3 may be a distinctive characteristic of the histopathologic phenotype of PCDH7-associated MN, as kidney biopsy results in only trace to 1+ staining by immunofluorescence.

It was shown that there were circulating autoantibodies against PCDH7, and in one instance, IgG eluted from kidney biopsy tissue was discovered to be reactive with PCDH7.

- **NETRIN G1 –**

Netrin G1 (NTNG1), a glycosylphosphatidylinositol (GPI)-anchored membrane protein expressed in neurons and healthy podocytes, was identified as a target antigen in three patients with MN who did not have any antibodies against other antigens and did not have any other autoimmune diseases [18]. All three patients had circulating IgG4-dominant anti-NTNG1 autoantibodies, enhanced NTNG1 expression in the kidney, and glomerular IgG4 deposits.

- **NEURAL ENDOPEPTIDASE –**

In a rare prenatal type of MN, NEP, which is expressed on podocytes, is the likely target. Anti-NEP antibodies from mothers who were alloimmunized during a previous pregnancy and have a hereditary defect in NEP induced MN with subepithelial immune deposits (anti-NEP and NEP) in the fetus/neonate[19-21]. After the maternal antibodies were cleared, the deposits in nephrotic syndrome vanished several months after birth. Despite the fact that complement-fixing IgG1 anti-NEP was also present in their kids, complement-fixing IgG4 anti-NEP was the major IgG subclass of anti-NEP in alloimmunized

NEP-deficient mothers. This discovery offers more proof that the observations in Heymann nephritis are applicable to the human condition, together with data demonstrating that C5b-9 is excreted in the urine of patients with recently developing MN.

- **INTRACELLULAR ANTIGENS -**

Antibodies against additional antigens expressed by podocytes, in addition to the target antigens mentioned above, may aid in the pathogenesis of MN[22-24]. For instance, 186 patients with MN, 36 patients with focal glomerulosclerosis, and 60 patients with IgA nephropathy had their serum IgG4 reactivity against aldose reductase, superoxide dismutase 2, and alpha-enolase, as well as the PLA2R and NEP, evaluated in the aforementioned study. In contrast to patients with other glomerular illnesses, patients with MN had elevated titers of IgG4 against the PLA2R, alpha-enolase, aldose reductase, and superoxide dismutase 2 in 60, 43, 34, and 28% of patients,respectively. One of the other three antibodies exhibited an elevated titer in almost half of the individuals who tested negative for PLA2R antibodies. It has been hypothesised that podocyte injury causes the intracellular enzymes to translocate to the cell surface where they are accessible to the circulating antibodies, amplifying the immune injury and potentially worsening the course of the disease, despite the fact that these antigens

are primarily intracellular and are probably not the primary cause of MN. A second investigation suggested that a negative clinical outcome was independently correlated with the existence and greater titers of antibodies against the intracellular antigens superoxide dismutase 2 or alpha-enolase.

- **CATIONIC BOVINE SERUM ALBUMIN -**

Fewer children with MN have antibodies to the cationic form of bovine serum albumin (BSA)[25]. It is believed that the BSA antigen, which was discovered in the immune deposits of biopsy samples from these patients, is absorbed from the relatively undeveloped paediatric intestinal tract in an undigested or partially digested form and then acts as a planted antigen within the glomerular capillary wall. In one instance, antibodies were eluted from the kidney biopsy sample that were reactive with bovine serum albumin but not human serum albumin.

- **POSSIBLE ANTIGENS IN SECONDARY MEMBRANOUS NEPHROPATHY**

In patients with secondary MN, additional glomerular immune deposits' components have been found. These include hepatitis B antigen, treponemal antigen, and Helicobacter pylori in the pertinent infections; double-stranded DNA in SLE; exostosin-1 and -2 in a subset of class V LN; protocadherin

FAT1 in recipients of hematopoietic cell transplants; thyroglobulin in thyroiditis; carcinoembryonic antigen and prostate-specific antigen. They are not proved to be pathogenic[26-28]

PATHOGENESIS -

Understanding of the pathogenesis of PMN has significantly increased as a result of studies over the last ten years. Current theories are largely based on earlier research using the Heymann models of MN in rats. These studies showed that the pathognomonic, exclusively subepithelial deposits of IgG were the result of in situ immune complex formation involving megalin, a rat podocyte membrane antigen, and that the associated proteinuria was primarily mediated by complement through the membrane attack complex C5b-9[29]. Debiec et al. in Paris in 2002 demonstrated that alloimmune MN in infants of neutral endoproteinase (NEP)-deficient mothers was mediated by maternal anti-NEP antibody that formed immune complexes in situ with NEP on the podocyte membranes of the infants, providing the first confirmation that PMN in humans involved an analogous mechanism [19]. IgG4 antibodies to podocyte-expressed PLA2R are present in the circulation and are also deposited in glomeruli in about 70% of adult patients with PMN, according to a seminal paper from Boston researchers Beck et al. in 2009[3]. This finding has since been supported by numerous other laboratories, with a range of 52%-78%.

Later, a second IgG4 antibody specific for THSD7A, a different podocyte membrane antigen with characteristics similar to PLA2R, was discovered in a smaller subset of PMN patients (2%-5%). Since both antibodies are negative in about 10% of individuals with typical PMN, it is likely that more autoantibodies against podocyte antigens will be discovered. Although uncommon, there have been reports of antibodies that are both PLA2R and THSD7A dual expressed[13].

Unless otherwise stated, the majority of the claims in this review are taken to apply to patients with either antibody, referred to in this study as anti-PLA2R/THSD7A. A higher frequency of related malignancies and a female predominance are the only notable clinical differences found so far for THSD7A. The malignancies that are most frequently linked to PMN express THSD7A. In one study, 20% of THSD7A-positive patients also had coexisting cancer, which was typically found within three months. One potential reason for the well-known link between MN and malignancy is suggested by the finding that THSD7A was expressed in the tumour in two cases. Since rats do not express PLA2R, the pathogenicity of anti-PLA2R has not yet been established[30-32].

PLA2R/THSD7A staining colocalized with IgG4 in glomerular deposits is another indicator that a disease is PLA2R/THSD7A-mediated. Following the removal of the antibody, staining lasts for weeks to months. Most antibody-positive patients exhibit positive PLA2R/THSD7A staining in the

glomeruli, compared to roughly 70% of antibody-negative patients, suggesting that up to 85%-90% of all PMN cases may be anti-PLA2R/THSD7A-mediated. There have been a few instances of anti-PLA2R-positive or assumed positive patients, particularly early in the course, who did not show glomerular PLA2R antigen staining. Patients with PMN include those who are free of systemic disease, anti-PLA2R (70%) or THSD7A (3%–5%) positive, anti-PLA2R/THSD7A negative but have positive glomerular staining for PLA2R/THSD7A (another 15%), anti-PLA2R/THSD7A negative but have positive glomerular staining for THSD7A (3%–5%), and and those (10%) who don't have glomerular staining or PLA2R/THSD7A antibodies but who could later: (1) develop detectable anti-PLA2R/THSD7A antibodies, (2) experience disease caused by a different anti-podocyte antibody, or (3) develop another autoimmune disease to which the MN could be considered secondary.

Some patients eventually achieve a threshold level of IgG4 and C5b-9 deposition that is sufficient to injure or activate podocytes to increase urine protein excretion and produce nephrotic syndrome. Proteinuria resolution (clinical remission) follows antibody disappearance (immunologic remission) by a week or two, just as proteinuria presentation lags behind initial antibody production by weeks or months. This difference between immunologic and clinical remissions is due to the lengthy periods of time needed to develop enough deposits to initially

cause proteinuria, as well as the time needed to clear subepithelial deposits, fix damage to the podocyte and capillary walls, and regain glomerular permselectivity. Proteinuria is therefore a suboptimal clinical indicator for the pathogenic disease processes that are the focus of current immunosuppressive treatments (IST).

In the majority of research using the Heymann rat models, C activation leading to sublytic C5b-9 attack on podocytes has been demonstrated to be the main mediator of anti-podocyte antibody-induced cellular injury and proteinuria. Although involvement for the traditional and alternative pathways have not been completely ruled out, the serologic and immunohistochemical data currently available in PMN are most consistent with complement activation by under-glycosylated IgG4 through the mannose binding lectin pathway. In the rat models, the complement effect involves a sublytic agonistic effect of C5b-9 insertion on the podocyte membrane to activate a number of signalling pathways that together result in an increase in the production of oxidants, proteases, growth factors, and extracellular matrix components as well as in the disruption of the slit diaphragm, apoptosis, autophagy, remodelling of the actin cytoskeleton, DNA damage with cell cycle arrest, and the fact that C3, C4d, and C5b-9 (but not C1q) are prevalent in glomerular deposits, complement activation products are higher in the serum, and serum and urine C5b-9 tend to match disease activity all point to a

comparable function for complement in human PMN. However, some studies of the Heymann models by Hall and colleagues, the transfer of anti-NEP alloimmune MN without complement activation, and an in vivo transfer study with human anti-THSD7A where heterologous phase proteinuria appears to precede detectable complement deposition all indicate that proteinuria in some human PMN may also be C-independent.

PATHOLOGY -

Even in nephrotic patients who test positive for anti-PLA2R/THSD7A, a diagnostic kidney biopsy is still the standard of care in the majority of facilities. Despite nephrotic-range proteinuria, the glomeruli may look completely normal under light microscopy in the early stages of the disease. Using an extracellular matrix dye like silver methenamine, changes in the basement membrane, including thickening and the development of subepithelial "spikes" of basement membrane on the exterior of the capillary wall, become visible over time. In patients who test positive for anti-PLA2R/THSD7A,immunofluorescence microscopy typically exhibits diffuse, homogenous, finely granular deposits of IgG4 along the outer surfaces of all capillary walls.

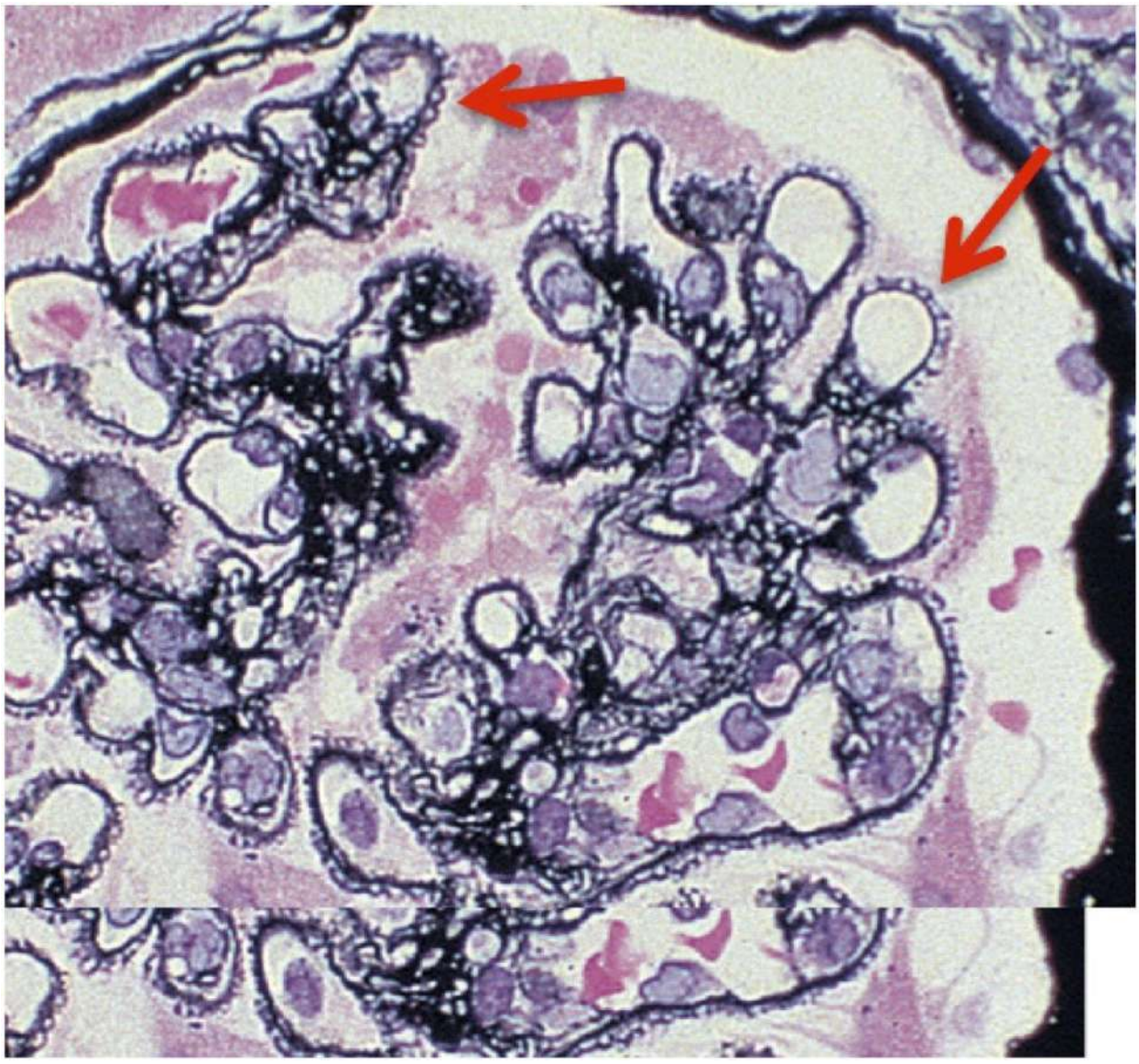


Figure 1 shows silver methenamine stained light microscopy image showing glomerulus with spikes of basement membrane from the outer surface of the basement membrane of the glomerulus

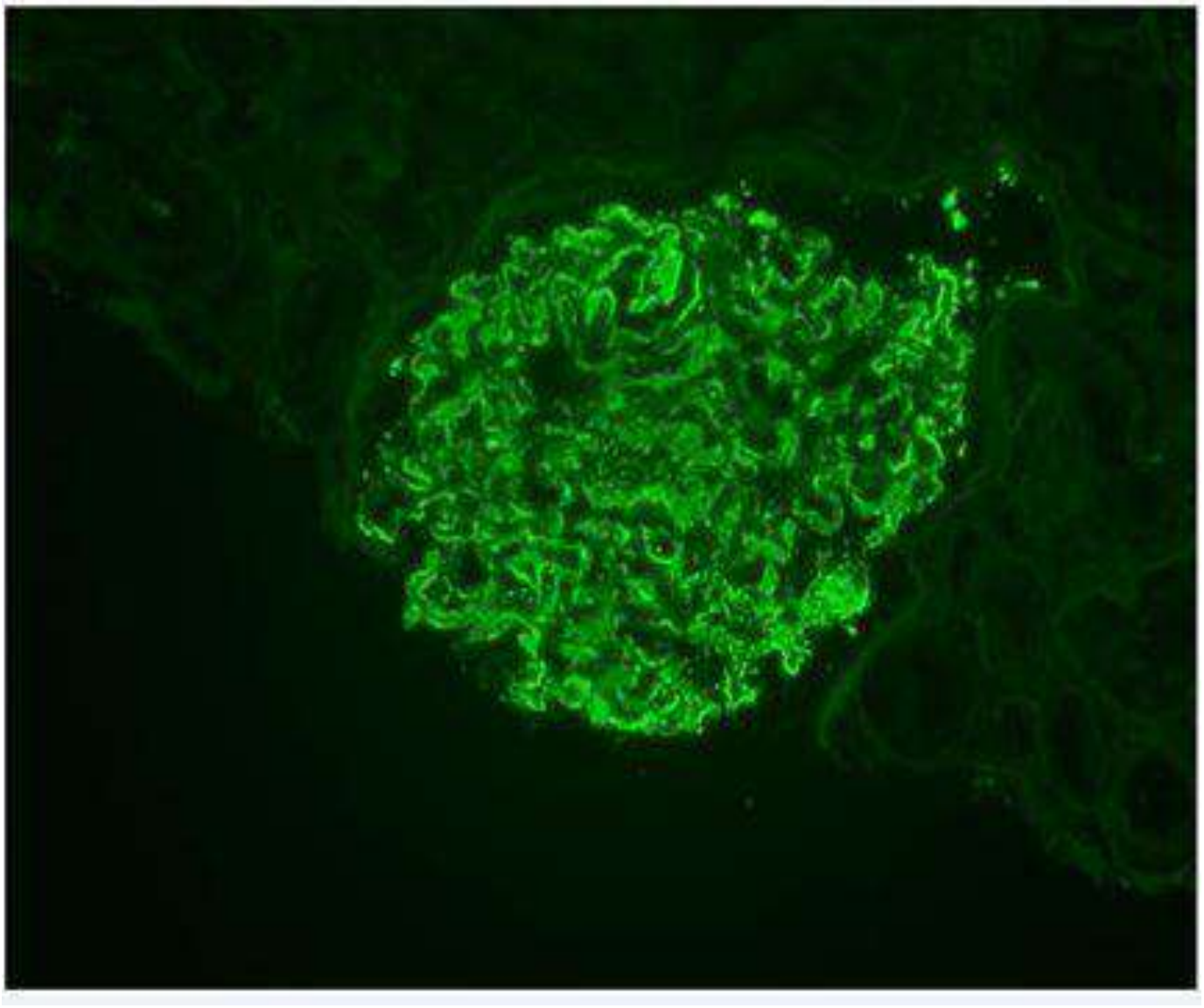


Figure 2. showing IgG4 distributed uniformly in all the glomeruli in a subepithelial distribution in a patient with PLA_2R associated primary membranous nephropathy

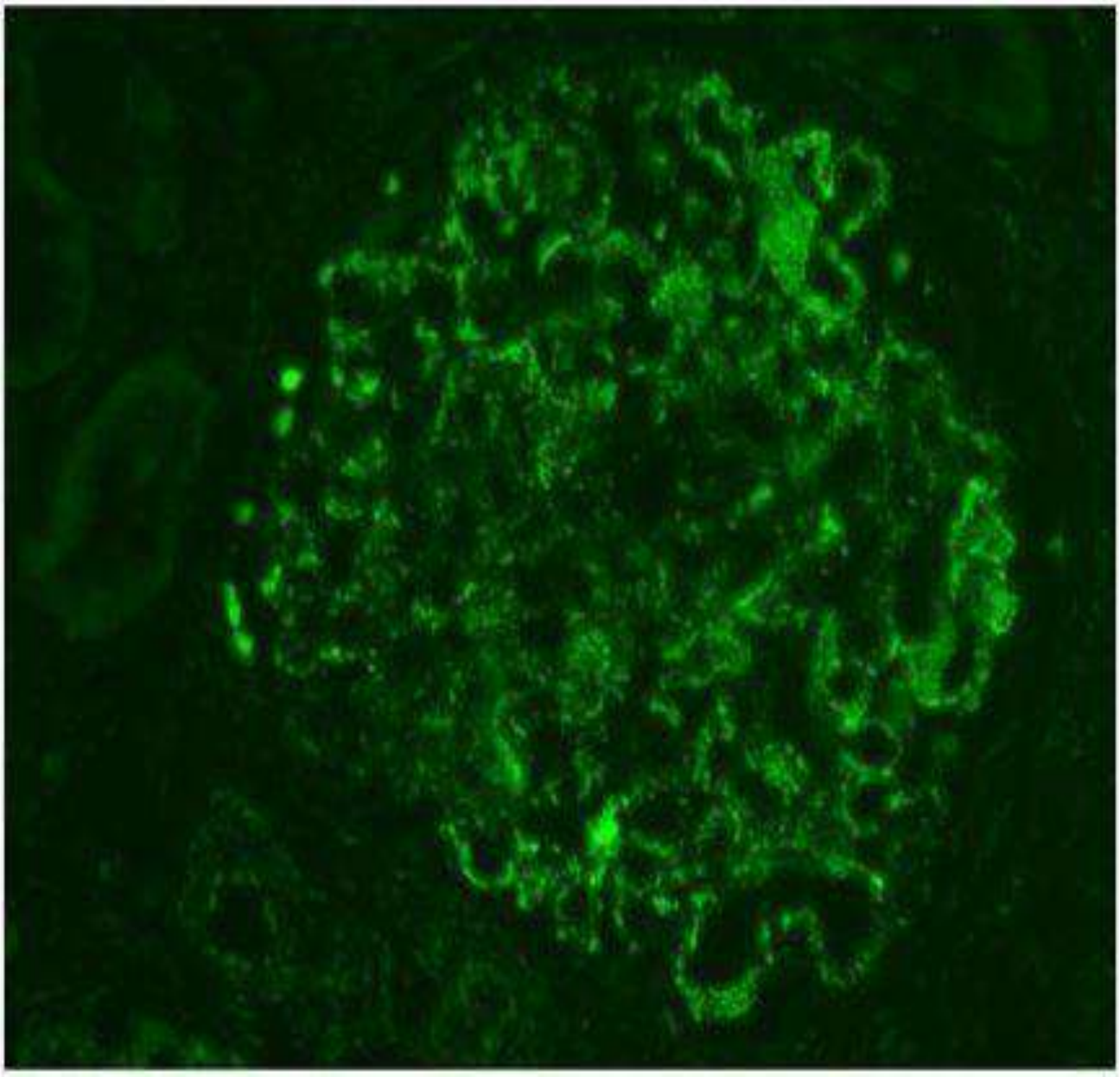


Figure 3. Showing PLA_2R antigen that is finely granular stained in a patient with PLA_2R associated primary membranous nephropathy

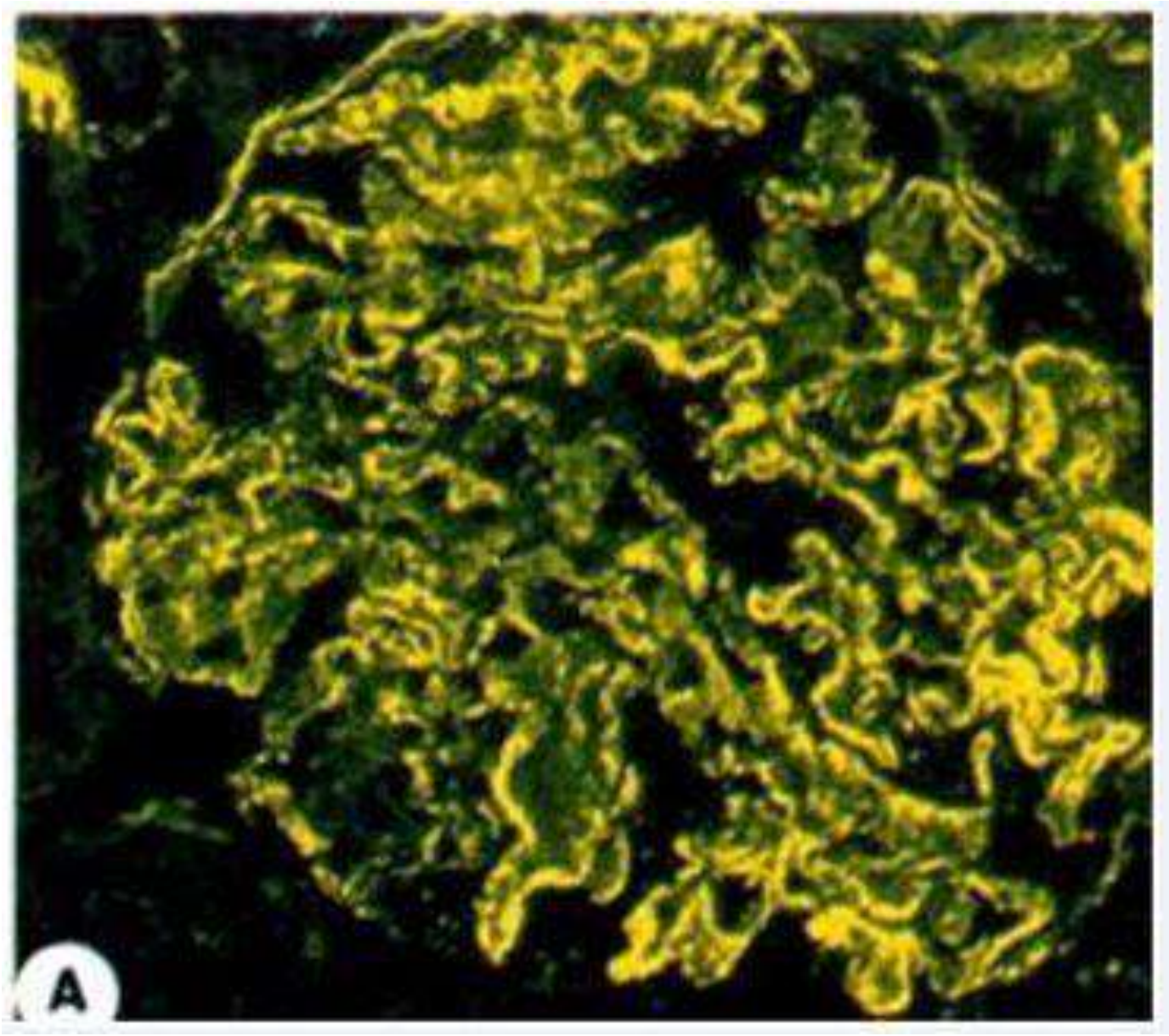


Figure 4. showing complement membrane attack complex (c3, c4d, c5b-9) which are fine granular staining

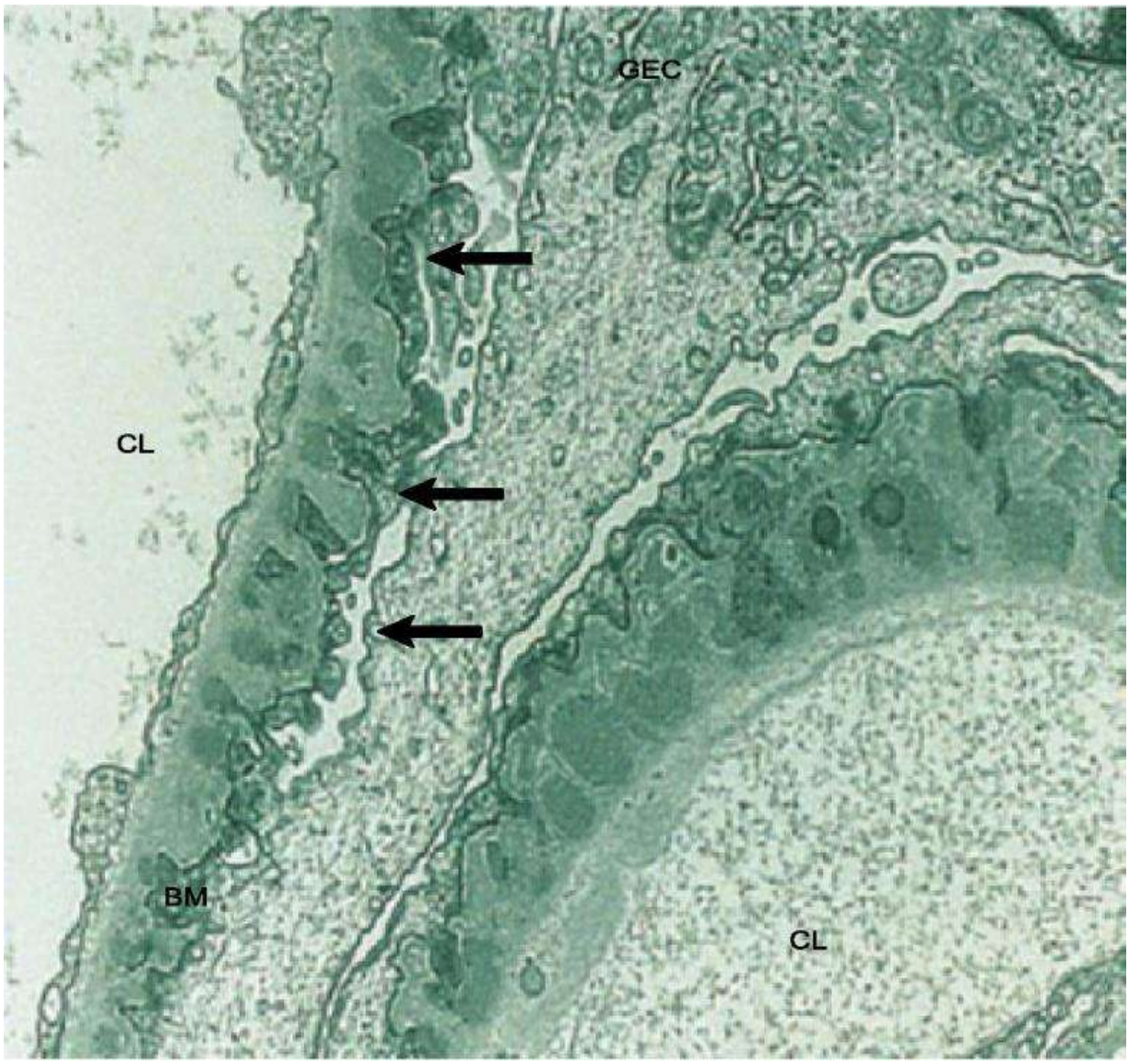


Figure 5. EM showing electron-dense deposits of PLA2R–anti-PLA2R immune complexes along the outer surface of the glomerular capillary wall

STAGES OF MEMBRANOUS NEPHROPATHY

On electron microscopy based on the location of the subepithelial deposits, Membranous nephropathy has four stages pathologically-

STAGE 1

In this stage there are electron dense deposits seen in the subepithelial space between podocytes and basement membrane

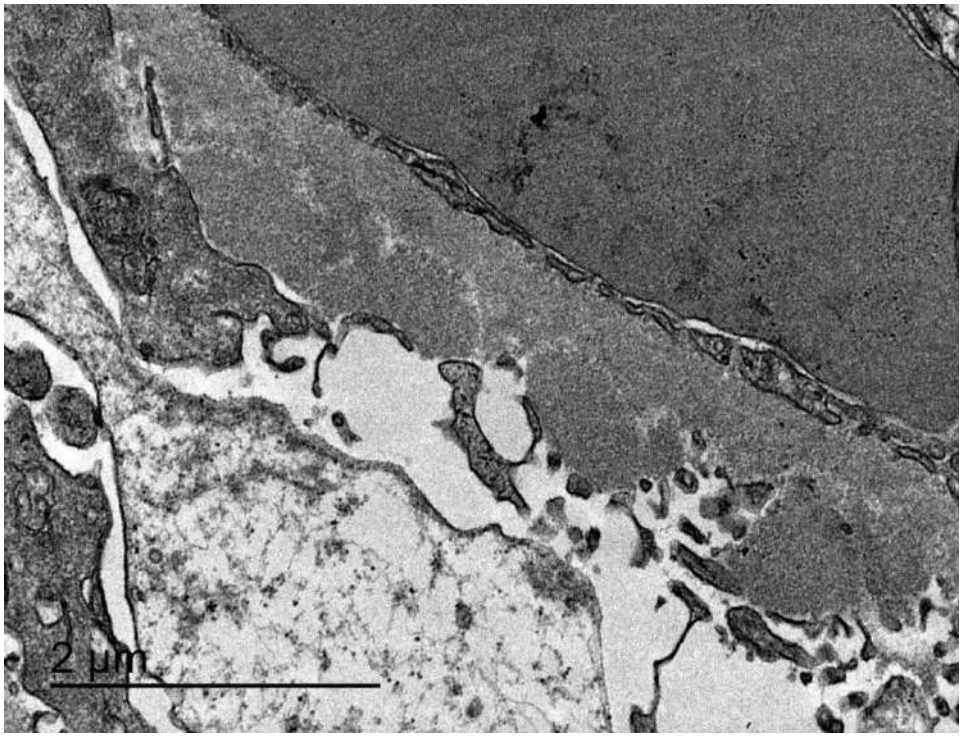


Figure 6. EM showing stage 1 membranous nephropathy

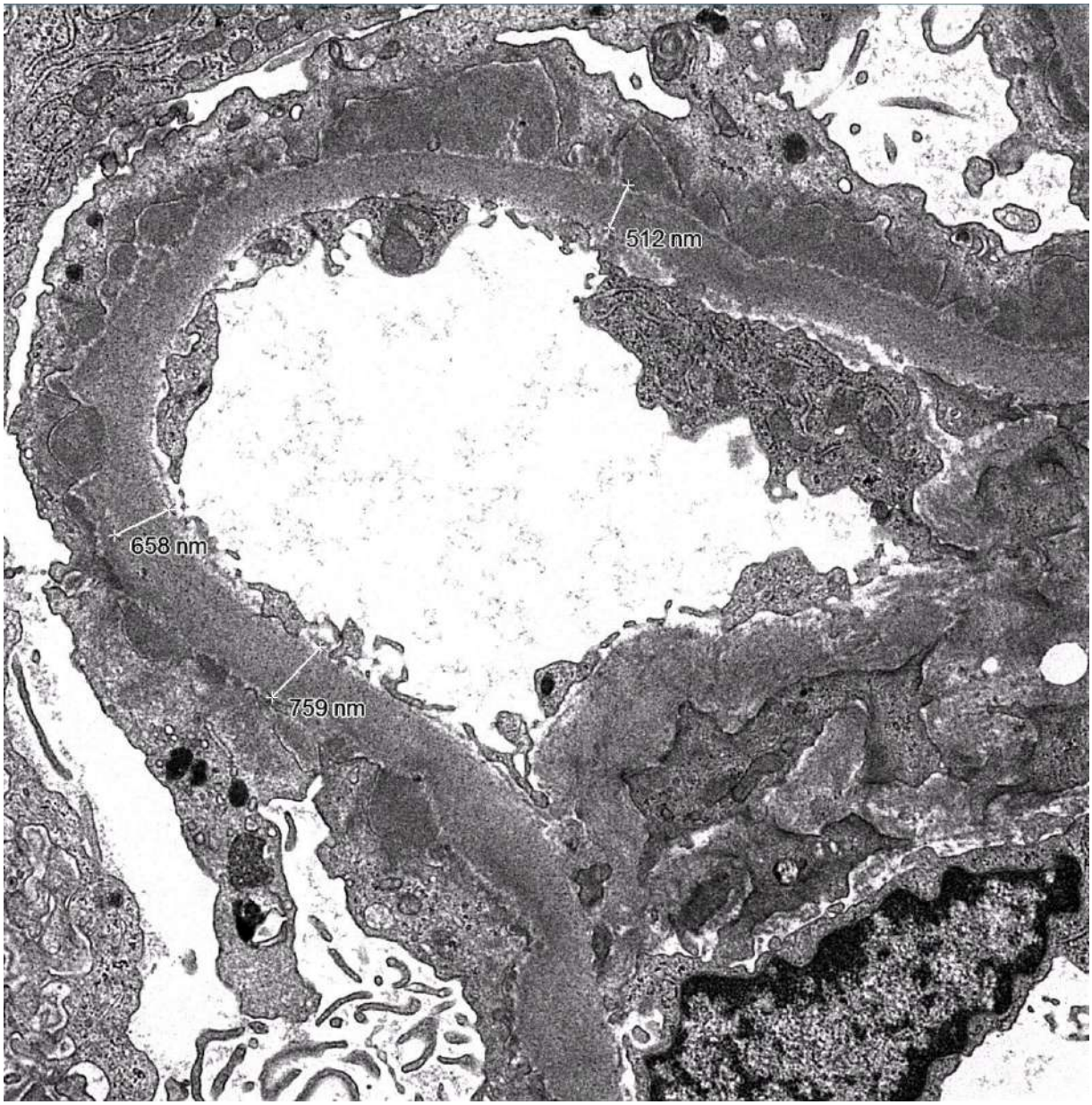


Figure 7. EM showing stage 1 membranous nephropathy

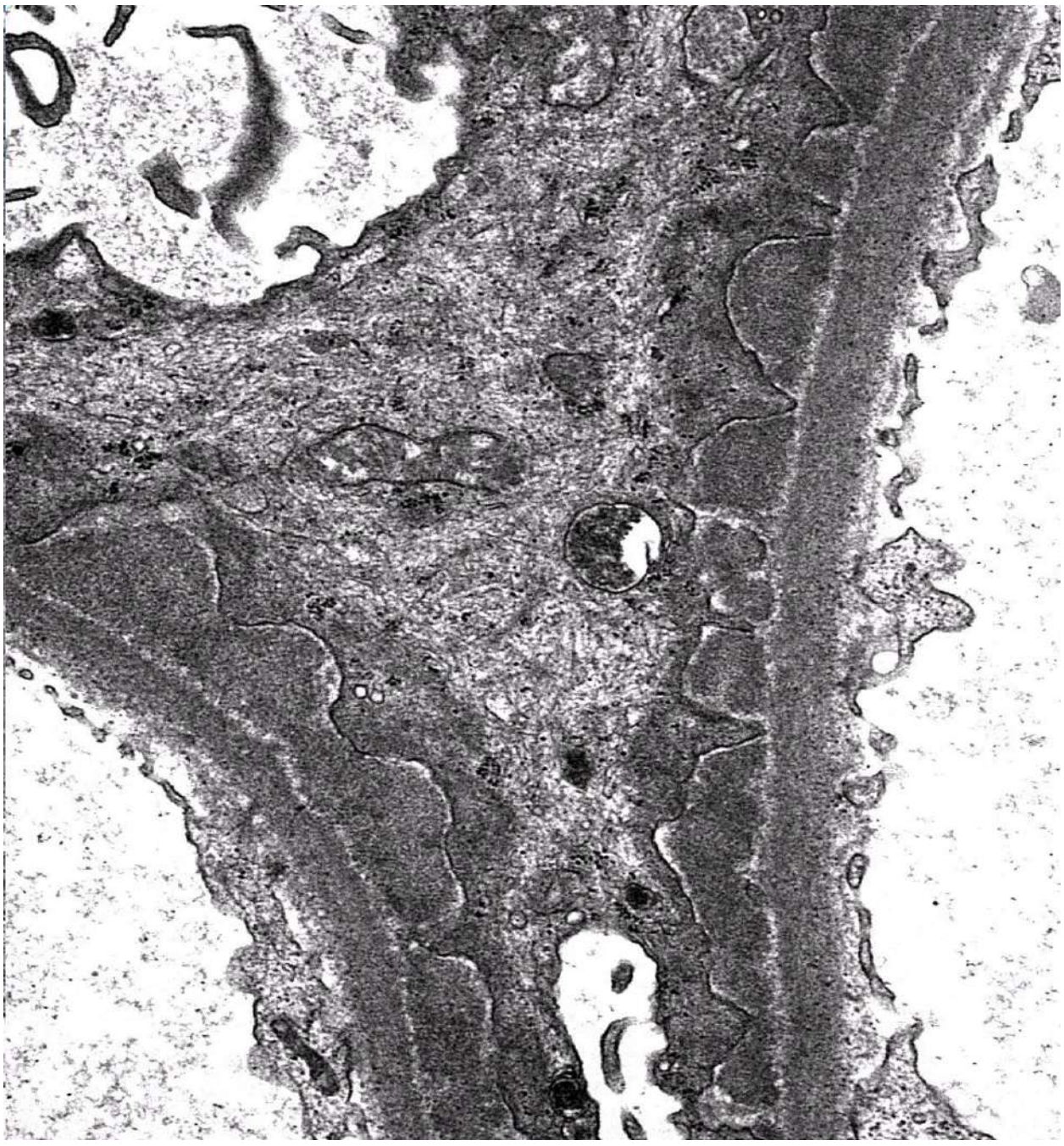


Figure 8. EM showing stage 1 membranous nephropathy (higher magnification**)**

STAGE 2 –

In this stage there are numerous spikes (projection) from the basement membrane in addition to the subepithelial deposits.

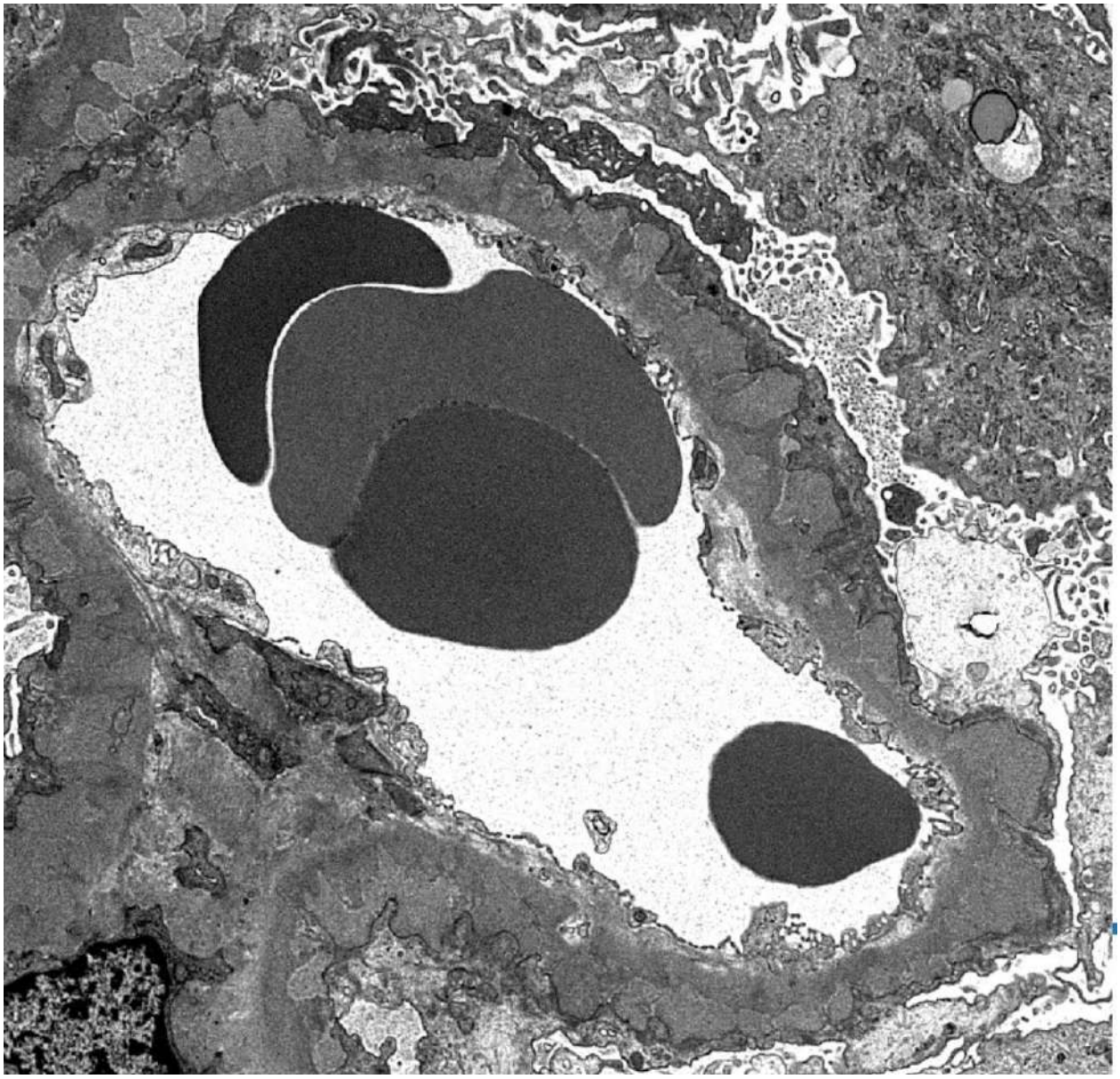


Figure 9. EM showing stage 2 membranous nephropathy

STAGE 3 –

In this stage the subepithelial deposits is surrounded and covered by newly formed basement membrane

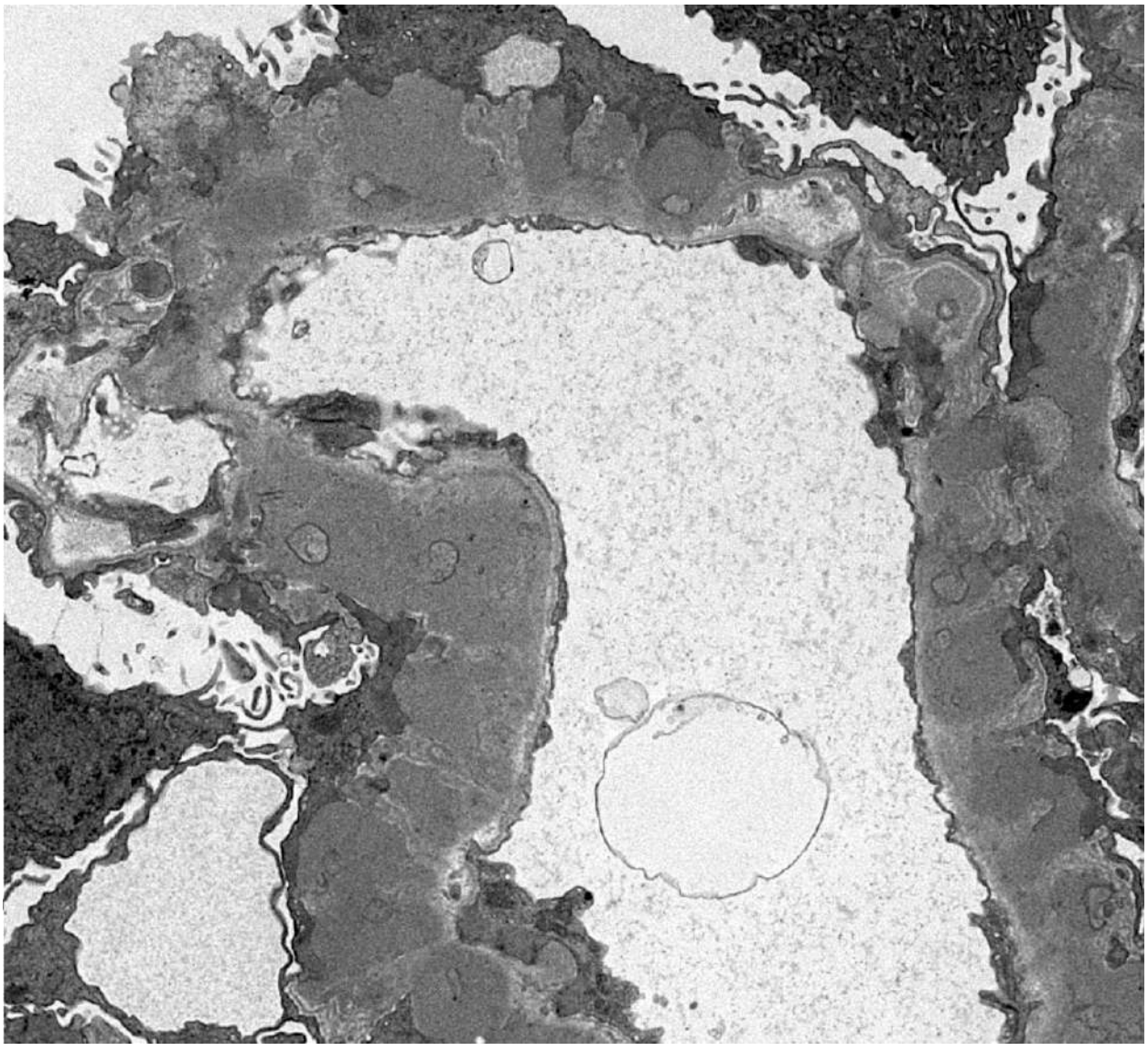


Figure 10. EM showing stage 3 membranous nephropathy

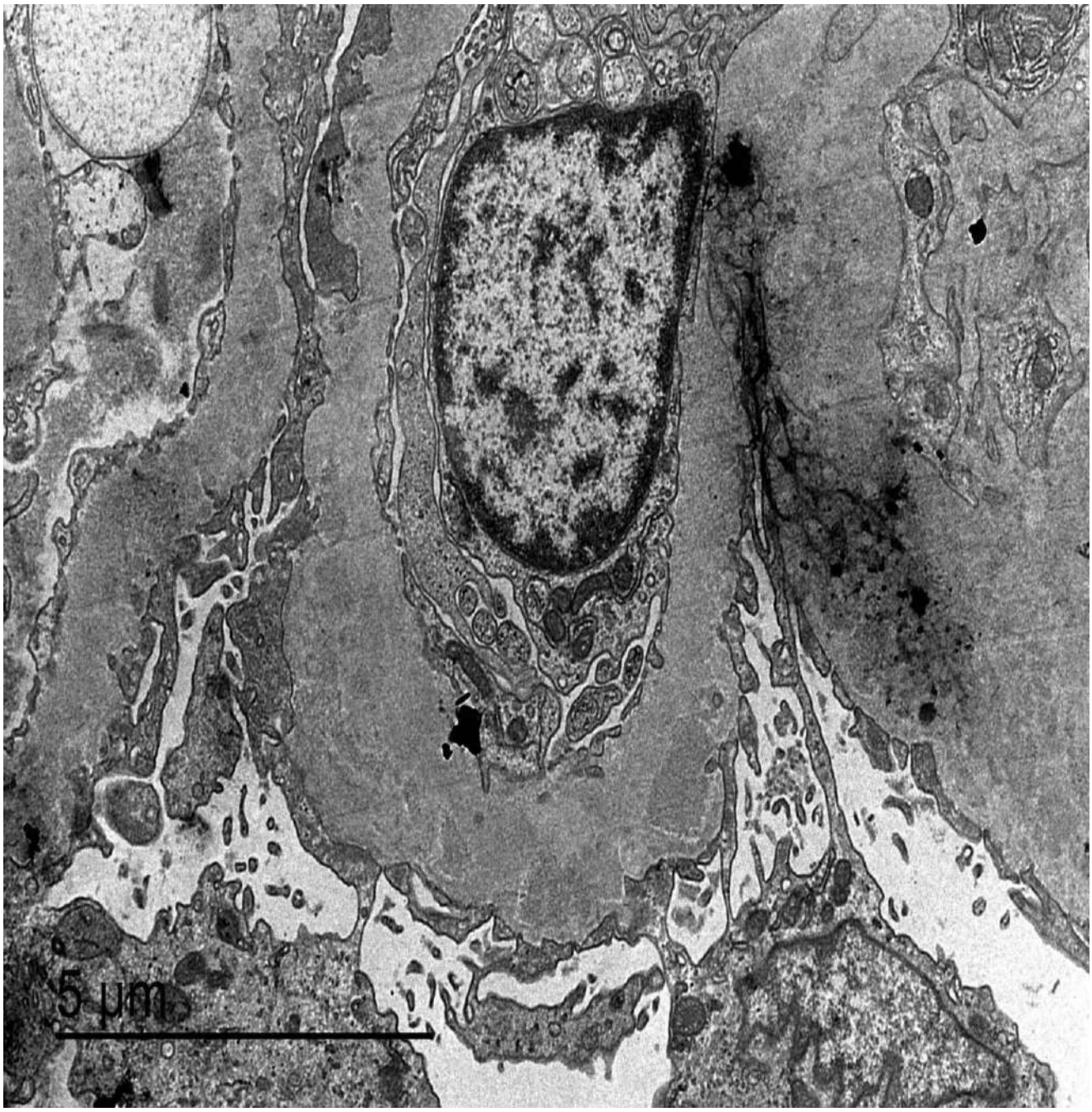


Figure 11. EM showing newly formed basement membrane surroundimg the subepithelil electron dense deposits

STAGE 4 –

In this stage the subepithelial deposits which were dense, now appear electron lucent areas

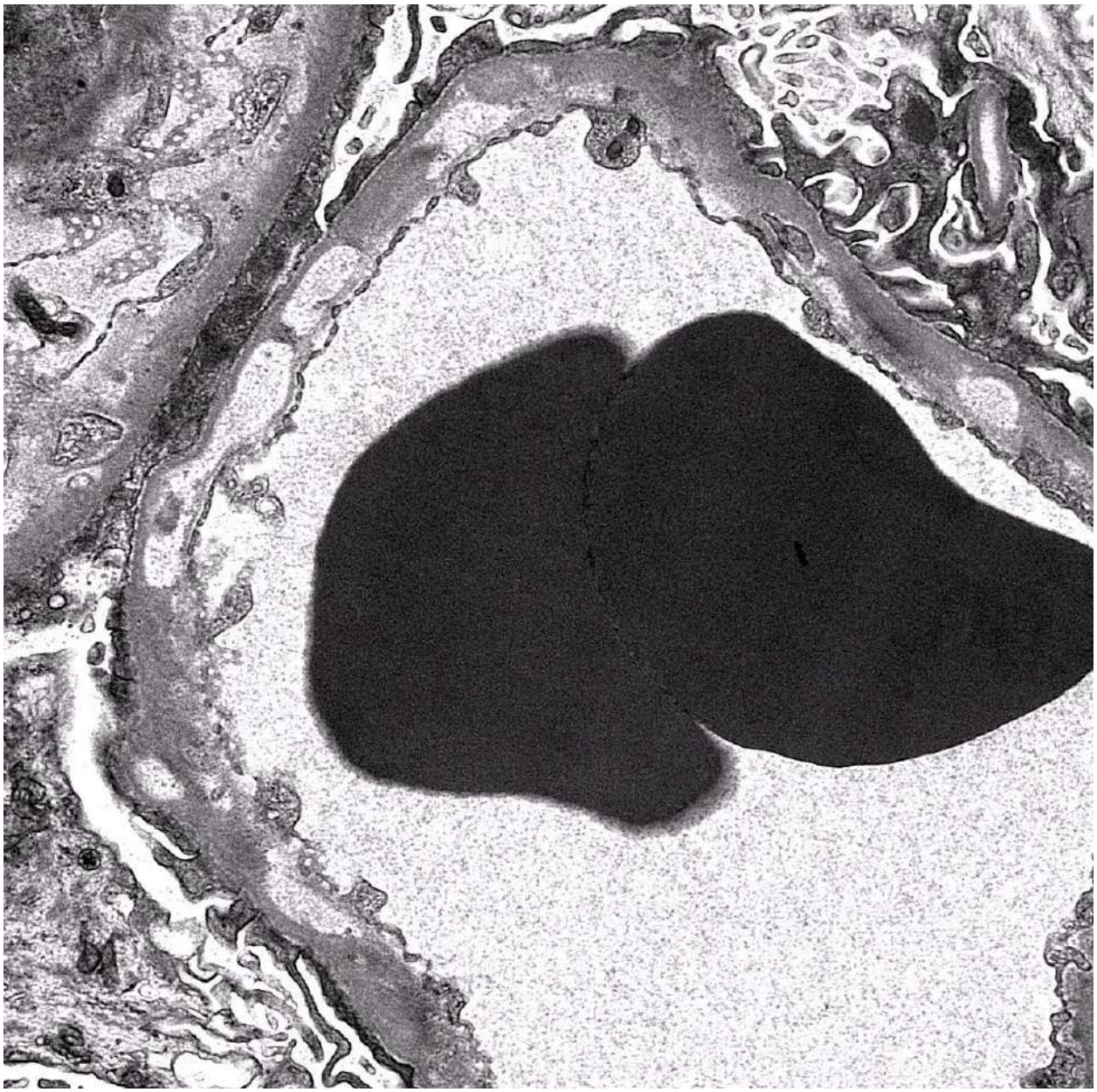


Figure 12. EM showing electron lucent subepithelial deposits

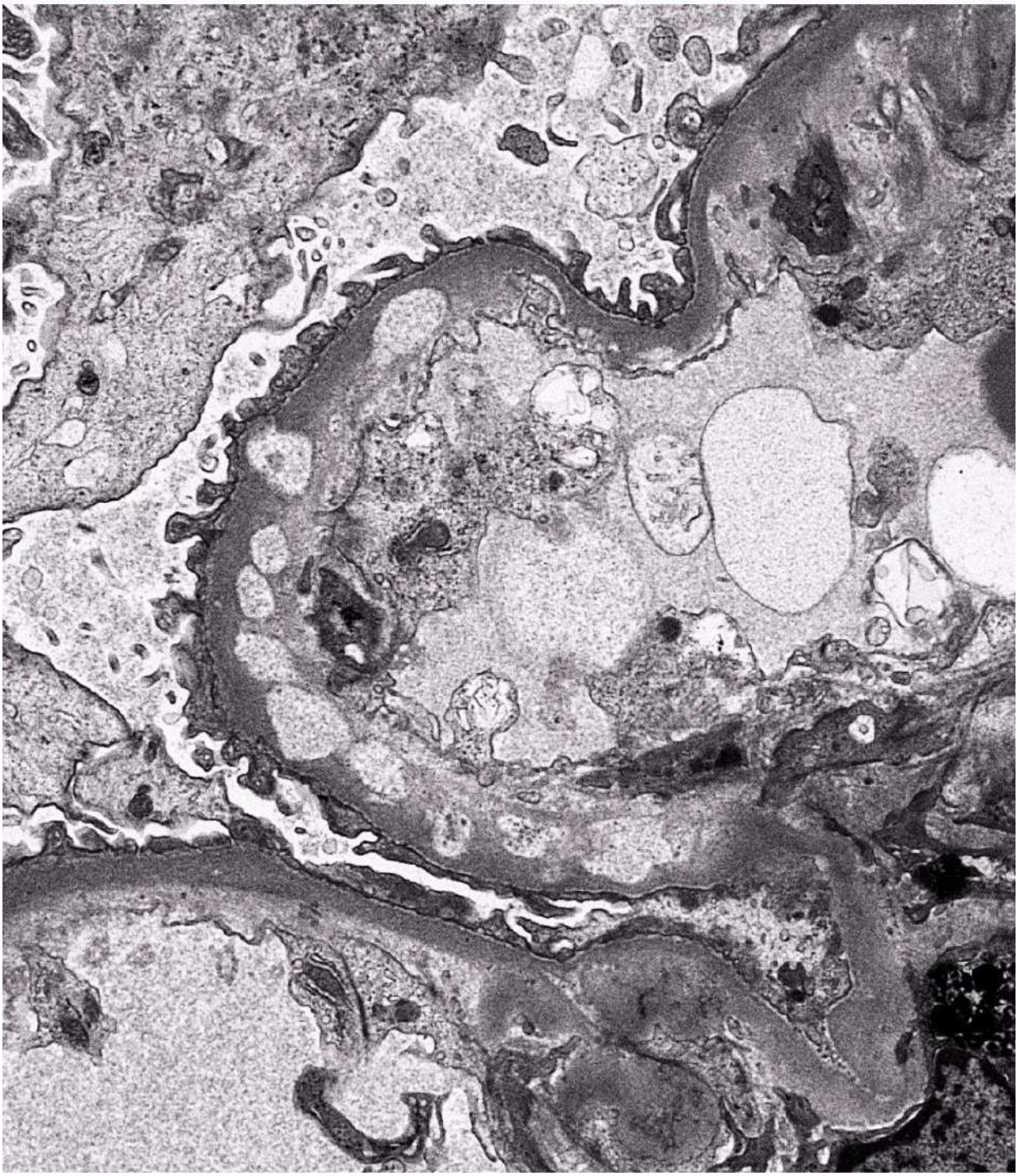


Figure 13. EM showing stage 4 membranous nephropathy

CAUSES OF MEMBRANOUS NEPHROPATHY

Major causes of membranous nephropathy

Primary:
▪ Circulating autoantibodies against podocyte antigens such as PLA2R, THSD7A, exostosin 1/exostosin 2, NELL1, semaphorin 3B, PCDH7, and HTRA1
Malignancy (may not be causative)
Infections:
▪ Hepatitis B virus
▪ Hepatitis C virus (rare)
▪ HIV (rare)
Systemic lupus erythematosus (WHO class V)
Other autoimmune diseases
Drugs:
▪ NSAIDs
▪ Penicillamine
▪ Bucillamine
▪ Gold salts
▪ Mercurial salt, elemental mercury
▪ Anti-TNF therapy
▪ Tiopronin
Thyroiditis
Sarcoidosis (uncommon)
De novo disease post kidney transplantation, caused by donor-specific anti-HLA antibodies
Hematopoietic cell transplant/GVHD

CLINICAL MANIFESTATIONS

- Most of the patients present with nephrotic syndrome which include
    - Proteinuria > 3.5 g/d
    - Edema
    - Hypoalbuminemia
    - Hyperlipidemia
- Thromboemboli – the risk increases when the serum albumin is < 2.8 g/dL
- Microscopic hematuria may be seen in 50% of petients. The abnormalities which can be seen on urine oval fat bodies, lipid droplets, red blood cell [36] and fatty casts.
- Reduced glomerular filtration rate
- Hypertension

FACTORS ASSOCIATED WITH WORSE RENAL OUTCOMES IN MEMBRANOUS NEPPHROPATHY

FACTORS	PREDICTORS
AGE	Older > Younger
GENDER	Males > Females
HYPERTENSION	Present
HLA TYPE	HLA/B18/DR 3/BFFL present
CREATININE	Above normal
SERUM ALBUMIN	<1.5 g/dL
NEPHROTIC SYNDROME	Present
PROTEINURIA	>8 g for >6 months
IgG EXCRETION	> 250 mg/day
BETA 2 MICROGLOBULIN	> 54 g/mmol creatinine
EXCRETION	>7 mg/mg of creatinine
c5b-9 EXCRETION	
BIOPSY CHANGES :	
GLOMERULAR FOCAL SCLEROSIS	PRESENT
TUBULOINTERSTITIAL DISEASE	PRESENT

PRIMARY MEMBRANOUS NEPHROPATHY – RISK STRATIFICATION

[39,40]

	Risk of progression			
	Low	**Moderate**	**High**	**Very high**
	Over an observation period of 3 to 6 months[¶], at least 2 of 3 criteria must be present:			2 or more of the following **at the time of diagnosis:**
Kidney function	▪ Normal or stable (<25% decrease) eGFR over the observation period	▪ Normal or stable (<25% decrease) eGFR over the observation period	▪ Decrease in eGFR ≥25%, not explained by other causes, **at any time** during the observation period	▪ Serum creatinine ≥1.5 mg/dL (≥133 micromol/L), considered due to active MN ▪ Decrease in eGFR ≥25% from baseline over the prior 2 years, considered due to active MN ▪ Severe, disabling, or life-threatening nephrotic syndrome[◇]
Proteinuria	▪ <4 g/day at the end of the observation period	▪ Between 4 and 8 g/day at the end of the observation period	▪ >8 g/day at the end of the observation period **or** Persistent nephrotic syndrome[Δ]	
Serum anti-PLA2R antibody levels (only in patients with anti-PLA2R antibody-positive MN)	▪ Serial titers are persistently low (arbitrarily defined as <50 RU/mL by ELISA) or are decreasing ≥25% by over the	▪ Serial titers are <150 RU/mL and stable or increasing by <25%	▪ Serial titers are high (arbitrarily defined as ≥150 RU/mL by ELISA) and not declining **or** are	

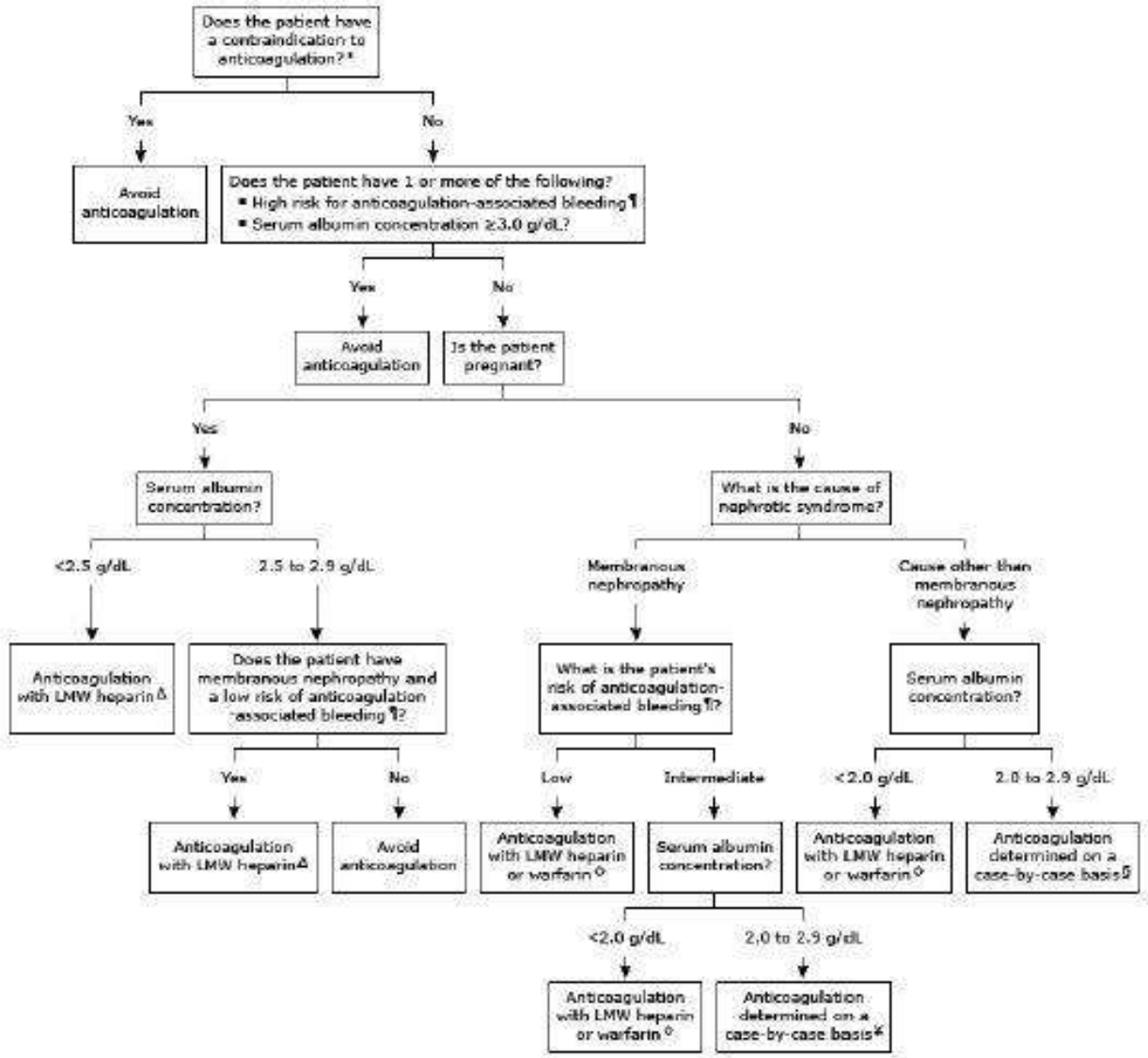
TREATMENT OF PRIMARY MEMBRANOUS NEPHROPATHY

CONSERVATIVE MANAGEMENT

One of the goals of the treatment of patients with primry membranous nephropathy is reducing the proteinuria and reducing the complications due to hypoalbuminemia. Supportive measures should be started at the time of diagnosis. These include inhibition of renin angiotensin system, adequate blood pressure control, treatment with anticoagulation either as prophylaxis or treatment, diuretics for edma and treating dyslipidemia. Not all patients require immunosuppressive therapy as one third of patients undergo spontaneous remission. One of the patients treated with conservative have spontaneous remission. Target blood pressure of 130/80 mmHg is suggested by KDIGO. Patient are started on anticoagulant if albumin < 2.5 mg/dL and as prophylaxis if patient is having venous thrombosis.

In a study conducted by polanco et al, which included 328 patients, 32% of patients had spontaneous remission. Patients with baseline proteinuria <8 g/24 hours, 8–12 g/24 hours and >12 g/24 hours had a spontaneous remission rate of 37%, 26% and 21% respectively[37].

APPROACH TO PROPHYLACTIC ANTICOAGULATION IN PATIENTS WITH NEPHROTIC SYNDROME



IMMUNOSUPPRESIVE THERAPY

Immunosuppresive therapy is initiated for patients who prsesnts with nephrotic syndrome or nephrotic range proteinuria of > 4 g/d for > 6 months or non nephrotic range proteinuria with increase in creatinine[38].

After 6 months of conservative treatment patients are categorized as following based on the Toronto risk score :

- Low risk (proteinuria of < 4g/d with normal serum creatinine and normal creatnine clearance)
- Moderate risk (proteinuria of 4-8 g/d with normal serum creatinine and creatinine clearance)
- High risk (persistent proteinuria of > 8g/d and/or deteriorating renal function)

The first line therapies include cytotoxic theray with glucocorticoids, rituximab and calcineurin inhibitors.

CYTOTOXIC THERAPY WTH GLUCOCORTICOIDS

This therapy is used to treat patients of moderate to high risk categories. An accepted regimen in this particular therapy is Modified Ponticelli regimen[41,42] .

- Patient is treated with Intravenous methyprednislone (1 g/day for 3 days) followed by oral prednisolone (0.5 mg/kg/d for 27 days) during months 1,3 and 5. At the end of these months prednisolone is discontinued without tapering.
- Patient is treated with oral cyclophosphamide (2 mg/kg/day) during the months 2,4 and 6. During this therapy, total leucocyte count are monitored serially and should be > 3500 cells/microL.

Chlorambucil which was used in the Pontcelli regimen was replaced by cyclophosphamide as the former had more side affects than cyclophosphamide[43].

RITUXIMAB

It is an anti CD20 monoclonal antibody. It is the preferred choice of immunosupprsive therapy for high risk patient[44]. Generally, rituximab is well tolerated. Adverse drug effects of rituximab include serum sickness, allergic reactions, opportunistic infections, hypogammaglubulinemia and anaphylaxis.

CALCINEURIN INHIBITORS

This group of drugs which includes cyclosporine and tacrolimus can be used as immunosuppressive therapy in patient moderate risk . If cyclosporine is chosen, the dosage of the drug is 3-5 mg/kg/day in 2 divided doses for a minimum of 6 months. Serial monitoring of the blood cyclosporine is done and is maintained at a level of 120-200 ng/mL. when tacrolimus is chosen, it is prescribed at a dose of 0.05 – 0.1 mg/kg/day in two didvided doses for a minimum of 6 months. The blood levels of tacrolimus should be maintained at 2-5 ng/mL.

MEMBRANOUS NEPHROPATHY AND RENAL TRANSPLANTATION

INTRODUCTION

Membranous nephropathy (MN), which is the cause of end-stage renal disease (ESRD) in the native kidney, can develop de novo in individuals who had another cause of ESRD initially or relapse in patients who had MN as the cause of ESRD in the native kidney.

PRE TRANSPLANT CONSIDERATION

- Every effort should be made to identify the kind of MN that was present in the native kidney, if not already known, in patients with end-stage renal disease (ESKD) attributable to MN who are being assessed for kidney transplantation. The most crucial target antigen in patients with primary MN is the phospholipase A2 receptor (PLA2R), hence it is crucial to ascertain whether the patient's MN was caused by autoantibodies against this antigen. If the patient's native kidney biopsy is accessible, it can be obtained and

immunostained to check for PLA2R inside immune deposits or to see if anti-PLA2R antibodies have ever been found in the patient's blood. Testing should be done if the patient has never had serum anti-PLA2R antibodies checked. A diagnosis of PLA_2R-associated MN is confirmed by the finding of PLA_2R antigen in the native kidney biopsy or by the presence of anti-PLA_2R antibodies in the serum.

- No additional testing is necessary if serum anti-PLA_2R antibodies are undetectable. These patients are thought to have a low probability of developing recurrent MN. At the time of transplantation, some specialists would repeat testing for anti-PLA_2R antibodies because certain stressors (such immunizations and illnesses) may be able to cause the antibodies to reappear.
- The risk of recurrence is high in patients with anti PLA_2R titres > 150 RU/ml[46]. Patients who are planned for transplant in the near future or who is planned for living donor renal transplant, efforts should be made to reduce the titres by atleast 50%.
- Prior to transplantation, treatment may entail rituximab (1 g followed by a subsequent 1 g dose 14 days later) and perhaps plasmapheresis (if transplant

is imminent), with documentation of a reduction in anti-PLA2R antibody levels before performing the surgery. However, the potential advantage of lowering or removing anti-PLA2R antibodies to lower the risk of recurrent illness must be balanced against the additional risk of this additive immunosuppression (i.e., B cell depletion) at the time of transplant. If rituximab is administered, the patient should ideally have already had all recommended vaccinations and boosters against coronavirus disease 2019 (COVID-19) infection. This is because rituximab may reduce the effectiveness of the vaccine.

- For most kidney transplant candidates, including those with MN as the cause of ESRD in the native kidneys, living-donor kidney transplantation is preferred over deceased-donor transplantation given the higher long-term graft survival associated with living-donor kidneys.

RECURRENT MEMBRANOUS NEPHROPATHY

INTRODUCTION

The reported incidence of recurrent MN in kidney transplant recipients with a history of MN in the native kidneys ranges between 10 and 45 percent[47-57]. A higher incidence is reported at centres where protocol biopsies are performed even in the absence of symptoms[58].

PATHOGENESIS :

Anti-phospholipase A2 receptor (PLA2R) antibodies –

The occasionally rapid recurrence of MN after transplantation has raised the possibility of the presence of a circulating factor. A circulating autoantibody, such as autoantibody to the M-type PLA2R, which has been linked to the pathogenesis of MN in native kidneys, is most likely the cause. Patients with recurrent MN have been found to have autoantibodies against PLA2R[59-61]. PLA2R and monotypic immunoglobulin G3 (IgG3) were colocalized in glomerular deposits in one of these patients, who experienced recurrent illness 13 days after transplantation [62]. Additionally, it was discovered that this patient had circulating anti-PLA2R antibodies of the same IgG3 kappa subclass seen in the glomerular deposits of both the native kidney and the allograft,

clearly indicating that this antibody was the root cause of the glomerular illness[63].

Circulating anti-PLA2R antibodies during or after kidney transplantation have been linked to an increased risk of recurrent MN according to several studies [64-67]. Clinical improvement with the resolution of proteinuria occurs in patients with disappearance of anti-PLA2R antibodies by the maintenance transplant immunosuppression or with particular treatment of recurrent MN[66-68]. Thus clinicians can identify patients who require treatment with increasing maintenance immunosuppression or drugs like rituximab by testing anti PLA2R antibodies at the time of kidney transplatation and serial monitoring of the same[46,68].

OTHER AUTOANTIBODIES

Patients with recurrent MN have been found to have additional autoantibodies implicated in original MN[69,70]. In one case report, pretransplant circulating antibodies to the protein thrombospondin type-1 domain-containing 7A (THSD7A) were linked to the recurrence of MN, with THSD7A antigen found in immunological deposits in the kidney allograft. In a different case report, anti-semaphorin 3B antibodies were present at the time of transplantation and

produced an early recurrence of semaphorin 3B-associated MN in the allograft, which had caused MN in a child and resulted in end-stage kidney disease (ESKD) by the time the patient was seven.

GENETIC FACTORS -

Human leukocyte antigen (HLA) loci and PLA2R1 (the gene for PLA2R) genetic variants are linked to the likelihood of recurrence. When the recipient had the HLA-A3 antigen, one study found that the chance of recurrence was 2.5 times higher [71]. The authors of another study speculated that regulation of antigen presentation by the allograft might be involved in the recurrence of the disease in light of the unexpected discovery that donor PLA2R1 and HLA-D polymorphisms were related with increased risk of recurrent MN[72].

CLINICAL PRESENTATION

Although they can appear much earlier (within weeks to months), clinical signs of recurrent MN are commonly seen 13 to 15 months following transplantation [54,55] . Proteinuria is the most prevalent clinical symptom, and the degree of proteinuria varies among patients. Protein excretion may be reduced in those with protocol biopsy-detected recurrent MN who don't have overt illness signs or symptoms.

Even in people who initially have minimal or no proteinuria, proteinuria often progresses. On initial presentation, the glomerular filtration rate (GFR) is frequently normal or very slightly reduced.

POST TRANSPLANT FOLLOW UP

After a renal transplant, patients are monitored intensely to look for any recurrence of the disease. We monitor the spot urine protein-to-creatinine ratio (UPCR) and the serum creatinine level in all patients for six to twelve months and thereafter every three to six months. Depending on the patient's pretransplant antibody status, we routinely check the serum anti-PLA2R antibody levels in patients with PLA2R-associated MN every one to three months for the first six to twelve months following transplantation. Patients who have elevated anti-PLA2R antibody titers at the time of transplant require once a month assessment.

TREATMENT

The treatment of recurrent membranous nephropathy depends on the degree of proteinuria and/or renal dysfunction. For mild disease patient may be initiated on supportive measures like ACEI/ARB, adequate blood pressure control, treatment of hyperlipidemia[58]. The patients are periodically monitored for disease progression as proteinuria may increase with the duration of disease[73], for moderate to severe disease patients are initiated on rituximab at a dose of 375

mg/m^2 and other supportive measures. The measurement of CD19+ B cells levels are done after each administration of rituximab. Patients who take rituximab continue to receive all other immunosuppressive treatments used to avoid rejection. Since there is little chance of leukopenia with rituximab, changing the dosage of other immunosuppressive medications is not required. The patients who respond to the therapy, their CD19+ B cells percentage is usually less than 1 percent. For patients with resistant disease who do not respond to rituximab, the preferred drug is cyclophosphamide (2-8 mg/kg/day for 8 to 12 weeks over other immunosuppressive agents.

MATERIALS AND METHODS

Institutional Ethics Committee approval was obtained for the study. After obtaining informed consent as per the inclusion and exclusion criteria patients with primary membranous nephropathy were included in the study. The Sampling method in the study was based on convenience samping.

The demographic details of the patient were recorded. A detailed clinical history of oliguria, pedal edema, abdominal distension and other relevant clinical history was recorded. Detailed clinical examination including complete systemic examination was done and findings were recorded. Patient's routine hematological investigation which included hemoglobin, total count , platelet count were recorded. Their baseline renal parameters were recorded which included serum urea, serum creatinine and electrolytes. Patient's liver function tests which included serum total and indirect bilirubin, liver enymes, total protein and albumin levels were recorded. Urine albumin and urine protein/creatinine ratio at presentation were recorded. The patients who were under low risk and moderate risk were on conservative treatment and there response to the treatment was recorded. Patient who didn't respond to the conservative management were initiated on Modified Ponticelli regimen and the response to the treatment was

recorded. Patients who had persistent poteinuria were initiated on tacrolimus. All the statistical data were analysed using SPSS softare.

INCLUSION CRITERIA

- Patients with biopsy proven membranous nephropathy with M type Phospholipase A2 Receptor (M-PLA_2R) antigen positivity/ serum M-PLA_2R antibody positivity.
- Patients with serum M-PLA_2R positivity in whom biopsy was not performed.

EXCLUSION CRITERIA

- Patients with secondary causes of membranous nephropathy.
- Patients not willing to participate in the study.

DESIGN OF THE STUDY – Ambispective

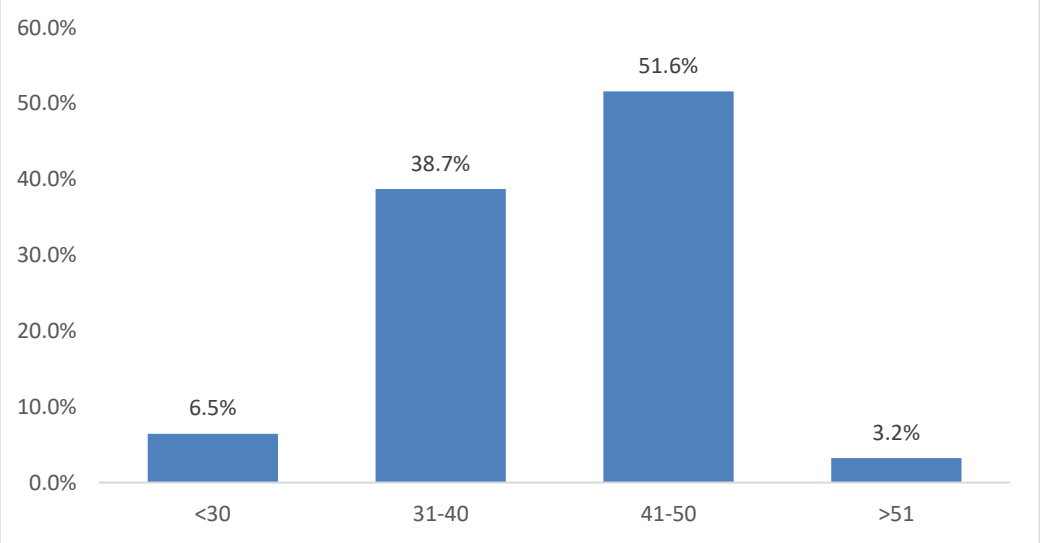
INTSTITUTIONAL ETHICAL COMMITTEE clearance – Approved

STUDY PERIOD – JULY 2022 to NOVEMBER 2022

RESULTS

TABLE-1.AGE DISTRIBUTION OF THE STUDY FROUP

AGE AT PRESENTATION	FREQUENCY	PERCENT
<30	2	6.5%
31-40	12	38.7%
41-50	16	51.6%
>51	1	3.2%
Total	31	100.0%

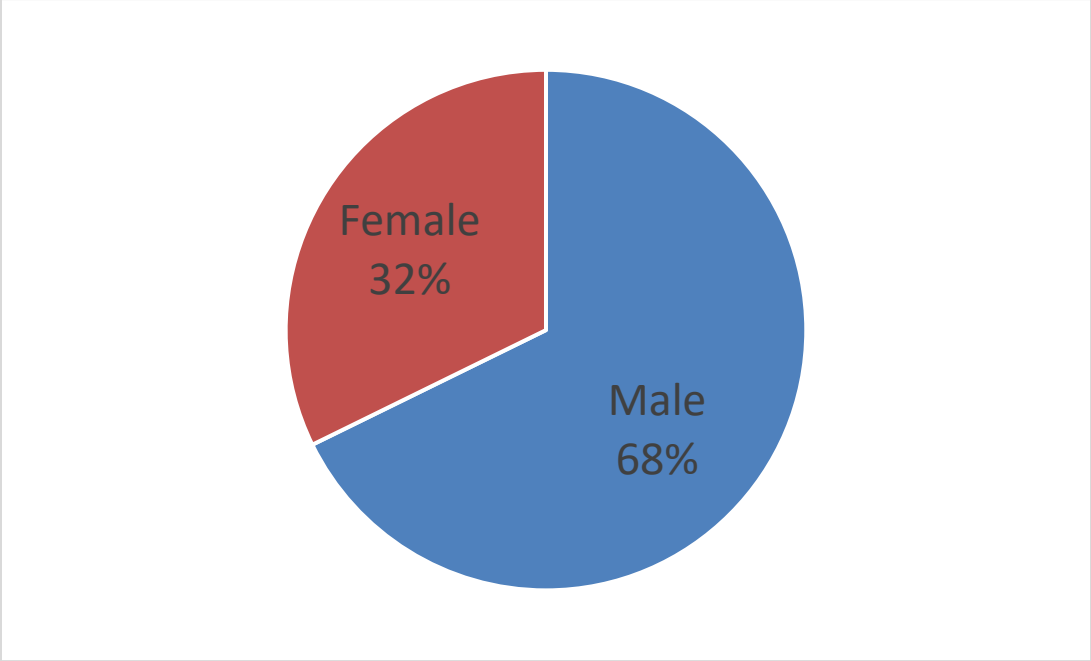


Maximum age – 54 years Minimum age – 28 years

Most of the patient belong age group of 41- 50 years (51.60 %)

TABLE 2. SEX DISTRIBUTION OF THE STUDY GROUP

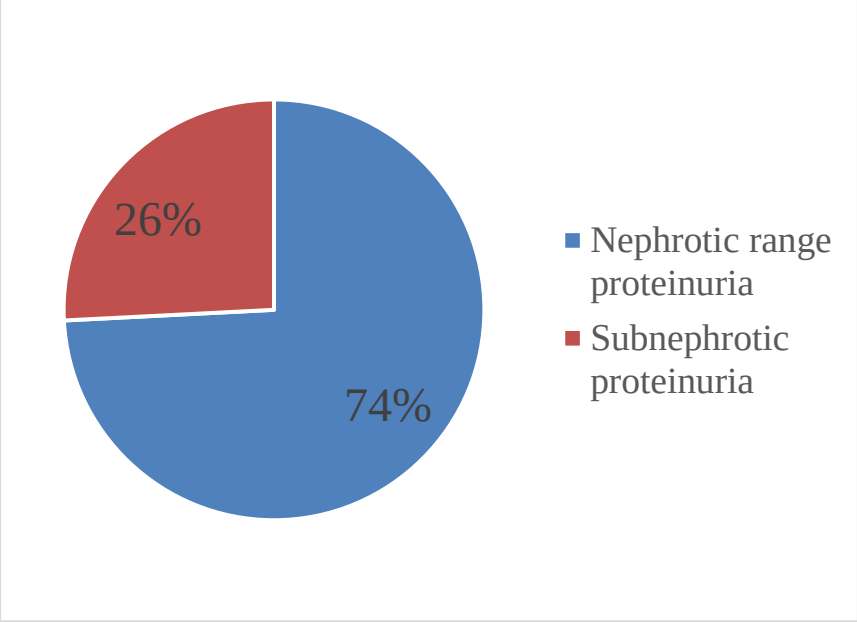
SEX	FREQUENCY	PERCENT
MALE	21	67.7%
FEMALE	10	32.3%
TOTAL	31	100.0%



Among the study group most of them were males (68%)

TABLE 3. DISTRIBUTION OF URINE ALBUMIN AT INITIATION

URINE ALBUMIN AT INITIATION	FREQUENCY	PERCENT
NEPHROTIC RANGE PROTEINURIA	23	74.2%
SUBNEPHROTC PROTEINURIA	8	25.8%
TOTAL	31	100.0%



74% of patients presented with nephrotic range proteinuria

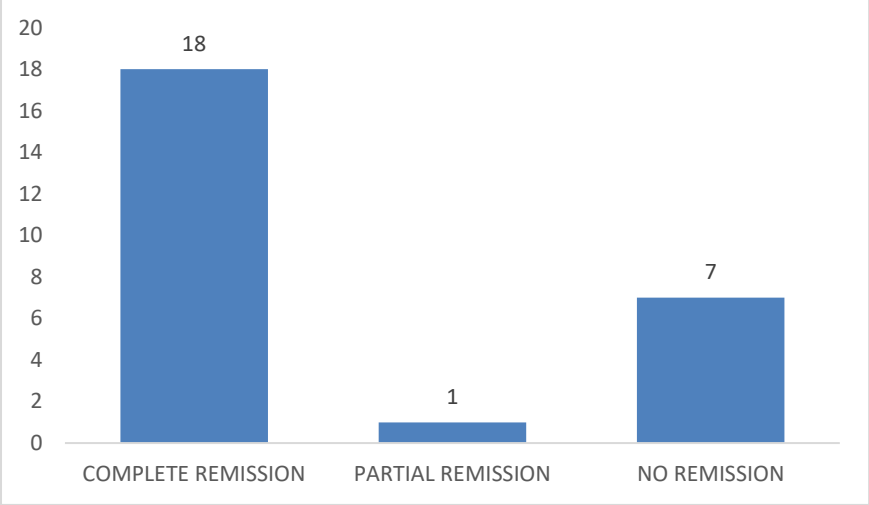
26% of patients presented with sub nephrotic proteinuria

Table 4 - RISK STRATIFICATION AND REMISSION – PERCENTAGE

RISK STRATIFICATION	PERCENTAGE	REMISSION	NO REMISSION
LOW RISK	48.4%	100%	-
MODERATE RISK	41.9%	84.5%	15.5%
HIGH RISK	9.7%	66.7%	33.3%

TABLE 5. DISTRIBUTION OF RESPONSE TO MODIFIED PONTICELLI REGIMEN

RESPONSE TO MODIFIED PONTICELLI REGIMEN	FREQUENCY	PERCENT
COMPLETE REMISSION	18	69.2%
PARTIAL REMISSION	1	3.8%
NO REMISSION	7	26.9%
TOTAL	26	100.0%



69.2 % of patients had complete remission

3.8% of patients had partial remission

26.9% of patients had no remission

Out of 31 patients, 28 patients were on conservative management and 3 patients were started on modified Ponticelli regimen since they were under high risk groups. After 6 months of conservative management 16.1% (5/31) had spontaneous remission. A total of 26 patients had received modified Ponticelli regimen. At end of 12 months after completion of modified Ponticelli regimen, 69.2 % (18/26) had complete remission, 3.8% (1/26) had partial remission, 26.9% (7/26) had no remission (as shown in table 5)

The 8 patients who had persistent proteinuria were initiated on tacrolimus. After 12 months of the treatment 1 patient had complete remission, 2 patient had partial remission.

COMPLICATONS

Leucopenia occurred in 3 patients, 2 patients developed type 2 diabetes mellitus. Three patients developed chronic kidney disease.

DISCUSSION

Primary membranous nephropathy is considered as autoimmune disease specific to kidney. According to previous studies the majority of age of presentation of primary MN is in the fourth to fifth decade. In our study as well, 51.6% (16/31) patients were withing the range of 41 – 50 years. 67.7% (21/31) of the patients were males and 32.3% (10/31) were females. Patients who are risk of renal failure or who present with complications, KDIGO recommends to initiate Modified Ponticelli regimen. In the original article published by Ponticelli et al, the regimen included methylprednisolone and chlorambucil for 6 months on alternate months. Due to the side effects of chlorambucil , it was replaced by cyclophophamide. A study by Ponticelli et al in 1998 was conducted in European population based on 2 regimens (methylprednisolone/ chlorambucil and methylprednisolone/ cyclophosphamide. The results of the study showed a remarkable rate of remission of 93% [76]. In caucassian population, a study was conducted by Ilan Rozenberg et al showed a total remission of 81 %. In 2007, a study by Jha et al. included 93 patients where modified Ponticelli regimen was compared with conservative management [74]. The remission rate was 73% and the patients who received treatment showed reduction in renal failure. In 2017, another study was conducted by Raja Ramachandran et al, where they compared

outcomes of patients treated with modified Ponticelli regimen and Tacrilimus with steroids[75].

After treatment, patients were followed up for 24 months. They found that the remission rate was 60% and 80% of cases at 18 and 24 months.in the tacrolimus and modified Ponticelli group respectively. It was also found that patients who were treated with tacrolimus had a higher relapse rate when compared to patients treated with modified ponticelli regimen. In a study conducted by polanco et al, which included 328 patients, 32% of patients had spontaneous remission

In our study, At end of 12 months after completion of modified Ponticelli regimen, 69.2 % (18/26) had complete remission, 3.8% (1/26) had partial remission, 26.9% (7/26) had no remission (as shown in table 5). The 8 patients who had persistent proteinuria were initiated on tacrolimus. After 12 months of the tacrolimus treatment 1 patient had complete remission, 2 patient had partial remission. 9.7 % (3/31) progressed to CKD. The results of our sudy were in concurrence with other published Indian studies.

LIMITATIONS –

This study was done in a smaller group of patients and hence a larger group of population of primany membranous nephropathy needs to be studied for knowing the outcomes of the IST in more detail. A longer follow up is to be needed to study the relapse rates and progression to CKD. Patients who were treated with tacrolimus wer already treated with modified Ponticelli regimen and hence more studies are needed to study the response to tacrolimus in patients not treated with modified Ponticelli regimen.

CONCLUSION

- 48.4% ,41.9% and 9.7% of the population were low risk, moderate risk and high risk population respectively.
- 83.9% of our study population were on immusuppresive therapy and 16.1% of the total study population had spontaneous remission.
- Patients who were put on modified Ponticelli regimen had a remission rate of 72%.
- The modified Ponticelli regimen was tolerated well by the patients.

BIBLIOGRAPHY

1. Bell ET . *Renal diseases*. London: Henry Kimpton, 1946

2. Jones DB. Nephrotic glomerulonephritis. Am J Pathol 1957

3. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009; 361:11.

4.Hofstra JM ,Fervenza FC , Wetzels JF . Treatment of idiopathic membranous nephropathy. Nat Rev Nephrol 2013

5. Stanescu HC , Arcos-Burgos M , Medlar A , *et al* . Risk HLA-DQA1 and $PLA_{(2)}R1$ alleles in idiopathic membranous nephropathy. N Engl J Med 2011;**364**:616–26

6. Beck LH. PLA2R and THSD7A: disparate paths to the same disease? J Am Soc Nephrol 2017

7. Cui Z , Xie LJ , Chen FJ , *et al* . MHC Class II risk alleles and amino acid residues in idiopathic membranous nephropathy. J Am Soc Nephrol 2017;**28**:1651–64

8.Cui Z, Xie LJ, Chen FJ, Pei ZY, Zhang LJ, Qu Z, Huang J, Gu QH, Zhang YM, Wang X, Wan g F, Meg LQ, Liu G, Zhou XJ, Zhu L, Lv JC, Liu F, Zhang H, Liao YH, Lai LH, Ronco P, Zhao MH. MHC Class II risk alleles and amino acid residues in idiopathic membranous nephropathy. J Am Soc Nephrol **28**: 1642–1650, 2017

9.Le WB, Shi JS, Zhang T, Liu L, Qin HZ, Liang S, Zhang YW, Zheng CX, Jiang S, Qin WS, Z hang HT, Liu ZH. DRB1*15:01 and HLA-DRB3*02:02 in -related membranous nephropathy. J Am Soc Nephrol **28**: 1642–1650, 2017

10. Kao L, Lam V, Waldman M, Glassock RJ, Zhu Q: Identification of the immunodominant epitope region in phospholipase A2 receptor-mediating autoantibody binding in idiopathic membranous nephropathy. J Am Soc Nephrol **26**: 291–301, 2015

11. Ren S, Wu C, Zhang Y, et al. An update on clinical significance of use of THSD7A in diagnosing idiopathic membranous nephropathy: a systematic review and meta-analysis of THSD7A in IMN. Ren Fail 2018; 40:306.

12. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domaincontaining 7A in idiopathic membranous nephropathy. N Engl J Med 2014; 371:2277.

13. Larsen CP, Cossey LN, Beck LH. THSD7A staining of membranous glomerulopathy in clinical practice reveals cases with dual autoantibody positivity. Mod Pathol 2016; 29:421.

14. Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. Kidney Int 2020; 97:163.

15 . Caza TN, Hassen SI, Dvanajscak Z, et al. NELL1 is a target antigen in malignancy-associated membranous nephropathy. Kidney Int 2021; 99:967.

16. Sethi S, Debiec H, Madden B, et al. Semaphorin 3B-associated membranous nephropathy is a distinct type of disease predominantly present in pediatric patients. Kidney Int 2020; 98:1253

17. Sethi S, Madden B, Debiec H, et al. Protocadherin 7-Associated Membranous Nephropathy. J Am Soc Nephrol 2021; 32:1249.

18. . Reinhard L, Machalitza M, Wiech T, et al. Netrin G1 is a Novel Target Antigen in Primary Membranous Nephropathy. J Am Soc Nephrol 2022.

19 . Debiec H, Guigonis V, Mougenot B, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med 2002; 346:2053.

20.Debiec H, Nauta J, Coulet F, et al. Role of truncating mutations in MME gene in fetomaternal alloimmunisation and antenatal glomerulopathies. Lancet 2004; 364:1252.

21. Nortier JL, Remiche G, Delrée P, et al. Antenatal Membranous Nephropathy and Type 2 (Axonal) Charcot-Marie-Tooth With Mutations in the Metallo-Membrane Endopeptidase Gene: A Call for Family Screening and Pharmacovigilance. Kidney Int Rep 2021; 6:1981.

22. Murtas C, Bruschi M, Candiano G, et al. Coexistence of different circulating anti-podocyte antibodies in membranous nephropathy. Clin J Am Soc Nephrol 2012; 7:1394.

23.Bruschi M, Carnevali ML, Murtas C, et al. Direct characterization of target podocyte antigens and auto-antibodies in human membranous glomerulonephritis: Alfa-enolase and borderline antigens. J Proteomics 2011; 74:2008.

24.Prunotto M, Carnevali ML, Candiano G, et al. Autoimmunity in membranous nephropathy targets aldose reductase and SOD2. J Am Soc Nephrol 2010; 21:507.

25. Debiec H, Lefeu F, Kemper MJ, et al. Early-childhood membranous nephropathy due to cationic bovine serum albumin. N Engl J Med 2011; 364:2101.

26. Ronco P, Debiec H. Molecular pathomechanisms of membranous nephropathy: from Heymann nephritis to alloimmunization. J Am Soc Nephrol 2005; 16:1205.

27. Sethi S, Madden BJ, Debiec H, et al. Exostosin 1/Exostosin 2-Associated Membranous Nephropathy. J Am Soc Nephrol 2019; 30:1123.

28. Sethi S, Madden B, Casal Moura M, et al. Hematopoietic Stem Cell Transplant-Membranous Nephropathy Is Associated with Protocadherin FAT1. J Am Soc Nephrol 2022; 33:1033.

29. Kerjaschki D: Pathomechanisms and molecular basis of membranous glomerulopathy. Lancet **364**: 1194–1196, 2004

30. Kerjaschki D: Pathomechanisms and molecular basis of membranous glomerulopathy. Lancet **364**: 1194–1196, 2004

31.Timmermans SA, Ayalon R, vanPaassen P, Beck LH Jr., vanRie H, Wirtz JJ, Verseput GH, Frenken LA, Salant DJ, Cohen Tervaert JW; Limburg Renal Registry: Anti-phospholipase A2 receptor antibodies and malignancy in membranous nephropathy. Am J Kidney Dis **62**: 1223–1225, 2013

32. Stahl PR, Hoxha E, Wiech T, Schröder C, Simon R, Stahl RA: THSD7A expression in human cancer. Genes Chromosomes Cancer **56**: 314–327, 2017

33. Fogo AB, Lusco MA, Najafian B, Alpers CE: AJKD atlas of renal pathology: Membranous nephropathy. Am J Kidney Dis **66**: e15–e17, 2015

34. Ma H, Sandor DG, Beck LH Jr..: The role of complement in membranous nephropathy. Semin Nephrol **33**: 531–542, 2013

35. Takano T, Elimam H, Cybulsky AV: Complement-mediated cellular injury. Semin Nephrol **33**: 586–601, 2013

36. Wasserstein AG. Membranous glomerulonephritis. J Am Soc Nephrol 1997; 8:664.

37. Polanco N, Gutiérrez E, Covarsí A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol 2010; 21:697.

38. KDIGO clinical practice guidelines for glomerulonephritis. KidneyInt 2012:139–274.

39.Cattran DC , Pei Y , Greenwood C . Predicting progression in membranous glomerulonephritis. Nephrol Dial Transplant 1992;**7**:48–52.

40. Cattran DC , Pei Y , Greenwood CM , *et al* . Validation of a predictive model of idiopathic membranous nephropathy: its clinical and research implications. Kidney Int 1997;**51**:901

41. Ponticelli C, Altieri P, Scolari F, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol 1998; 9:444.

42. Jha V, Ganguli A, Saha TK, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol 2007; 18:1899.

43. Ponticelli C, Passerini P, Salvadori M, et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. Am J Kidney Dis 2006; 47:233.

44. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. N Engl J Med 2019; 381:36

45. Cravedi P, Ruggenenti P, Sghirlanzoni MC, Remuzzi G. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2007; 2:932.

46. Leon J, Pérez-Sáez MJ, Batal I, et al. Membranous Nephropathy Posttransplantation: An Update of the Pathophysiology and Management. Transplantation 2019; 103:1990.

47. Josephson MA, Spargo B, Hollandsworth D, Thistlethwaite JR. The recurrence of recurrent membranous glomerulopathy in a renal transplant recipient: case report and literature review. Am J Kidney Dis 1994; 24:873.

48. Berger BE, Vincenti F, Biava C, et al. De novo and recurrent membranous glomerulopathy following kidney transplantation. Transplantation 1983; 35:315.

49. Mathew TH. Recurrence of disease following renal transplantation. Am J Kidney Dis 1988; 12:85.

50. Kotanko P, Pusey CD, Levy JB. Recurrent glomerulonephritis following renal transplantation. Transplantation 1997; 63:1045.

51. Cosyns JP, Couchoud C, Pouteil-Noble C, et al. Recurrence of membranous nephropathy after renal transplantation: probability, outcome and risk factors. Clin Nephrol 1998; 50:144.

52. Floege J. Recurrent glomerulonephritis following renal transplantation: an update. Nephrol Dial Transplant 2003; 18:1260.

53. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. Am J Transplant 2006; 6:2535.

54. Dabade TS, Grande JP, Norby SM, et al. Recurrent idiopathic membranous nephropathy after kidney transplantation: a surveillance biopsy study. Am J Transplant 2008; 8:1318.

55. Sprangers B, Lefkowitz GI, Cohen SD, et al. Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. Clin J Am Soc Nephrol 2010; 5:790.

56. Moroni G, Gallelli B, Quaglini S, et al. Long-term outcome of renal transplantation in patients with idiopathic membranous glomerulonephritis (MN). Nephrol Dial Transplant 2010; 25:3408.

57. Allen PJ, Chadban SJ, Craig JC, et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. Kidney Int 2017; 92:461.

58. Ponticelli C, Glassock RJ. Posttransplant recurrence of primary glomerulonephritis. Clin J Am Soc Nephrol 2010; 5:2363.

59. Stahl R, Hoxha E, Fechner K. PLA2R autoantibodies and recurrent membranous nephropathy after transplantation. N Engl J Med 2010; 363:496.

60. Debiec H, Martin L, Jouanneau C, et al. Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. Am J Transplant 2011; 11:2144.

61. Blosser CD, Ayalon R, Nair R, et al. Very early recurrence of anti-Phospholipase A2 receptorpositive membranous nephropathy after transplantation. Am J Transplant 2012; 12:1637

62. Debiec H, Hanoy M, Francois A, et al. Recurrent membranous nephropathy in an allograft caused by IgG3κ targeting the PLA2 receptor. J Am Soc Nephrol 2012; 23:1949.

63. Beck LH Jr. Monoclonal anti-PLA2R and recurrent membranous nephropathy: another piece of the puzzle. J Am Soc Nephrol 2012; 23:1911.

64. . Gupta G, Fattah H, Ayalon R, et al. Pre-transplant phospholipase A2 receptor autoantibody concentration is associated with clinically significant recurrence of membranous nephropathy post-kidney transplantation. Clin Transplant 2016; 30:461.

65. Grupper A, Cornell LD, Fervenza FC, et al. Recurrent Membranous Nephropathy After Kidney Transplantation: Treatment and Long-Term Implications. Transplantation 2015.

66. Kattah A, Ayalon R, Beck LH Jr, et al. Anti-phospholipase A_2 receptor antibodies in recurrent membranous nephropathy. Am J Transplant 2015; 15:1349.

67. Quintana LF, Blasco M, Seras M, et al. Antiphospholipase A2 Receptor Antibody Levels Predict the Risk of Posttransplantation Recurrence of Membranous Nephropathy. Transplantation 2015; 99:1709.

68. Seitz-Polski B, Payré C, Ambrosetti D, et al. Prediction of membranous nephropathy recurrence after transplantation by monitoring of anti-PLA2R1 (M-type phospholipase A2 receptor) autoantibodies: a case series of 15 patients. Nephrol Dial Transplant 2014; 29:2334.

69. Tomas NM, Hoxha E, Reinicke AT, et al. Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. J Clin Invest 2016; 126:2519.

70. Fila M, Debiec H, Perrochia H, et al. Recurrence of Anti-Semaphorin 3B-Mediated Membranous Nephropathy after Kidney Transplantation. J Am Soc Nephrol 2022; 33:503.

71. Batal I, Vasilescu ER, Dadhania DM, et al. Association of HLA Typing and Alloimmunity With Posttransplantation Membranous Nephropathy: A Multicenter Case Series. Am J Kidney Dis 2020; 76:374.

72. Berchtold L, Letouzé E, Alexander MP, et al. HLA-D and PLA2R1 risk alleles associate with recurrent primary membranous nephropathy in kidney transplant recipients. Kidney Int 2021; 99:671.

73. Rodriguez EF, Cosio FG, Nasr SH, et al. The pathology and clinical features of early recurrent membranous glomerulonephritis. Am J Transplant 2012; 12:1029.

74 Jha V, et al. Outcome of idiopathic membranous nephropathy prospective study. Am Soc Nephrol 2007; 18:1899-904.

75. Ramachandran R, et al. RCT, Two year follow up study in IMN with Tacrolimus and corticosteroids vs Cyclophosphamide and corticosteroids. Kidney Int 2017; 2:610-616.

76. Ponticelli C, et al. An RC T, methylPrednisolone plus chlorambucil versus methylPrednisolone plus Cyclophosphamide in IMN. J Am Soc Nephrol 1998; 9:444- 450.

77. Rozenberg I, Kotliroff A, et al. outcome of idiopathic membranous nephropathy. IMAJ 2018; 20:186-189.

78. . Laluck BJ Jr, Cattran DC. Prognosis after a complete remission in adult patients with idiopathic membranous nephropathy. Am J Kidney Dis 1999; 33:1026

ANNEXURES

PROFORMA

PROFORMA NO.

A STUDY ON CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY- A SINGLE CENTRE EXPERIENCE

NAME:

AGE/ SEX:

OCCUPATION:

ADDRESS:

CONTACT NUMBER:

DIAGNOSIS:

HISTORY

- Swelling of legs
- Reduced urine output
- Breathlessness
- Frothy urine
- Intake of native medications
- History of infectious episodes if any
- History of whether hospitalisation was required for the infectious episodes

PAST HISTORY:

Diabetes mellitus/ Systemic hypertension /Chronic kidney disease / Malignancy

Rheumatoid arthriti / Systemic lupus erythematosus / HBV/HCV/HIV status

GENERAL EXAMINATION:

Consciousness,

Orientation to time, place and person

Pallor/ Icterus / Cyanosis / Clubbing / Pedal edema / lymphadenopathy

VITALS:

Blood pressure / Pulse rate / respiratory rate / Temperature/ SpO_2

SYSTEMIC EXAMINATION:

CVS (Cardiovascular system):

RS (Respiratory system):

Abdomen:

CNS (Central Nervous system):

INVESTIGATIONS

Blood hemogram: WBC count - Hb –

PT - INR -

Blood sugar -

Blood urea -

Serum creatinine -

Total Proteins - Serum Albumin –

ANA profile

HBsAg/HCV/HIV -

Urine routine – Urine PCR –

Renal biopsy (if done) –

M-PLA_2R antibody (if done) –

TREATMENT :

CONSERVATIVE (ACEI/ ARB/ STATINS) -

STEROIDS (METHYL PREDNISOLONE / PREDNISOLONE) -

CYCLOPHOSPHAMIDE -

TACROLIMUS/RITUXIMAB -

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg. No(CDSCO).ECR/270/Inst./TN/2013/RR-20
EC Reg. No(DHR).EC/NEW/INST/2021/1618
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CERTIFICATE OF APPROVAL

To
Dr.NIKHIL V JAIN,
MD General Medicine,
Post Graduate student,
Institute of Internal Medicine,
Madras Medical College,
Chennai-600003.

Dear Dr. NIKHIL V JAIN,

The Institutional Ethics Committee has considered your request and approved your study titled **"CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY - A SINGLE CENTRE EXPERIENCE"- NO.04072022.** The following members of Ethics Committee were present in the meeting held on **06.07.2022** conducted at Madras Medical College, Chennai 3.

1. Prof.P.V.Jayashankar,MS Orth.,D.Orth.,M.Ch Orth (Liverpool) :Chairperson
2. Prof.N.Gopalakrishnan,MD.,DM., FRCP, Director, Inst.of Nephrology,MMC,Ch. : Member Secretary
3. Prof. K.M.Sudha, Prof. Inst. of Pharmacology,MMC,Ch-3 : Member
4. Prof. Alagarsamy Jamila ,MD, Vice Principal, Stanley Medical College, Chennai : Member
5. Prof.Meena Suresh, MD.,DGO.,Prof.of Obst & Gynaec, IOG,Chennai : Member
6. Prof.S.Lakshmi, Prof. of Paediatrics ICH Chennai :Member
7. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
8. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
9. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003.

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு :

CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY - A SINGLE CENTRE EXPERIENCE

ஆய்வாளர் பெயர் : மரு. நிக்கில் V. ஜெயின்

ஆய்வு நிலையம் : பொது மருத்துவப் பிரிவு,
சென்னை மருத்துவக் கல்லூரி, சென்னை-3.

இந்த ஆய்வில் தங்களை பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கலாமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனையின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்

தேதி :

பங்கேற்பாளர் கையொப்பம் /
இடது கட்டைவிரல் ரேகை

தேதி :

ஆய்வு ஒப்புதல் படிவம்

ஆய்வு தலைப்பு :

CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY - A SINGLE CENTRE EXPERIENCE

பெயர் :

வயது :

பால் :

தேதி :

உள்நோயாளி எண் :

ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

நான் ஆராய்ச்சியாளருடன் ஒத்துழைப்பேன் என்றும், எனக்கு ஏற்படக்கூடிய ஆசாதாரண நிகழ்வுகள் பற்றியும் உடனடியாக ஆராய்ச்சியாளரிடம் தெரிவிப்பேன் என்று உறுதி கூறுகிறேன். இந்த ஆய்விலிருந்து எப்போது வேண்டுமானாலும் எக்காரணமும் கூறாமல் என்னை விடுவித்துக்கொள்ளலாம் என்பதை அறிவேன்.

என்னிடம் இருந்து பெறப்படும் தகவல்களை அரசு, வரைமுறை அதிகாரிகள் ஆகியோர்களுடன் பகிர்ந்துகொள்ள ஆராய்ச்சியாளருக்கு அனுமதி அளிக்கிறேன். என்னுடைய சிகிச்சைக்கட்டுகளை பார்வையிட உரிமை உண்டு. என்னுடைய தகவல்களின் அடையாளம் இரகசியமாக வைக்கப்படும் என்பதை அறிவேன்.

இந்த ஆராய்ச்சியில் பங்கேற்க தன்னிச்சையாக முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் / ரேகை

பங்கேற்பவர் பெயர்

இடம் :

தேதி :

ஆய்வாளர் கையொப்பம்

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ANTI PLAGIARISM CERTIFICATE

This is to certify that the dissertation work titled "**A STUDY ON CLINICAL PROFILE AND OUTCOME OF PRIMARY MEMBRANOUS NEPHROPATHY – A SINGLE CENTRE EXPERIENCE**" of the candidate **Dr. NIKHIL V JAIN** with Registration Number **200120100520** for the award of **M.D. degree** in the branch of **GENERAL MEDICINE** is original. I personally verified the urkund.com website for plagiarism Check. I found that the uploaded thesis file contained Introduction to Conclusion pages and result showed **11 percentage** of plagiarism.

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85

MASTER CHART

S.NO.	Age	Sex 1 - MALE 2 - FEMALE	HTN 0 - YES 1 - NO	DM 0 - YES 1 - NO	HYPOTHYROID 0 - YES 1 - NO	OTHERS 0 - YES 1 - NO	ANA 0 - POSITIVE 1 - NEGATIVE	ENA 0 - POSITIVE 1 - NEGATIVE	Viral marker: 0 - POSITIVE 1 - NEGATIVE	Time to initiation of Modified Pomicelli 0-0 month: 1- 6 months:	Indication massive proteinuria - 1 EPRF - 2 life threatening complication - 3 no response to conservative treatment - 4
1	43	1	1	1	1	1	1	1	1	1	4
2	39	2	1	1	1	1	1	1	1	1	4
3	37	1	1	1	1	1	1	1	1	1	4
4	40	2	1	1	1	1	1	1	1	0	1
5	41	1	1	1	1	1	1	1	1	1	1
6	54	1	1	1	1	1	1	1	1	1	4
7	46	1	1	1	1	1	1	1	1	1	4
8	50	2	1	1	1	1	1	1	1	1	1
9	47	2	1	1	1	1	1	1	1	1	1
10	35	2	1	1	1	1	1	1	1	0	1
11	45	1	1	1	1	1	1	1	1	1	4
12	36	1	1	1	1	1	1	1	1	1	1
13	42	1	1	1	1	1	1	1	1	1	4
14	41	2	1	1	1	1	1	1	1	0	4
15	33	1	1	1	1	1	1	1	1	1	4
16	38	2	1	1	1	1	1	1	1	1	4
17	28	1	1	1	1	1	1	1	1	1	4
18	41	1	1	1	1	1	1	1	1	1	4
19	45	1	1	1	1	1	1	1	1	1	4
20	41	2	1	1	1	1	1	1	1	1	4
21	45	1	1	1	1	1	1	1	1	1	4
22	30	1	1	1	1	1	1	1	1	1	4
23	43	1	1	1	1	1	1	1	1	1	4
24	47	2	1	1	1	1	1	1	1	1	4
25	40	1	1	1	1	1	1	1	1	1	4
26	39	1	1	1	1	1	1	1	1	1	4
27	37	1	1	1	1	1	1	1	1		
28	42	1	1	1	1	1	1	1	1		
29	41	1	1	1	1	1	1	1	1		
30	40	1	1	1	1	1	1	1	1		
31	39	2	1	1	1	1	1	1	1		

Complications during treatment course 0 - yes 1 - no	Urine Alb @ initiation	UPCR @ initiation	24 hour urinary protein @ initiation	Creat @ initiation	Renal failure at presentation 0 - YES 1 - NO	Albumin @ initiation	RESULTS POST MPR COMPLETION 0 - COMPLETE REMISSION 1 - PARTIAL REMISSION 2 - NO REMISSION	Sequence 0 - MPR 1 - MPR-TACRO 3- N/A	Last Creat	RESULT 0 - complete remission 1 -spontaneous remission 2 - partial remission 3 - no remission and CKD
0	2	6	6.8	0.8	1	1.7	2	1	0.7	2
1	3	3.3	4	1	1	2	2	1	0.9	0
1	2	4.5	5.4	1	1	2.5	2	1	0.7	2
0	2	8.1	8	0.6	1	2	0	0	1	0
0	2	7.2	7.65	1	1	2.3	2	1	2.1	3
1	2	3.6	4.5	1	1	2.8	0	0	0.8	0
1	2	5.2	4.9	0.9	1	3	0	0	0.8	0
1	2	4.3	4	0.8	1	2.6	2	1	0.8	2
1	2	4.6	5.1	0.6	1	2.1	0	0	0.7	0
1	2	8	9.7	0.8	1	2.1	1	1	2.3	3
1	2	6	5.6	1	1	2.5	2	1	0.9	2
0	2	5	5.8	0.9	1	2.6	2	1	2.8	3
0	2	6.2	7	0.6	1	2.5	0	0	0.5	0
1	2	13.5	4.1	0.9	1	1.4	0	0	0.6	0
1	2	5.2	5.8	0.7	1	2.6	0	0	0.9	0
1	2	4.6	4.9	0.6	1	2.9	0	0	0.8	0
1	2	3.9	4.5	0.9	1	2.8	0	0	0.6	0
1	2	3.7	4	0.7	1	2.5	0	0	0.7	0
1	3	2.9	3.2	0.8	1	3	0	0	0.5	0
1	3	3	4	0.7	1	2.3	0	0	0.8	0
1	2	4.4	5.1	0.6	1	2.4	0	0	0.6	0
1	3	3.1	3.9	0.8	1	2.9	0	0	1	0
1	3	3.2	4.1	0.6	1	2.6	0	0	0.8	0
1	2	4.12	3.8	0.5	1	2.5	0	0	0.7	0
1	2	3.9	4.2	0.8	1	2.7	0	0	0.6	0
1	2	3.75	4.1	0.6	1	2.2	0	0	0.8	0
1	3	2.5	2	0.7	1	2.9		3	0.8	1
1	2	3.65	3.8	0.6	1	2.8		3	0.7	1
1	3	2.7	3	0.5	1	2.9		3	0.6	1
1	3	2.9	3	0.7	1	3		3	0.7	1
1	2	3.5	4	0.7	1	2.7		3	0.9	1