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MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS; CLINICAL, ETIOLOGICAL AND RENAL OUTCOME AT THE NEPHROLOGY DEPARTMENT, HASSAN II UNIVERSITY HOSPITAL

THESIS

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LIST OF ABBREVIATIONS

MPGN; Membranoproliferative Glomerulonephritis

IC-MPGN; Immune complex-mediated Membranoproliferative Glomerulonephritis

DDD; Dense Deposit Disease

EDD; Electron Dense Deposit

IF; Immunofluorescent Microscopy

EM; Electron Microscopy

Ig; Immunoglobulin

GBM; Glomerular Basement Membrane

RCA; Regulating complement factor

CR1; Complement Receptor 1

FH; Factor H

FI; Factor I

FB; Factor B

DAF; Decay accelerating factor

RPGN; Rapidly progressive Kidney failure

RPKF; Rapidly progressive Kidney failure

C4BP; C4 binding Protein

AKI; Acute Kidney Injury

CKD; chronic kidney disease

ESRD; End-stage renal disease.

VCD: Valcade Endoxan Dexamethasone (treatment Protocol)

MMF: Mycophenolate Mofetil

UTP: urinary total protein

UTI: Urinary tract Infection

eGFR: estimated Glomerular filtration rate

GFR: Glomerular filtration rate

MDRD: Modification of diet in renal disease

SPE: Serum protein Electrophoresis

SIFE: Serum immunofixation electrophoresis

MGRS: Monoclonal gammopathy of renal significance

MGUS: Monoclonal gammopathy of undetermined significance

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

IQR: Interquartile range

SLE: Systemic Lupus Erythematosus

PRB: Percutaneous renal biopsy

RASi: Renin-Angiotensin System Inhibitor

SCr: Serum creatinine

GN: Glomerulonephritis

EAGLE: Evaluating the Morphofunctional Effects of Eculizumab Therapy in Primary Membranoproliferative Glomerulonephritis (Trial)

MPGNr : recurrent MPGN

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INTRODUCTION

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, is a rare kidney disorder that represents a specific histological pattern of glomerular injury rather than a distinct disease entity. Consequently, identifying MPGN on a kidney biopsy marks the beginning of a diagnostic investigation to uncover its underlying cause rather than providing a definitive diagnosis[1].

Histologically, MPGN is characterized by marked glomerular hypercellularity and thickening of the glomerular basement membrane, as observed through kidney biopsy, immunofluorescence, and electron microscopy. Typical findings include significant glomerular hypercellularity, thickening of capillary walls with electron-dense deposits, and splitting of the basement membrane caused by mesangial interposition.[1]

MPGN can be classified into primary (idiopathic) and secondary forms, with secondary MPGN being more common in adults and primary MPGN more frequently observed in children[2,3]. The previous classification system, based on the location of electron-dense deposits, defined three types of MPGN: type I, type II, and type III[4]. Recent classifications, however, are based on pathogenesis and etiology, distinguishing MPGN with immune complex or monoclonal Ig deposits (with or without complement deposition) from MPGN with complement deposition caused by dysregulation of the complement system.[5]

MPGN is more prevalent in underdeveloped countries and less common in developed countries[6].

Despite histological differences, clinical manifestations of MPGN overlap significantly. Patients may present with:

- nephrotic syndrome (40-70% of cases),
- acute nephritic syndrome (20-30%),
- asymptomatic proteinuria and hematuria detected during routine urine analysis (20-30%),
- or recurrent episodes of gross hematuria (10-20%).[4]

Hypocomplementemia is a variable, present in some but not all cases.[7]

The treatment approach depends on the specific type of MPGN, whether immune complex-mediated or complement-mediated and the underlying causal disease. Available treatment options include anti-proteinuric drugs, immunosuppressive agents, and renal transplantation.

The long-term clinical course of MPGN is chronic and parallels the histological progression. It often progresses slowly and inexorably toward end-stage renal disease.[7,8]

Due to the rarity of this pathological entity, studies involving large sample sizes remain limited.

This study aims to describe and analyze the clinical, etiological, and evolutionary profile of MPGN at the Nephrology Department of Hassan II University Hospital, focusing on all patients diagnosed with the MPGN pattern via kidney biopsy.

DEFINITION

The term **membranoproliferative glomerulonephritis (MPGN)** describes a pattern of renal injury characterized by mesangial expansion due to mesangial and endocapillary hypercellularity, an increased mesangial matrix, and thickened capillary walls exhibiting a double-contour appearance, commonly referred to as the "tram-track" sign. This pattern can occur in the context of immune complex deposition, monoclonal protein deposits, or other organized deposits, such as in fibrillary glomerulonephritis. It may also result from complement-mediated disease or reflect a response to chronic endothelial injury with cell interposition but without deposits, as seen in chronic thrombotic microangiopathy (TMA)[9].

The MPGN pattern was first described by Jones in 1957, who observed these changes in methenamine-silver-impregnated sections following renal biopsy [10]. Initially, it was identified as a form of chronic glomerulonephritis associated with persistent hypocomplementemia by West et al. and Gotoff et al [11].

MPGN was subsequently classified into three types based on ultrastructural features observed under electron microscopy [11]. A later classification, known as the "Mayo Clinic" classification, introduced an etiopathogenesis-based framework. This system categorized MPGN into subtypes involving immune complex or monoclonal immunoglobulin deposition in the glomeruli and those linked to complement deposition arising from dysregulated complement system abnormalities [5,12,13]. While MPGN is often idiopathic and commonly observed in children,

secondary forms are more frequently encountered in adults. These secondary causes are usually associated with chronic infectious diseases such as hepatitis B and C [14–17], autoimmune disorders, or malignant conditions [18].

Classification of MPGN

Historically, **membranoproliferative glomerulonephritis (MPGN)** has been classified into three types—Type I, Type II, and Type III—based on ultrastructural characteristics and the location of electron-dense deposits observed under electron microscopy (EM). However, this classification was not grounded in etiopathogenesis, highlighting the need for a more modern classification that elucidates the pathogenesis of these deposits [5,12,13].

Traditional Classification of MPGN

MPGN Type I

MPGN Type I [19], is the most common form of MPGN. Histologically, it exhibits the characteristic MPGN pattern, including mesangial proliferation, cellular interposition, and a double-contour appearance under EM. Immunofluorescence (IF) microscopy reveals deposits of immunoglobulins (Ig) and complement component C3, or predominantly C3 deposits, within the glomerular basement membrane (GBM) [3].

MPGN Type II

MPGN Type II, also known as Dense Deposit Disease (DDD) [20], is defined by the presence of mesangial and intramembranous, highly electron-dense deposits (EDD) under EM. Bright staining for C3 is observed under IF, without significant immunoglobulin deposition [3].

MPGN Type III

MPGN Type III is characterized by electron-dense deposits located in subendothelial, intramembranous, and subepithelial regions, as seen under EM. IF microscopy may reveal either a combination of immunoglobulin (Ig) and C3 deposits or predominantly C3 deposits [3].

MPGN Type III is further sub-classified into the Burkholder type and the Anders/Strife type:

- The **Burkholder type** exhibits features similar to MPGN Type I, with the addition of numerous subepithelial EDD [21].
- The **Anders/Strife type** is distinguished by the presence of large, variably dense intramembranous deposits that connect subepithelial and intramembranous regions [22].

MPGN Type III is often considered an intermediate form, as it shares characteristics of both Type I and Type II [3].

Table 1:The traditional classification of MPGN by location of electron-dense deposits based on Electron Microscopy.[23]

MPGN type	Electron microscopic appearances	Typical immunostaining	Serum complement	Other
I	Discrete electron dense material in mesangium and subendothelial GBM	IgG ± IgA ± IgM + C3 + C1q	Normal ± reduced C4 and C3	Infections, autoimmune disease, cryoglobulinaemia
II	Dense transformation of GBM lamina densa	C3 only	Reduced C3, normal C4	C3NeF
III	Subendothelial and subepithelial GBM electron dense deposits	IgG ± IgA ± IgM + C3 + C1q	Normal ± reduced C4 and C3	Infections, autoimmune disease, cryoglobulinaemia

New MPGN Classification

The traditional classification of MPGN lacked clarity regarding etiopathogenesis and did not adequately address the role of immune complexes and complement deposits.

The **Mayo Clinic classification** of MPGN provides a more precise framework by dividing the disease into two broad pathogenetic pathways [24]:

1. **Immune complex-mediated MPGN**: Characterized by the deposition of immune complexes or monoclonal immunoglobulins in the glomeruli, with or without associated complement deposition.

2. **Complement-mediated MPGN**: Arising from complement deposition due to dysregulation of the complement system.

3. **MPGN without immunoglobulin or complement deposition** — A histologic pattern that may resemble MPGN on light microscopy can be seen in the healing phase of thrombotic microangiopathies (eg, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome), antiphospholipid antibody syndrome, nephropathy associated with bone marrow transplantation, chronic kidney allograft nephropathy, radiation nephritis, and malignant hypertension.

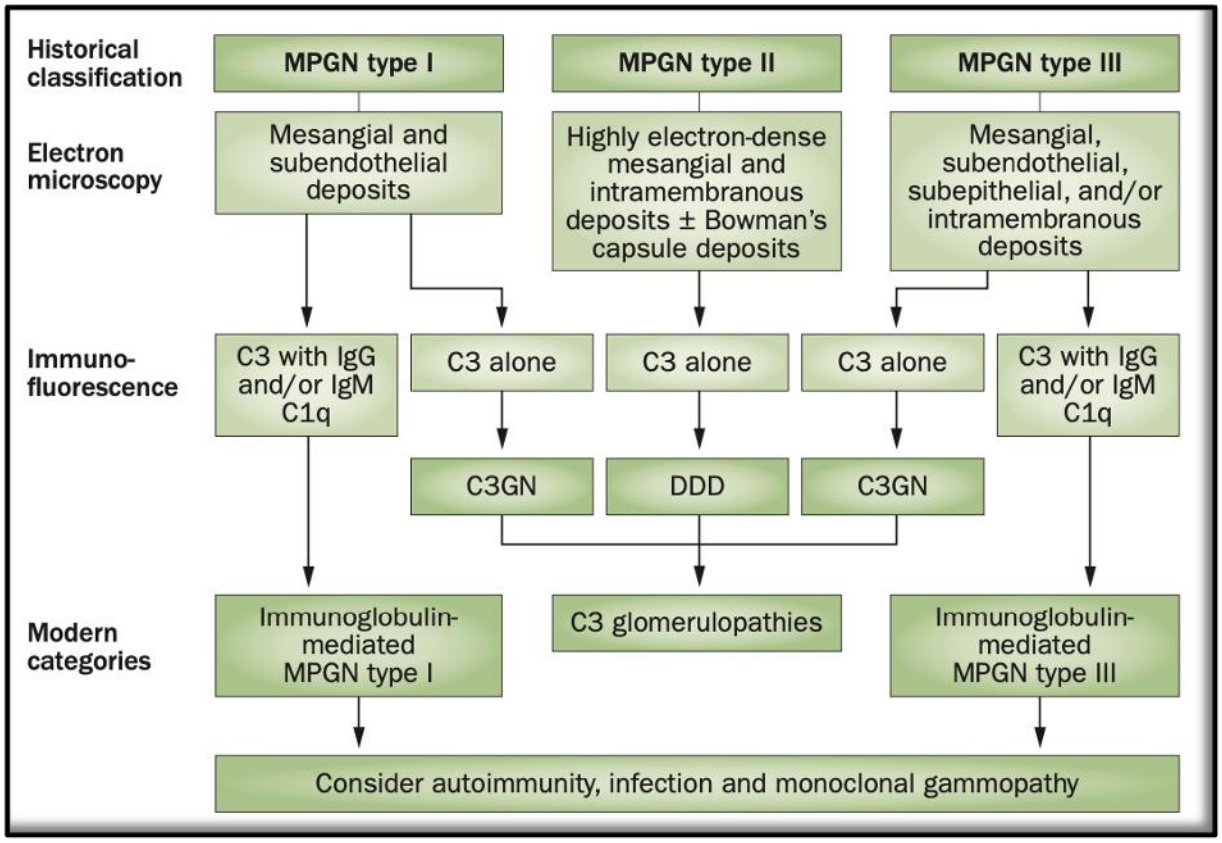


Figure 1:Relationship between historical and modern classification of glomerulonephritis with membranoproliferative morphology [1].

PATHOPHYSIOLOGY OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

The pathophysiology of MPGN is largely based on dysregulation or hyperactivation of the complement system.

THE COMPLEMENT SYSTEM

The complement system is a crucial component of innate immunity, consisting of three interacting pathways that recognize and eliminate pathogens and modified self-antigens. It plays a vital role in host defense, and inflammation, and serves as a bridge between innate and adaptive immunity. It's functions include opsonization, cell lysis, and removal of injured cells and debris [25,26].

Complement activation pathways

There are three principal complement activation systems, namely the alternate, classical, and lectin pathways. These systems are characterized by a cascade of events involving inactive zymogens that are successively cleaved and activated. All pathways converge at the C3 resulting in the formation of the activation products C3a, C3b, C5a, and the membrane attack complex (C5b, C6, C7, C8, C9). [26]

Formation of C3 convertase

Classical Pathway

In the classical pathway IgM, IgG of other foreign and non-self-antigens

bind to pentraxins or C1 complex, a multimeric complex consisting of C1q, C1r, and C1s molecules.[26]

The pathway is activated when the C1q portion of the multimeric C1 complex binds to the Fc portion of the IgG or IgM leading to the activation of C1s and C1r. C4 and C2 are then cleaved by C1s to form the classical pathway C3 convertase, C4bC2a.[26]

Pentraxins are evolutive proteins that are synthesized in the liver and other tissues in response to an infection and can recognize pathogens and eliminate them by directly binding to C1q [26].

Lectin Pathway

Mannose-binding lectin (MBL), Ficolin, and other MBL-associated proteins known as MASPs bind to carbohydrates on the surfaces of pathogens, including yeast, bacteria, parasites, and viruses.

There are four structurally related MASPs, 1, 2, 3, and MASPs 19, which is a truncated form of MASPs 2.

The lectin pathway occurs when MASP undergoes a conformational change to become MASP 2 after binding to the pathogen surface. MASP 2 then cleaves C4 to form C4a and C4b. C4b induces C2 after it attaches itself to the surface of the pathogen. C2 is later cleaved to form C2a and C2b by MASP 2. The lectin pathway C3 convertase, C4bC2a is formed after C4b binds to C2a. [26]

Alternative Pathway

The alternative pathway (AP) provides an immediate line of defense that does not require prior immunization. It recognizes a wide variety of potential pathogens within minutes after these organisms come in contact with the plasma proteins C3, factor B, and Factor D.[27]

An initial AP C3 convertase (C3(H20)Bb) is produced in the presence of Factor B and Factor D after spontaneous hydrolysis of C3 to C3(H20) through a constant low activation phenomenon called the “tick-over”[28].

The initial C3 convertases from all pathways cleave native C3 into its two active fragments, C3a and C3b, and C3b gets covalently attached to nearby surfaces. In the absence of complement regulators, surface-deposited C3b can be gradually amplified through the formation of the final AP C3 convertase (C3bBb) and cleavage of more C3 in the absence of complement regulator [29].

Other triggers like properdin, various proteins, lipids, and carbohydrate structures on foreign surfaces can directly activate the AP[30-33]. The alternative pathway also represents an amplification loop for the classical and Lectin pathways.[34]

Complement System Regulators

Numerous proteins present in the fluid phase, bound to the cell membrane, or complement receptor regulators known as regulators of complement activity (RCAs), tightly control complement activity[35,36]. RCAs can be general or specific to the activation or terminal pathway. C4 binding protein (C4BP), vitronectin (S Protein), clusterin, Factor I(FI), Factor H (FH), and Factor H-like (FHL-1) [37,38] are fluid phase regulators, whereas examples of membrane-bound RCA include decay accelerating factor (DAF or CD55), membrane cofactor protein (MCP or CD46), complement receptor 1 (CR1 or CD35), and CD59[38,39].

Complement regulators in the glomerular environment, like the MAC inhibitory protein, CD59, and the membrane cofactor protein, CD46, inhibit terminal complement pathways and control the proximal complement pathways, respectively [40].

RCAs maintain homeostasis through two processes namely, cofactor activity and decay-accelerating activity.

Cofactor activity refers to proteolytic cleavage of C3b and C4b. In this process, a cofactor protein binds to fragments from the cleaved C3b and C4b, which is then proteolytically inactivated by a serine protease factor.

These fragments serve as ligands for other complement receptors that facilitate the clearance of targets.

In the decay-accelerating activity mechanism, the catalytic domain (serine protease) of a C3 or C5 convertase is dissociated. [41]

Fluid phase inhibitors

C4 binding protein (C4BP)

C4BP regulates the CP and the LP by accelerating the decay of the CP C3 convertase and also serves as a cofactor for the serine protease factor I(FI). [42]

Factor I

Complement factor I is a serum serine protease that cleaves C3b and C4b into inactive fragments C4c and C4d in the presence of its cofactors, that is FH and C4BP[42,43].

Factor H and related proteins

Factor H is the main AP RCA that regulates the AP in both the fluid and cell membrane phases. It is coded by the CFH gene and possesses a C-terminal for surface recognition and an N-terminal that promotes cofactor and decay accelerating complement activities[44].

Factor H prevents the formation of C3 convertase by accelerating the decay of C3bBb. It also acts as a cofactor for factor I, leading to the cleavage and inactivation of C3b. [42,45]

Five proteins show sequence and structural homology to CFH; these are, therefore, termed complement factor H-related proteins (CFHR) 1-5. They possess diverse functions. CFHR1 has been recently identified in controlling C5 activation[46], and CFHR1, CFHR2, and CFHR5 act as CFH antagonists by competing with CFH binding and CFH-mediated regulation at physiological concentration due to their shared dimerization motif[47].

C1inhibitor

C1 inhibitor inhibits C1r and C1s proteases of the CP and MASP-1 and MASP-2 protease of the LP[42].

Membrane-bound Inhibitors

Complement receptor type 1(CR1)/ CD35

It's a glycoprotein expressed predominantly on erythrocytes and leukocytes, that acts as a receptor for C3b and C4b. It is responsible for the removal of complement-opsonized microbes, cells, or immune complexes through their transport to the liver or spleen.

it functions as a complement inhibitor by acting as a cofactor for FI-mediated cleavage and inactivation of C3b and C4b, a mechanism analogous to the function of C4bp and FH. In addition, CR1 can accelerate the decay of C3 and C5 convertases. [42]

Membrane Cofactor Protein (MCP, CD46)

It is a transmembrane protein mostly associated with the control of the AP convertase and also the LP and CP. It has similar functions to CR1 by acting as a cofactor of FI in the cleavage and inactivation of C4b and C3b but doesn't promote decay of C3 or C5 convertases. It can, however, block the formation of C3 and C5 convertase by binding to C4b and C3b. [42]

Decay Accelerating Factor (CD55)

The DAF inhibits the formation of both CP and AP C3 convertases and also accelerates their decay. DAF is attached to the cell membrane via glycosyl-phosphatidylinositol(GPI). [42]

CD59 (Protectin)

It's a glycosyl-phosphatidylinositol (GPI) anchored protein, a terminal pathway inhibitor that binds to C8 and C9, thus interfering with C9 binding, polymerization, and pore formation.[42]

DRIVERS OF COMPLEMENT DISEASE

Genetic and acquired drivers of the complement factors can lead to dysregulation of the complement system.

Genetic Drivers

Genetic modifiers such as mutations in complement FH, FI, mutations in membrane cofactor proteins (MCP, CD46), genetic variants of C3 and C5 after mutation, and mutations in complement regulatory proteins (CFHR1-5) [40].

Acquired Drivers

These acquired drivers are usually autoantibodies to complement factors, environmental factors like infections, paraproteinemia, and monoclonal gammopathies as well as complement consumption during a chronic autoimmune disease.

The most common acquired driver is the C3 Nephritic factor (C3Nef). C3Nefs are autoantibodies, mainly IgG or IgM, that bind to the C3 convertase. They mostly recognize a neoepitope on the C3bBb complex, but some are known to bind solely to C3b or Bb. Some require the presence of properdin while others are properdin-independent [48]. They stabilize membrane-bound and

fluid-phase AP C3 convertase, protecting it from regulatory mechanisms and increasing its half-life tenfold [49,50].

The C4 Nephritic factor (C4Nefs), autoantibodies (mainly IgG) to the classical pathway C3 convertase C4bC2b prolong the half-life of the convertase by preventing both the intrinsic and the C4b-binding protein-CR1- or DAF-mediated extrinsic decay. This leads to enhanced C3 and C5 cleavage. They also protect C4b fragments from factor I. [48]

Other acquired drivers include C5Nefs that are C5 convertase (C3bBbC3b) stabilizing autoantibodies and autoantibodies of Factor B, Factor H, and C4b2a(CP C3 convertase).[51]

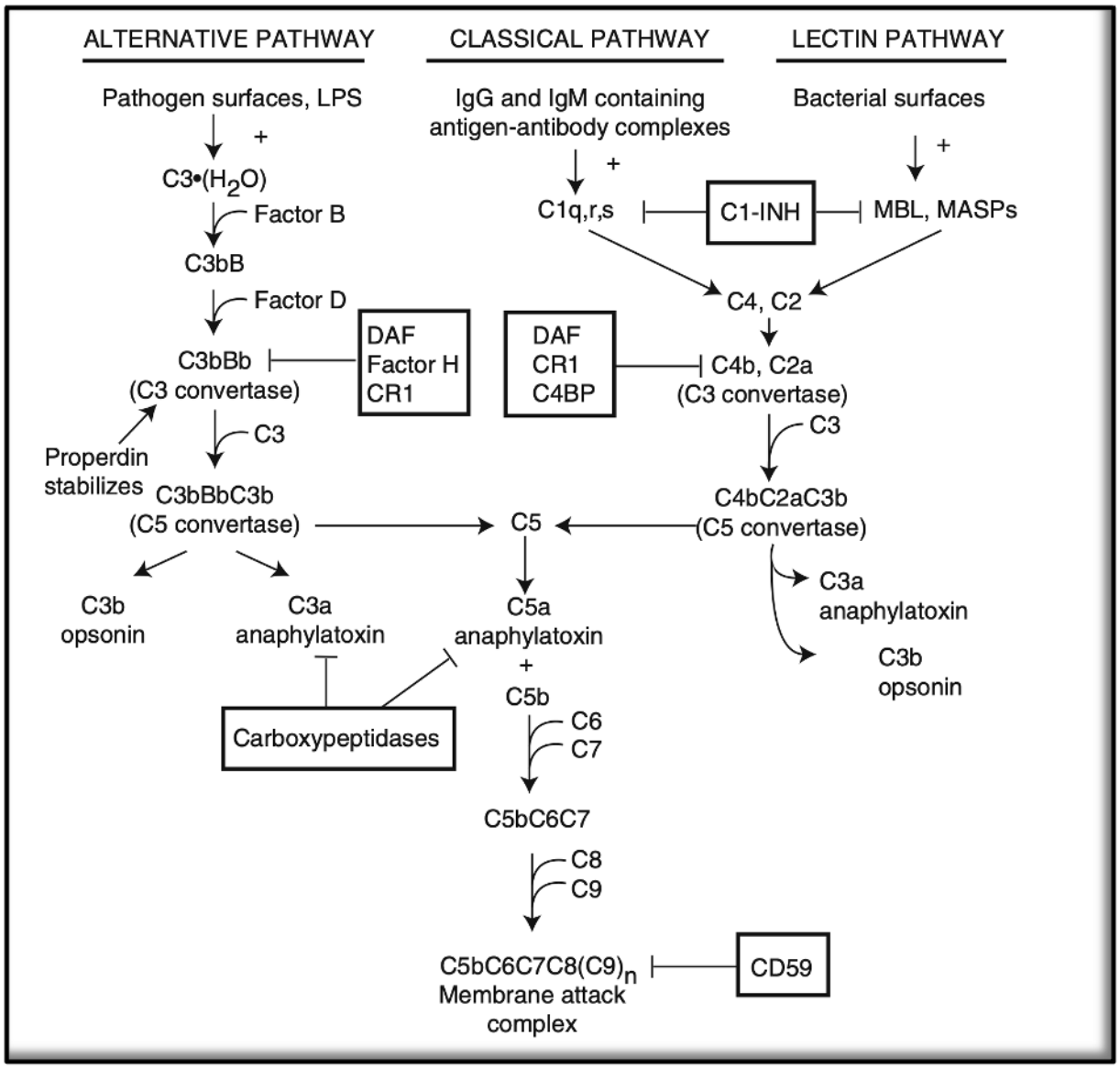


Figure 2: Summary of the activation pathways and their regulators in the box [26]

PATHOGENESIS OF IMMUNE-COMPLEX/MONOCLONAL IMMUNOGLOBULIN MEDIATED MPGN.

Immune complex-mediated MPGN (IC-MPGN) results from the deposition of circulation immune complexes in the glomeruli due to chronic antigenemia and/or circulating immune complexes seen in chronic infections and autoimmune diseases [52,53]. Monoclonal immunoglobulin-mediated MPGN is due to paraproteinemia deposits in the glomeruli due to monoclonal gammopathies [54].

It occurs in three phases: the injury phase, the proliferative phase, and the reparative phase.

- In the injury phase, immune complex deposits in the glomeruli activate the classical and terminal complement pathways in the mesangium and along the capillary walls, which accounts for hypocomplementemia.
- This leads to an influx of leukocytes releasing cytokines and proteases that cause damage to the capillary walls, resulting in hematuria and proteinuria in the proliferative phase.
- Reparative changes follow, forming a new basement membrane and the entrapment of immune complexes, complement factors, cellular elements, and matrix material, resulting in double contours along the capillary walls. [5]

A large number of IC-MPGN are a result of viral infections from Hepatitis B and C [14-17]. In developing countries, chronic bacterial

infections like endocarditis, shunt nephritis, and abscesses, as well as fungal and parasitic infections, are also associated with MPGN.[55–58]

Cases of IC-MPGN have been reported in autoimmune diseases like systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, and mixed connective tissue disorders.[59–62]

Monoclonal gammopathy of undetermined significance (MGUS) or monoclonal gammopathy of renal significance) (MGRS) is also one of the causes of immunoglobulin-mediated MPGN [54,63].

In recent findings, AP dysregulation due to genetic defects in CFH, C3, CFI, and CFB genes[64] and acquired defects like C3NeFs or autoantibodies of FH, FB, and C3b in complement AP genes [65,66] have also been incriminated in the pathogenesis of IC-MPGN/Monoclonal-mediated MPGN [67].

Pathogenesis of IC-MPGN is summarized in (Figure 3) below.

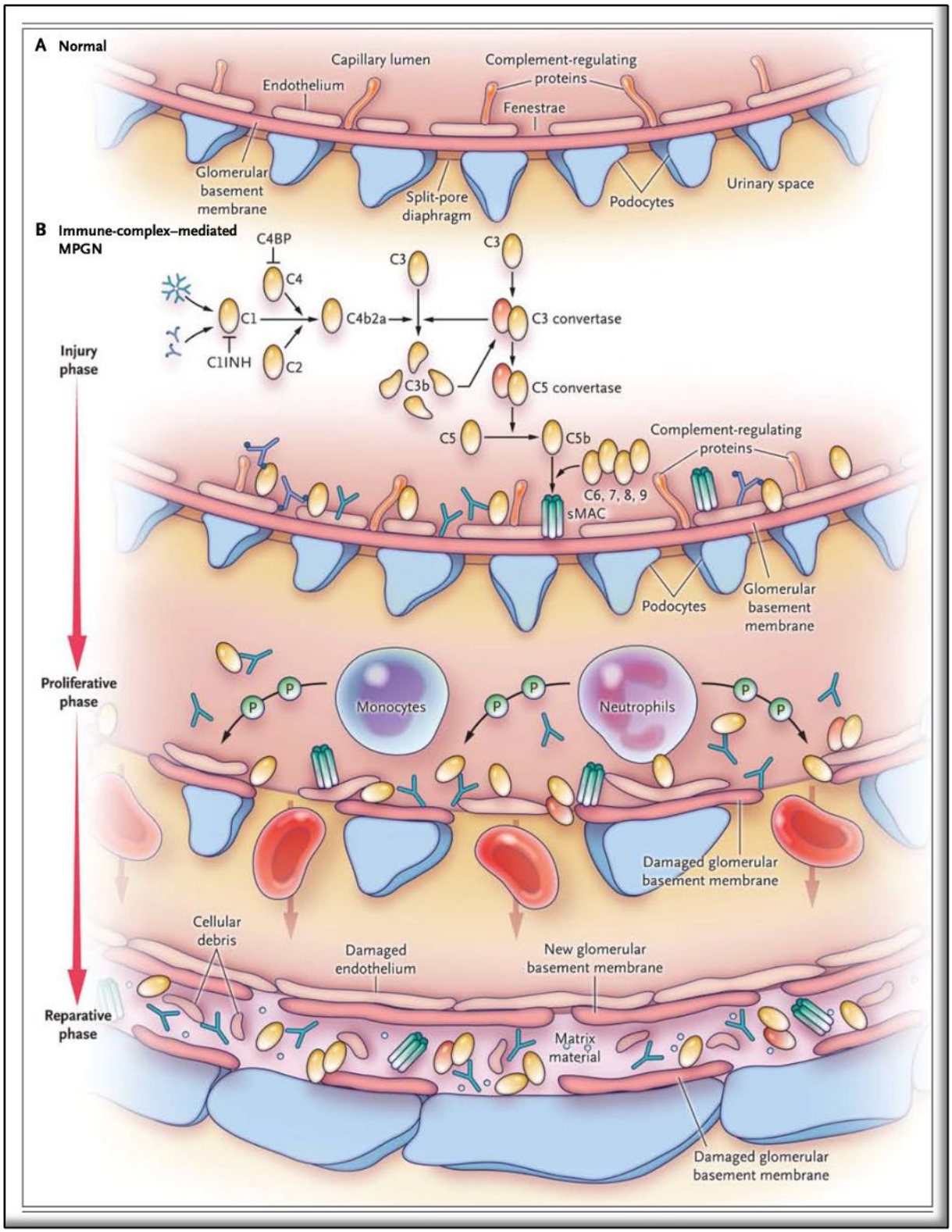


Figure 3:Pathogenesis of Immune complex-mediated MPGN[5]

C3 GLOMERULOPATHY

Recently, complement-mediated MPGN has been broadly reclassified under the term C3 glomerulopathies, which encompasses all disorders in which complement C3 accumulates in the kidney in the absence of significant immunoglobulin deposition [23]. 65-75% of light microscopy findings of C3 glomerulopathy are in favor of complement-mediated MPGN [51,64].

C3 glomerulopathies (C3G) are a group of rare kidney diseases characterized by complement dysregulation occurring in the fluid phase and in the glomerular microenvironment, which results in prominent complement C3 deposition along the capillary walls and mesangium in kidney biopsy samples, the two major subgroups are DDD and C3 glomerulonephritis C3GN.[68]

In IF, both subgroups share the same diagnosis criteria, with a bright stain for C3 twofold more than any other immuno-reactant[69]. EM findings help differentiate DDD from C3GN, where DDD possesses very dark intramembranous osmiophilic deposits that are sausage-shaped or look like Chinese calligraphy, whilst EM deposits in C3GN are light in color and often have the appearance of fluffy grey clouds within mesangial cells or as light, amorphous subendothelial humps[51].

Morphologically, in EM, DDD regroups the historically known MPGN type II. In contrast, C3GN often regroups MPGN type III of Strife and Anders with glomerular basement membrane thickening and a variable combination of subendothelial, intramembranous, and subepithelial deposits associated

with fraying of the lamina densa. A few, however, have more discrete subendothelial deposits and favor MPGN type I[70].

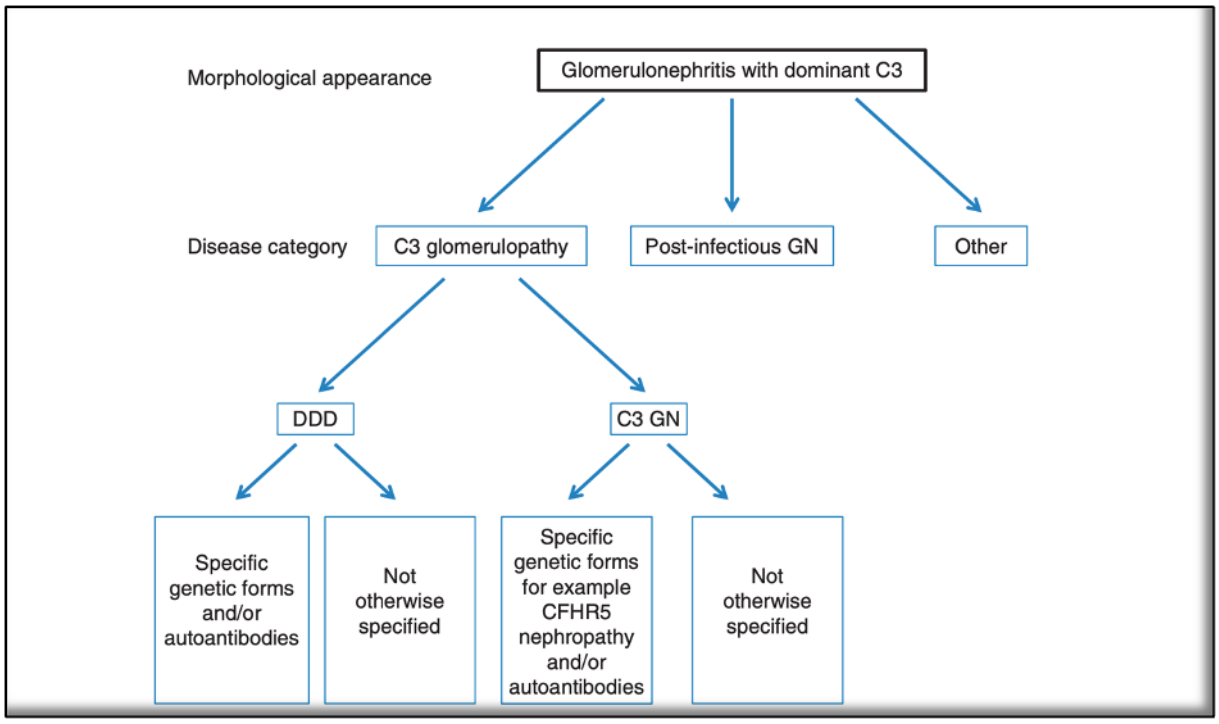


Figure 4:an approach to the disease classification in a biopsy showing the morphological changes of glomerulonephritis with dominant C3[70].

Pathophysiology complement-mediated MPGN

Complement-mediated MPGN is attributed to dysregulation in the alternate complement pathway[71].

Genetic and acquired factors of the AP complement system, such as mutations in factor H, factor I, and factor H-related protein 5 as well as antibodies like antibody to C3 (C3Nef), autoantibody FH, autoantibody FB, autoantibody FI to RCAs, result in dysregulation of the AP [44,72-75].

Also, heterozygous mutations in C3 in the fluid phase render the mutant C3 resistant to cleavage by C3 convertase and inactivation by factor

H. Consequently, the generation through the "tick-over" mechanism of an abnormal C3 convertase that cleaves C3 produced by the normal C3 allele, resulting in increased levels of C3 breakdown products [5,76]

Certain genetic polymorphisms in factors H and B, membrane cofactor protein, and C3 are also associated with MPGN [77,78].

However, only a few patients have relatives with the same disease due to the complexity of the complement system [79,80]. C3GN is more common than DDD in patients diagnosed with familial C3G [79].

Polymorphisms in the gene encoding factor H, particularly the Tyr402His allele variants, are amongst the most extensively studied. Compared to the Tyr402 variant, the His402 variant is more frequently observed in patients with MPGN and alternative pathway abnormalities. Functional studies show that His402 disrupts Factor H's ability to regulate cell surface C3 convertase [71,81,82].

Monoclonal immunoglobulin deposits in the glomeruli can alternatively activate the AP directly or block the RCAs, which results in monoclonal immunoglobulin-induced C3G [83]

Regardless of the mechanism, dysregulated AP produces activated complement products, including C3b and terminal complement factors. These products are distributed on the surfaces of endothelial glomeruli, causing acute injury and triggering inflammation in the inflammation or proliferative phase. [84,85]

A reparative phase ensues, during which a new mesangial matrix results in mesangial expansion as well as the formation of a new basement

membrane, entrapping capillary wall deposits, along with cellular elements derived from inflammatory, mesangial and endothelial cells within the new basement membrane material; this results in thickening of the capillary walls and the formation of double contours along the capillary walls. The new glomerular membrane looks like a duplicated basement membrane, hence the name tram tracks or doubled contours[5].

Figure 5 summarizes the pathological process of MPGN genesis.

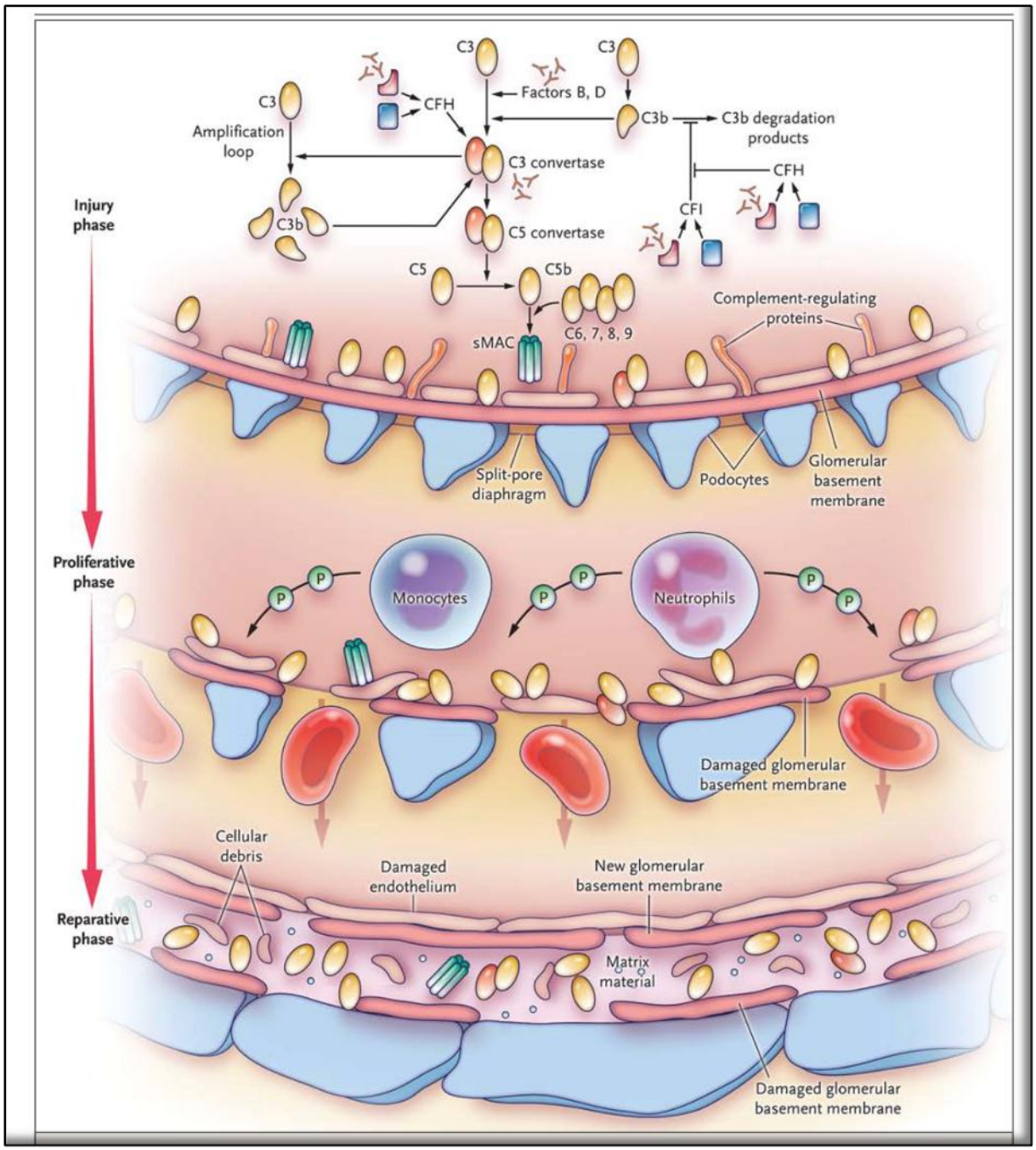


Figure 5:Pathogenesis of Complement-mediated MPGN [5]

PATIENTS AND METHODS

PATIENTS

1. Type of Study

We collected retrospective clinical data on patients diagnosed with MPGN, based on renal biopsy findings after reviewing all the renal biopsy data at the Nephrology Department of Hassan II University Hospital.

2. Duration of study

The study spanned a period of 13 years, from December 2011 to December 2024

3. Population studied

All patient files of MPGN were collated from the department's archives and Hosix.com (the hospital electronic database) at the Hassan II University Hospital.

A nephrology resident and a senior professor reviewed the pathology reports and laboratory results of all patients in detail to ensure accurate diagnosis and attribution of underlying causes.

MPGN types I, II, and III were reclassified to IC-MPGN or C3-MPGN after examining IF findings.

4. Selection Requirement

a. Inclusion Criteria

i. Patients with histological diagnostics of MPGN after kidney biopsy.

ii. Patients with a complete file

iii. Age > 18 years old

b. Exclusion Criteria

i. Patients with an incomplete file

ii. Age < 18 years old

iii. Patients with an MPGN pattern but a known systemic lupus erythematosus diagnosis were excluded.

METHOD

a. Studied Variables

Data collected through the medical database include;

- Demographic data;
  - Age,
  - Sex,
  - Occupation
  - Origin
- Health Insurance

Clinical data from the medical records on Hosix.com and medical records archives of the Nephrology department.

  - Comorbidities (Diabetes, Dysthyroidism, Cardiopathy, Asthma, hypertension)
  - History of infectious diseases (Tuberculosis, Viral and Bacterial infections, parasite infections)
  - History of autoimmune diseases, malignant hemopathy
  - Family history of renal pathology
  - Alcoholism, smoking, use of recreational drugs
- The biological data examined were;

- Urinary total protein, glomerular filtration rate (GFR in ml/mn/1.73m²) according to the MDRD formula, full blood count (FBC), electrolyte test, renal function test, liver function test, serum complement factors C3-C4, autoimmune disease lab work.

Histological diagnosis was based on an anatomopathological examination of the renal parenchyma obtained by renal biopsy. The histological elements studied are;

- signs of activity (endocapillary proliferation, exudation, extra-capillary cell proliferation, and interstitial inflammation)
- signs of chronicity (glomeruli in “sealing bread”, fibro-cellular or fibrous extra capillary crescents, interstitial fibrosis, and tubular atrophy).

The appearance in immunofluorescence (IF) allowed us to differentiate between immune complex or monoclonal mediated MPGN and MPGN with dysregulated complement system.

C3 glomerulopathy was defined as the presence of dominant C3 staining (2 orders in magnitude compared to immunoglobulins) on immunofluorescence microscopy, with minimal or no staining for immunoglobulins.

We also did an etiological workup searching for a secondary cause of MPNG.

- Antibody serology test for hepatitis, syphilis, and HIV,

- infectious workup (echocardiogram, chest x-ray, ENT examination, microscopic urinalysis)
- Immunological workup for systemic lupus erythematosus, vasculitis
- Serum protein electrophoresis and serum immunofixation electrophoresis for malignant hemopathy

We analyzed the different therapeutic modalities: symptomatic treatment, corticosteroid therapy, immunosuppressive drugs, and renal replacement therapy.

Renal status (Urinary total protein, serum creatinine, hematuria) was recorded at the last clinical follow-up to define the renal outcome: complete remission, partial remission, or no remission (worsening).

b. Definitions of Clinical Terms

Nephrotic syndrome was defined as 3.0 g/24hrs, Albuminemia <30 mg, Proteinemia < 60mg. Nephritic syndrome was defined as proteinuria < 1g/dl associated with high blood pressure with or without peripheral edema.

Patients were defined as positive for hematuria if microscopic examination showed five or more red blood cells per high-power field (HPF) and positive for macro-hematuria if blood was visible to the naked eye.

The renal outcome of our patients was categorized according to etiological classification (primary or secondary MPGN) {Table VIII}, identified causes (secondary MPGN), and IF microscopy (new MPGN classification) {table X}

c. Definition of Renal Outcome based on the KDIGO recommendations [86]

- **Complete remission:**

Disappearance of all clinical signs of the disease, normalization or return to baseline of serum creatinine and proteinuria less than or equal to 0.5g/24h.

- **Partial remission:**

Improvement in clinical signs of disease, improvement or stabilization of serum creatinine, and reduction of proteinuria by more than 50% below the nephrotic syndrome threshold without reaching a value of less than 0.5g/24h.

- **Worsening:** Absence of improvement, worsening of symptoms, or ESRD.

d. Statistical Analysis

Statistical analysis of the variables was carried out using SPSS 26.0 software at the epidemiology laboratory of the Faculty of Medicine and Pharmacy in Fez.

Qualitative variables were expressed as percentages, quantitative variables as mean and standard deviation (median, minimum, and maximum), and comparisons were made using the Fischer exact test (qualitative variables) or the non-parametric Mann-Whitney test (quantitative variables). A value of $p<0.05$ is considered significant.

RESULTS

Demographic Data

We identified 50 patients with a histological finding of MPGN on kidney biopsy, of which 36 remained following the application of the exclusion criteria, 22 primary MPGN patients (61.1%) and 14 secondary MPGN patients (38.9%).

17 were males (47.2%) whereas 19 were females (52.8%) with a male-to-female sex ratio of 0.895. The mean age of the patients was 48.17 ± 15.36 years. (Table 2)

Table 2: Demographic Characteristics of patients

Characteristics	Values (percentage)
Age: mean age	 48,17 ± 15,36
Males	17 (47.2%)
Females	19 (52.8%)
Geographical origin • Rural • Urban	 14 (38.9%) 22 (61.1%)
Medical Insurance	32 (88.9%)

Age groups

The largest age group were patients older than 55 years (38.89%) and the second largest age group were patients between the ages of 45 years and 55 years (27.78%). (Figure 5)

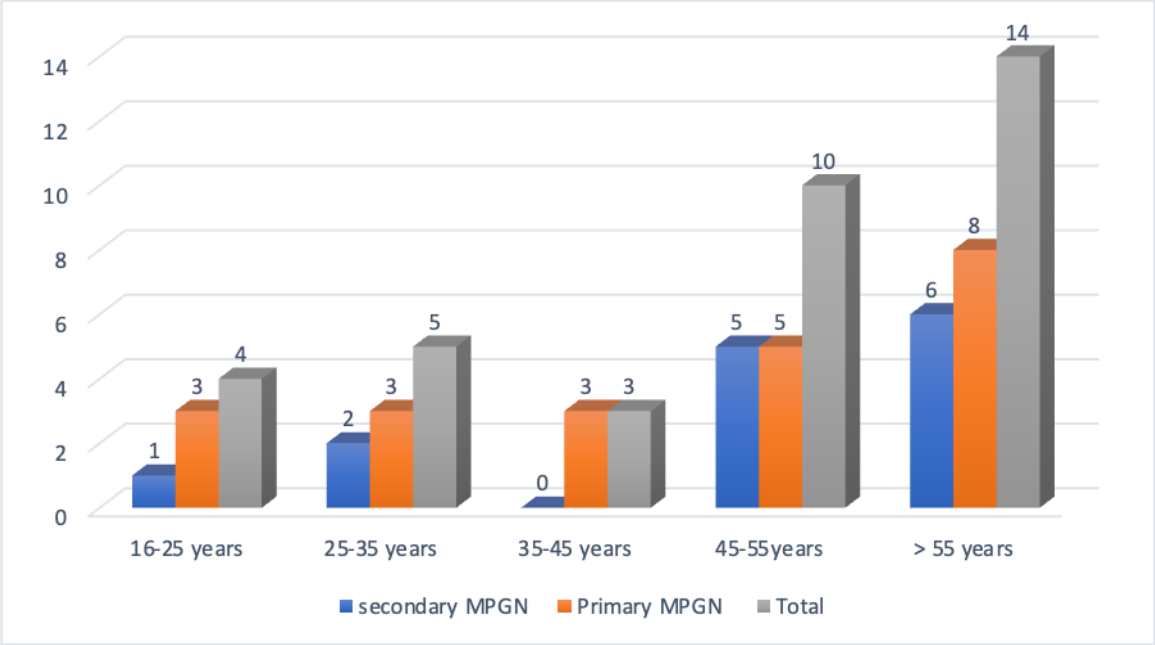


Figure 6:Age groups in our series and their corresponding number of cases.

Incidence

The highest number of MPGN were recorded in 2023 and 2024 (figure 7).

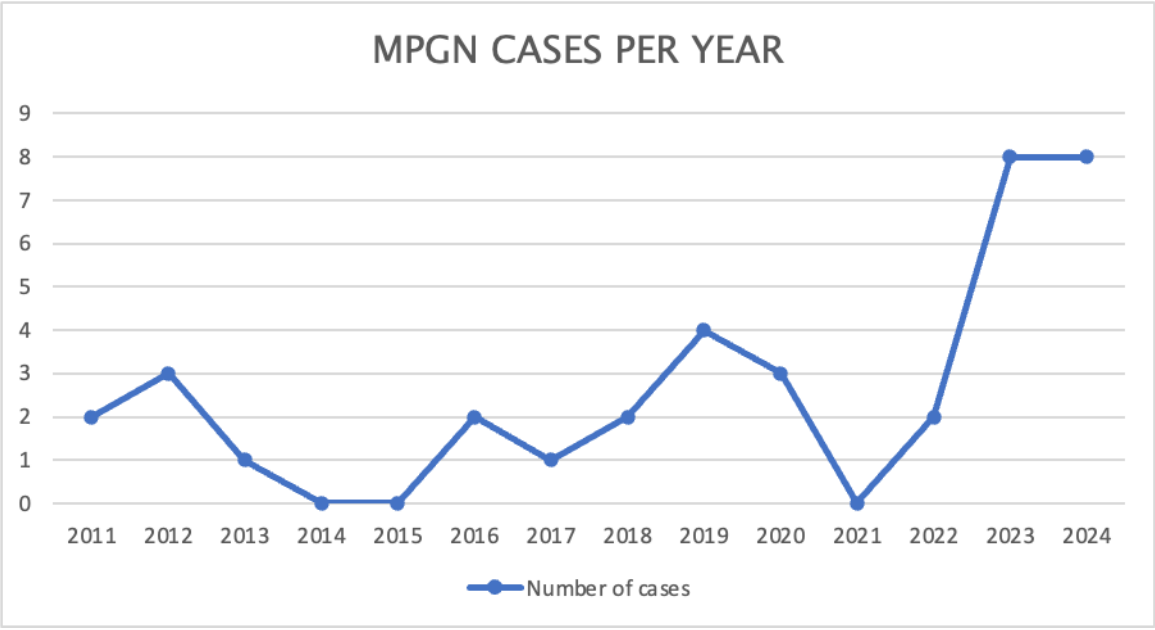


Figure 7:Cases recorded from 2011 to 2024 in our series

CLINICAL DATA

Medical follow up

13 patients had a medical follow up of more than 6 months, with 6 being between 6 to 12 months and 7 being more than 12 months (figure 8).

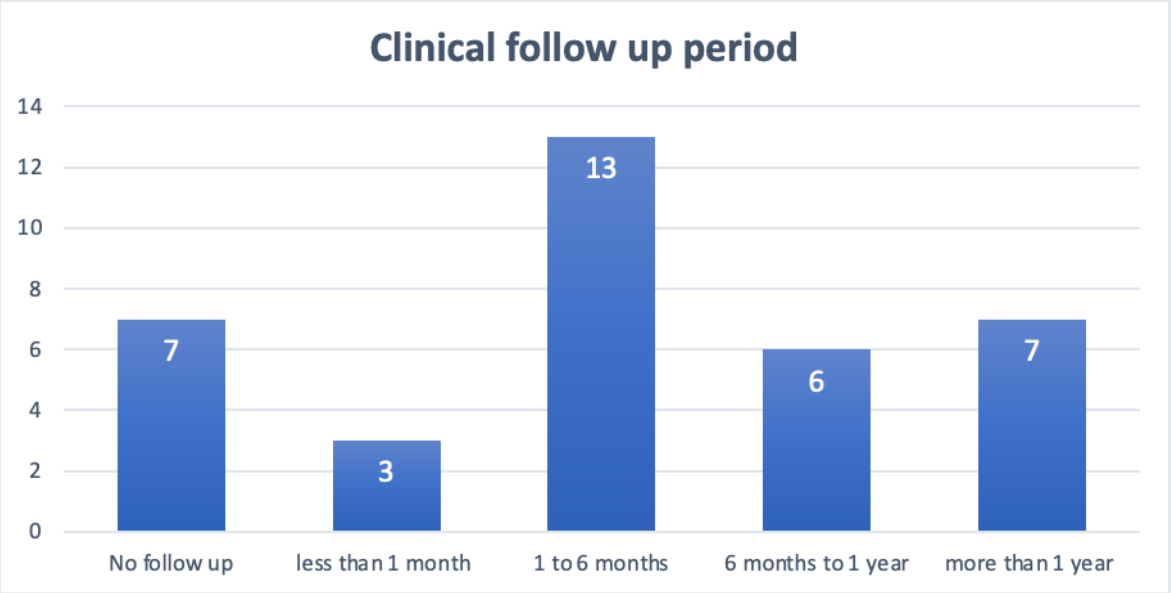


Figure 8:Duration of clinical follow-up.

Clinical Presentation At Diagnosis

The reasons for hospital admissions were nephrotic syndrome in 15 patients (41.7%), kidney failure in 15 patients (41.7%) associated with proteinuria in 2 patients, hypertensive crises in 3 patients, and RPGN in 1 patient, peripheral edema in 2 patients, hemoptysis associated with RPKF in 1 patient (2.8%), 3 patients with isolated proteinuria (8.3%). (Figure 9).

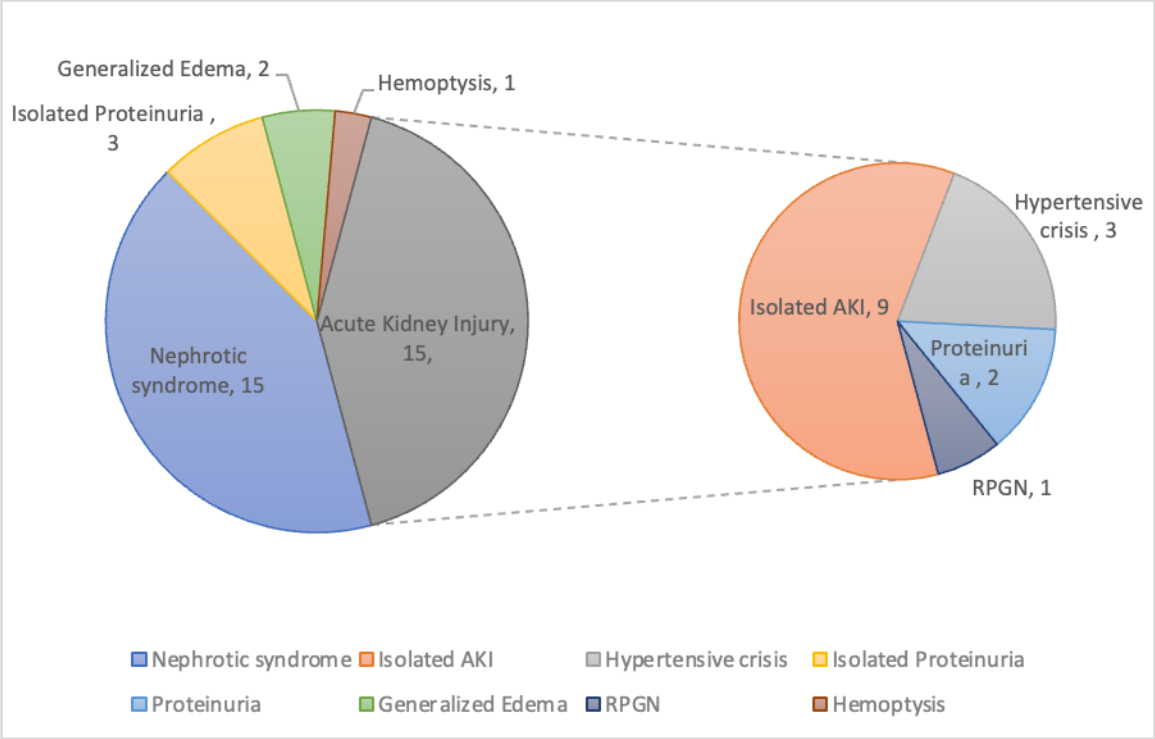


Figure 9:Patients' admission motifs in our series

Clinical Examination

Medical history of diabetes in 3 patients (8.3%), history of hyperthyroidism in 2 patients (5.6%), history of cardiopathy in 2 patients (5.6%), a family history of nephropathy in 3 patients (8,3%).

20 patients (55.6%) were hypertensive at admission, with a mean systolic pressure of 144.89 ± 25.49 and a mean diastolic pressure of 82.86 ± 12.38.

Hematuria was reported in 20 patients (55.6%) of which 4 were macroscopic and 16 were discovered after a routine dipstick urinalysis. 34 patients (94.4%) had normal diuresis.

During clinical examination, 23 patients (63.9%) had pitting edema, 3 patients had ascites (8.3%), and 5 patients had dyspnea (13.9%).

Documented systemic extrarenal signs include polyarthralgia in 2 patients, and hemoptysis in 1 patient. (Table 3)

Table 3: Characteristics of patients in our study

Characteristics	Number of cases (%)
History;	
- Family history of nephropathy	3 (8.3%)
- Surgical History	6 (16.7%)
- Medicine / Toxic	
o Cigarettes	3 (8.3%)
o Alcohol	2 (5.6%)
o Medicinal plants / Cannabis	7 (19.4%)
o Drug addiction	1 (2.8%)
Medical Co-Morbidities;	
- Diabetes	3 (8.3%)
- Hyperthyroidism	2 (5.6%)
- Cardiopathy	2 (5.6%)
- Tuberculosis	1 (2.8%)
- Asthma	3 (8,3%)
- Hypertension	11 (30.6%)
Clinical symptoms	
- pitting edema	23 (63.9%)
- Hematuria	20 (55.6%)
- Proteinuria	36 (100%)
- Oliguria	1 (2.8%)
- Anuria	1 (2.8%)
Documented extrarenal Signs	
- Polyarthralgia	2 (5.6%)
- Hemoptysis	1 (2.8%)

Blood Work-Up

The mean urinary total protein (UTP) at presentation was 4.060 ± 2.624 g/day (Tables 4). Microscopic urinalysis revealed hematuria in 18 patients (58.1%) with positive culture in 3 patients (9.7%). The C3 complement factor was low in 15 (50%) out of 30 patients, and the C4 complement factor was low in 4 patients (20%).

The mean eGFR (estimated Glomerular filtration rate) calculated according to the MDRD (modification of diet in renal disease) formula was 38.55 ± 32.21 ml/min/1.73 $m^{2.}$ (figure 10).

Table 4: urine and blood workup data

Test	Mean values
Urine;	
• **Urinary total protein (UTP)**	4.060 ± 2.624 g/24hr
Blood;	
• **Urea**	1.241± 0.927 g/l
• **Creatinine**	36.43 ± 39.81 mg/l
• **eGFR**	38.55 ± 32.21 (3-121) ml/min/1.73 m^2
• **Albumin**	29.28 ± 8.52 g/l
• **Protides**	60.45 ± 12.22 g/l
• **Natremia**	135.9 ± 5.94 mmol/l
• **Kalemia**	4.771± 0.854 mmol/l
• **Calcemia**	85.09 ± 7.76 mg/l
• **Uric acid**	90.11± 31.54 mg/l
• **CRP**	22.59 ± 24.40 mg/l

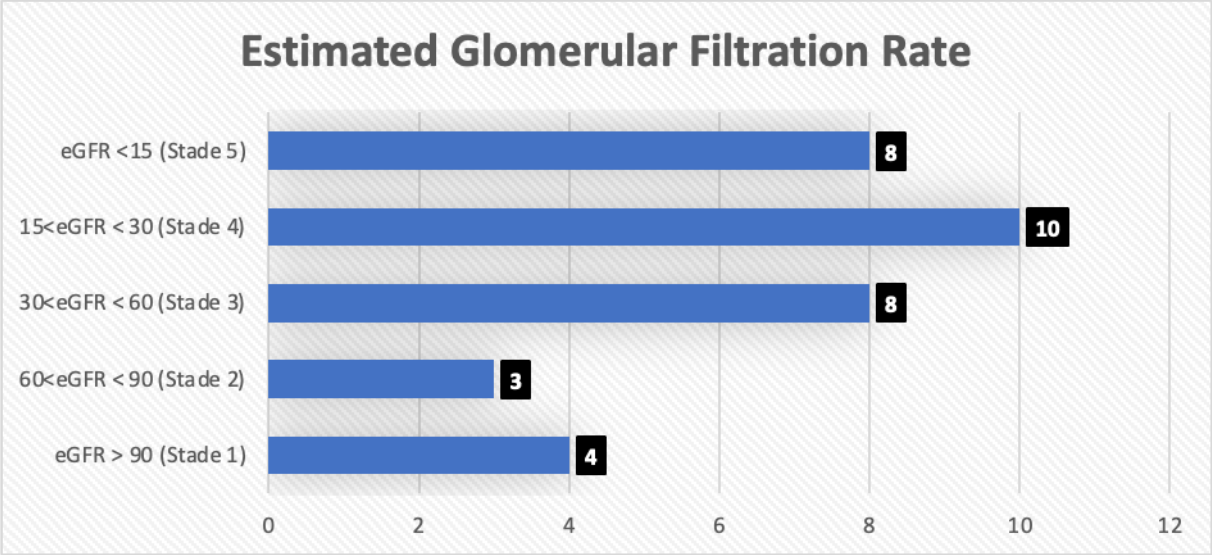


Figure 10:Estimated Glomerular Filtration Rate Of Patients At Diagnosis

Syndromic Presentation

Renal presentation of patients was nephrotic syndrome in 15 patients, nephritic syndrome in 6 patients, isolated proteinuria in 13 patients, and RPGN in 2 patients. (Figure 11)

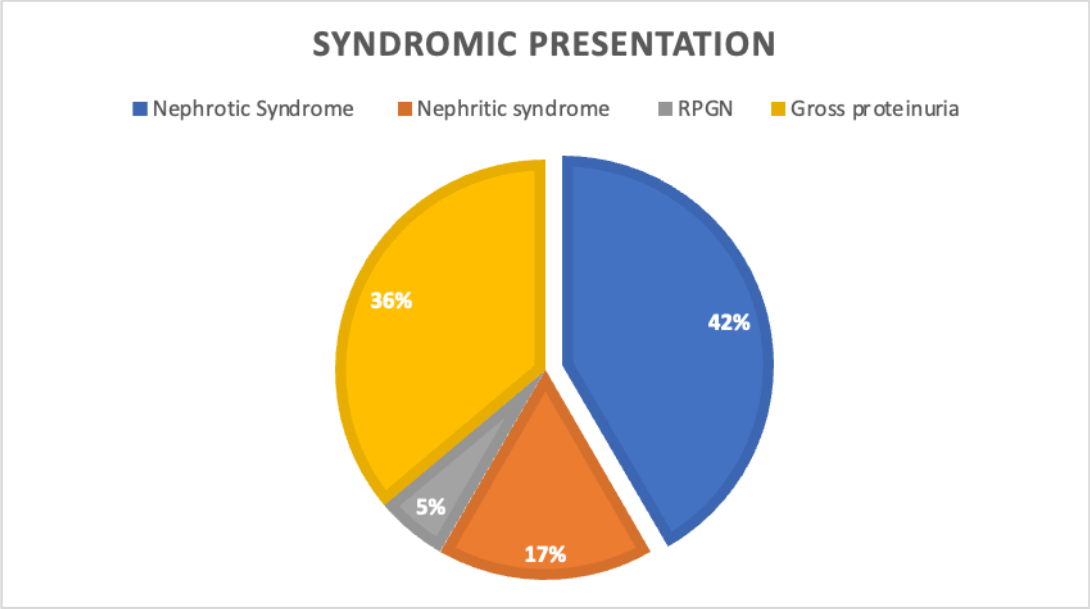


Figure 11:Syndromic Presentation Of Patients In The Series.

Etiological Work Up

The etiological blood work covered urinary tract infections, syphilis, hepatitis, tuberculosis, malignant hemopathy, and vasculitis. (Table 5)

Table 5:Results of etiological blood workup

Secondary MPGN	Patients (%)
Hepatitis	4 (28.6%)
• Hepatitis B	2
• Hepatitis C	2
Syphilis	1 (7.1%)
Malignant Hemopathy	4 (28.6%)
• Hodgkin lymphoma	1
• Waldenstom macroglobulinemia	1
• MGRS	1
• Multiple Myeloma	1
Urinary Tract infections	3 (21.4%)
Pleural Tuberculosis	1 (7.1%)
Anca associated Vasculitis (anti-MPO)	1 (7.1%)

RENAL BIOPSY

The indications of renal biopsy were;

- Impure nephrotic syndrome in 13 patients (36.1%)
- Isolated proteinuria in 4 patients without AKI representing (11.1%).
- Kidney injury in 19 patients associated with Proteinuria (52,8%).

All patients had proteinuria. 29 patients (80.6%) had associated kidney injury.

Renal Biopsy Results

The mean number of glomeruli in biopsied renal tissue was 12.91± 5.12.

Light Microscope findings

Light microscopy findings were grouped into glomerular lesions, vascular lesions, and tubulointerstital lesions (Table 6, 7 & 8)

Table 6:Glomerular Lesions Under Light Microscopy

Light Microscope	Patients (Percentage)
Mesangial Proliferation	17 (47.2%)
Mesangial hypercellularity	18 (50.0%)
Double contour	19 (52.8%)
Glomeruli in “Sealing Bread”	12 (33.3%)
Endocapillary proliferation	10 (27.8%)
Extracapillary proliferation	6 (16.7%)
Focal Segmental Glomerular Hyalinosis (FSGH)	11 (30.6%)

Table 7:Vascular Lesions Under Light Microscopy

Light Microscope	Patients (Percentage)
Normal	23 (63.9%)
Arterial hyalinosis	6 (16.7%)
Fibrinoid endarteritis	4 (11.1%)
Onion skin-like appearance	3 (8.3%)

Table 8:Tubulointerstitial Lesions under Light Microscopy

Fibrosis (%)	Patients (Percentage)
≤ 5%	13 (36.1%)
> 5- 30%	13 (36.1%)
>30%	10 (27.8%)

IMMUNOFLUORESCENT MICROSCOPE FINDINGS

Of the 36 patients, 32 patients (88.9%) had immunofluorescent microscopy (IF), the remaining 4 patients were classified as MPGN based on light microscopy evaluation alone.

The two major diagnoses were 19 IC-MPGN patients and 13 C3-MPGN patients (Figure 12).

The immune deposit distribution under IF microscopy was dominated by C3 deposits 96.9% (figure 13).

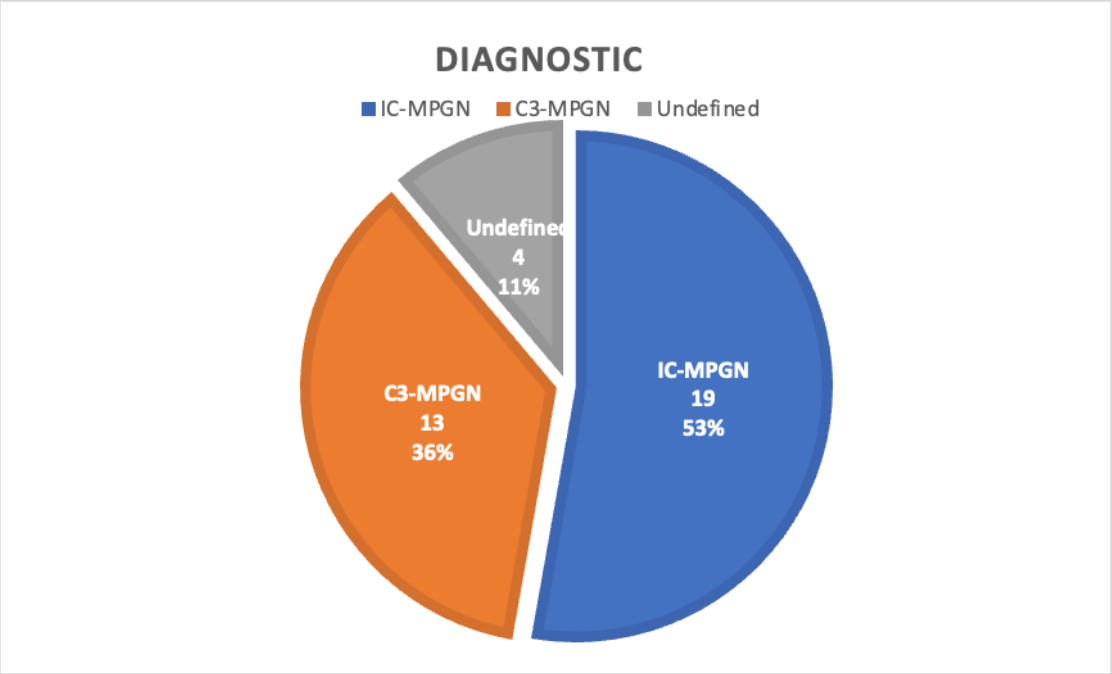


Figure 12:MPGN Diagnosis Retained after IF Microscopy.

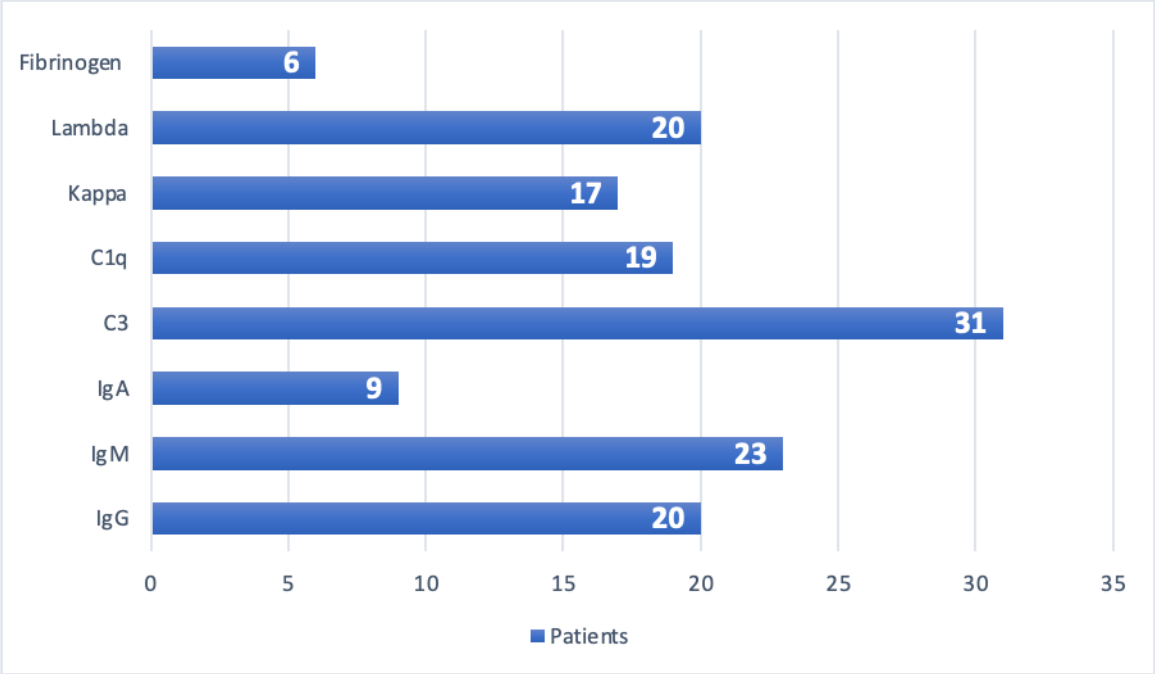


Figure 13:Immune deposits distribution under IF microscopy in our Patients

DISTRIBUTION OF PATIENTS BASED IMMUNOFLUORESCENCE MICROSCOPY MPGN CLASSIFICATION

19 (52) out of 36 patients were diagnosed with IC-MPGN, 13 patients (36.1) had C3-MPGN, with 4 patients having undefined MPGN. (Table 9).

Table 9:Clinical And Demographical Data Of IC-MPGN and C3-MPGN

Variable	IC-MPGN (N= 19)	C3-MPGN (N=13)
Gender		
• Male, n (%)	10 (52.6)	6 (46.2)
• Female, n (%)	9 (47.4)	7 (53.8)
Etiology based Diagnostic		
• Primary, n (%)	9 (47.4)	10 (76.9)
• Secondary, n (%)	10 (52.6)	3 (23.1)
Age (years), mean	52.2 ± 14.4	45.2 ± 16.4
Hypertension, n (%)	11 (57.9)	8 (61.5)
• SBP, median (IQR), mmHg	147 (90 - 225)	145 (120 - 190)
• DBP, median (IQR), mmHg	82 (60 - 115)	81 (60-95)
Lower extremity edema, n (%)	13 (68.4)	8 (61.5)
Clinical presentation at onset		
• Nephrotic syndrome, n (%)	7 (36.8)	5 (38.5)
• Acute Kidney Injury, n (%)	7 (36.8)	5 (38.5)
• Isolated Proteinuria, n (%)	2 (10.5)	1 (7.7)
• Generalized Edema, n (%)	1 (5.3)	1 (7.7)
• Rapidly progressive GN, n (%)	1 (5.3)	1 (7.7)
• Hypertensive Crisis, n (%)	1 (5.3)	0
Hematuria, n (%)	11 (57.9)	6 (46.2)
• Polyarthralgia, n (%)	1 (5.3)	1(7.7)
• Hemoptysis, n (%)	1 (5.3)	0
P anca (Anti MPO)	1 (5.3)	0
Low serum C3 level, n (%)	5 (26.3)	7 (53.8)
Low serum C4 level n (%)	2 (10.5)	2 (15.4)
eGFR at presentation, median (IQR), mL/min/1.73 m²	25 (4 - 109)	29.5 (5-121)
eGFR < 15 mL/min/1.73 m² , n (%)	6 (31.6)	2 (15.4)
Serum albumin, median (IQR), g/l	32 (13.6 - 44)	33.5 (15-41)
Urine total protein (g/24hr), mean	3.71± 1.86	4.21± 3.96
Hypergammaglobulinemia (SPE), n (%)	3 (15.8)	0

ETIOLOGICAL DISTRIBUTION OF MPGN

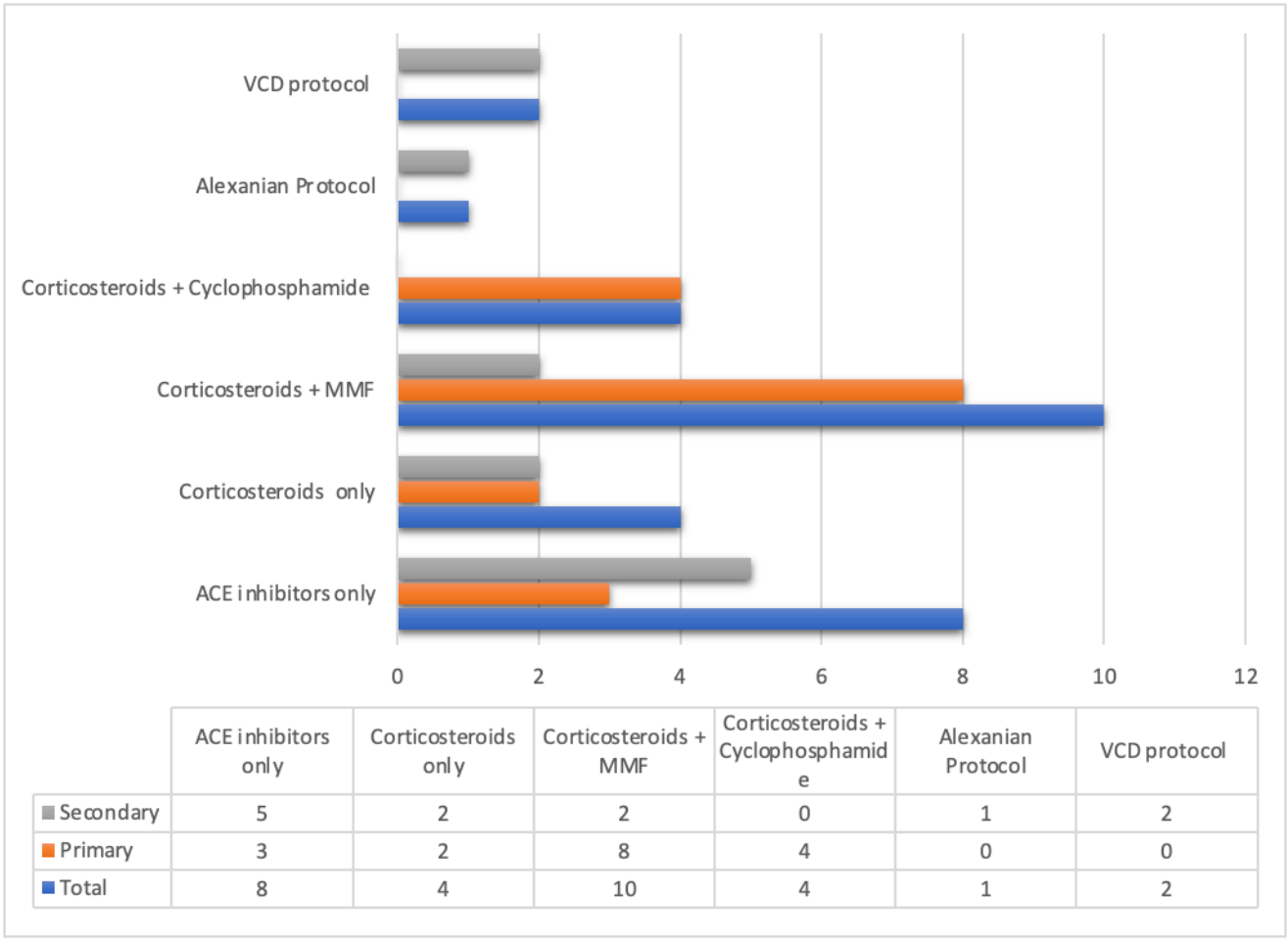
14 (38.8 %) out of 36 patients were diagnosed with secondary MPGN, while the remaining 22 patients (61.1%) had no apparent cause after a thorough etiological workup (Table 10).

Table 10:Clinical And Demographical Data Of Primary And Secondary MPGN

Variable	Primary (N= 22)	Secondary (N=14)
Gender		
• Male, n (%)	11 (50)	6 (42.9)
• Female, n (%)	11 (50)	8 (57.1)
Classification of MPGN		
• IC-MPGN, n (%)	9 (40.1)	10 (71.4)
• C3-MPGN, n (%)	10 (45.5)	3 (21.4)
• Undefined MPGN, n (%)	3 (13.6)	1 (7.1)
Age (years)	46.86 ± 16.96	50.2 ± 12.75
Hypertension, n (%)	13 (59.1)	6 (42.9)
• SBP, median (IQR), mmHg	142.5 (90-225)	136 (119-166)
• DBP, median (IQR), mmHg	81.5 (60-115)	82 (67-100)
Lower extremity edema, n (%)	12 (54.5)	11 (78.6)
Clinical presentation at onset		
• Nephrotic syndrome, n (%)	9 (40.1)	6 (42.9)
• Acute Kidney Injury, n (%)	8 (36.4)	3 (21.4)
• Isolated Proteinuria, n (%)	1 (4.5)	2 (14.3)
• Generalized Edema, n (%)	0	2 (14.3)
• Rapidly progressive GN, n (%)	1 (4.5)	1 (7.1)
• Hypertensive Crisis, n	3 (13.6)	0
Hematuria, n (%)	11 (50)	7 (50)
• Polyarthralgia, n (%)	1 (4.5)	1 (7.1)
• Hemoptysis, n (%)	0	1 (7.1)
P anca (Anti MPO), n (%)	0	1 (7.1)
Low serum C3 level, n (%)	10 (45.5)	5 (35.7)
Low serum C4 level n (%)	1 (4.5)	3 (21.4)
eGFR at presentation, median (IQR), mL/min/1.73 m²	23 (3 - 121)	29.5 (4 - 109)
eGFR < 15 mL/min/1.73 m² , n (%)	6 (27.3)	2 (14.3)
Serum albumin, median (IQR)	32.5 (13.6 - 45)	25.5 (16 - 44)
Urine total protein (g/24hr), mean	3.57 ± 1.62	4.69 ± 3.49
Hypergammaglobulinemia (SPE), n (%)	0	4 (28.6)

TREATMENT

Of 36 patients, 28 (77.8%) started treatment (Figure 14). One patient was started on corticosteroids + MMF and later switched to corticosteroids + cyclophosphamide due to non response. However, only 23 patients (63.9%) followed through with the treatment; one patient succumbed during management. (Figure 14).



	ACE inhibitors only	Corticosteroids only	Corticosteroids + MMF	Corticosteroids + Cyclophosphamide	Alexanian Protocol	VCD protocol
Secondary	5	2	2	0	1	2
Primary	3	2	8	4	0	0
Total	8	4	10	4	1	2

Figure 14:Management plan for patients in our series.

TREATMENT OF SECONDARY MPGN PATIENTS

Table 11:Treatment and renal outcome based on IF Microscopy classification of secondary MPGN patients.

DIAGNOSTIC	ETIOLOGY	PU/24HR	TREATMENT	RENAL OUTCOME
IC-MPGN	Multiple Myeloma	4.1	Alexanian protocol	Worsening
IC-MPGN	MGRS	3.78	VCD protocol	Worsening
IC-MPGN	Waldenström macroglobulinemia	5.4	VCD protocol	Complete remission
IC-MPGN	Churg et Straus	1.6	ACE inhibitors only	Worsening
IC-MPGN	Hepatitis B	5	ACE inhibitors only	Partial Remission
IC-MPGN	Hepatitis B	8	Corticosteroids + MMF	Worsening
IC-MPGN	UTI	1.4	Antibiotherapy + ACE inhibitors	Complete remission
IC-MPGN	UTI	1	Antibiotherapy + ACE inhibitors	Complete remission
IC-MPGN	Hepatitis C	2	Not treated	Lost to follow up
IC-MPGN	Tuberculosis	5.6	Corticosteroids + MMF + Antituberculous drug	Lost to follow up
C3-MPGN	UTI	14	Corticosteroids + Antibiotherapy	Lost to follow up
C3-MPGN	Syphilis	4.08	Not treated	Lost to follow up
C3-MPGN	Hepatitis C	0.36	ACE inhibitors only	Complete remission

RENAL OUTCOME OF PATIENTS IN OUR SERIES

Of the 36 patients, 23 (63.9%) were assessed after treatment. For Secondary MPGN, 10 out of 14 patients completed treatment (Table 12,13 &14).

Table 12:Global Renal Outcome Of Patients In Our Series With, Primary And Secondary MPGN Series.

Variable	Primary (N= 13)	Secondary (N=10)	Total (N= 23)
Complete remission, n (%)	**8** (61.5)	**4** (40)	**12** (52.2)
Partial Remission, n (%)	**1** (7.7)	**2** (20)	**3** (13.0)
▪ *Mean proteinuria (g/24hr)*	*1.00*	*0.99 ± 0.26*	*0.99 ± 0.19*
Worsening, n (%)	**4** (30.8)	**4** (40)	**8** (34.8)
▪ *Mean proteinuria (g/24hr)*	*3.66 ± 0.91*	*4.60 ± 3.71*	*4.12 ± 2.55*
▪ **Deteriorating renal function, n (%)**	2 (50)	0	4 (50)

Table 13:Renal Outcome Based On Etiology In Our Series

Etiology, n (%)	Complete Remission, n (%)	Partial Remission, n (%)	Worsening, n (%)
Bacterial Infection, 3 (60)	2 (66.7)	0	1 (33.3)
Viral Infection, 3 (75)	1 (33.3)	1 (33.3)	1 (33.3)
Malignant Hemopathy, 3 (75)	1 (33.3)	1 (33.3)	1 (33.3)
Vasculitis, 1 (100)	0	0	1 (100)

Table 14:Renal Outcome Based On New MPGN Classification

New Classification, n (%)	Complete Remission, n (%)	Partial Remission, n (%)	Worsening, n (%)
IC-MPGN, 12 (52.2)	4 (33.3)	3 (25)	5 (41.7)
C3-MPGN, 9 (39.1)	6 (66.7)	0	3 (33.3)
Unknown, 2 (8.7)	2 (100)	0	0

PROGNOSTIC FACTORS

The only significant prognostic factor of non-response in our study was the use of only corticosteroids with a P-value of 0.032. (Table 15)

table 15:Prognostic factors of non-response in our study

FACTORS	P VALUE
Sex	0.657
Age	
• 16 – 25	1.000
• 25 – 35	0.589
• 35 – 45	1.000
• 45 – 55	1.000
• > 55	1.000
Etiology (Primary MPGN /Secondary MPGN)	0.685
Diagnosis (IC- MPGN/ C3-MPGN)	1.000
High BP at admission	0.221
Nephrotic syndrome	0.179
Nephritic syndrome	1.000
Proteinuria > 5g/day	1.000
Severe Chronic disease (30 > GFR > 15)	0.621
End Stage Renal Disease (GFR <15)	0.269
Low C3 Complement	0.149
Mesangial Proliferation	0.667
Mesangial hypercellularity	0.685
Double Contour appearance	0.376
“Sealing in Bread”	1.000
Endocapillary Proliferation	1.000
Extracapillary Proliferation	1.000

Focal segmental hyalinosis	1.000
Arterial hyalinosis	1.000
Normal arterioles (arteries)	0.369
Fibrosis Endarteritis	0.526
Onion skin-like appearance	1.000
IgG	0.400
IgM	0.657
IgA	1.000
C3	0.526
C1q	1.000
Kappa	0.667
Lambda	0.221
Fibrinogen	0.621
Corticosteroids only	0.032
ACE- inhibitors	0.176
Corticosteroids + MMF	0.657
Corticosteroids + Cyclophosphamide	0.348
Alexanian Protocol	0.348
VCD protocol	0.526

RENAL SURVIVAL

The mean survival time of our patients was 55.67 ± 5.92 months.

(figure 15) and a 58% chance of renal survival at 71 months post diagnosis.

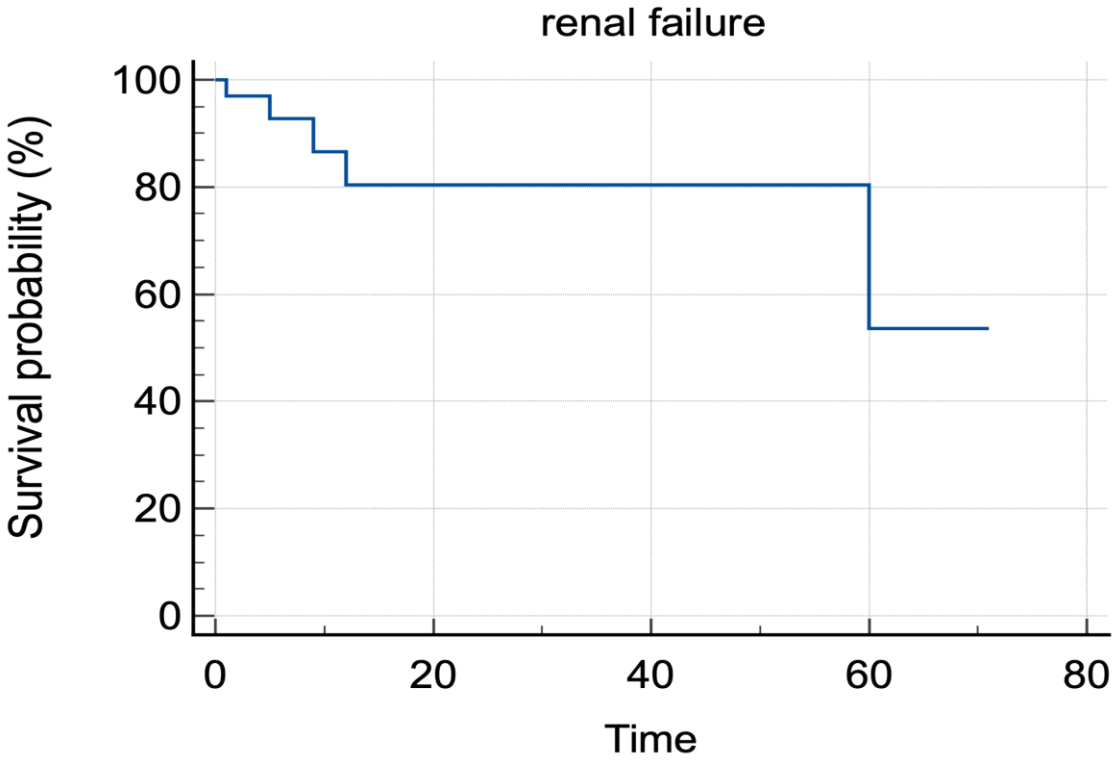


Figure 15:Global renal survival of patients (Kaplan Meier curve)

DISCUSSION

We report here a retrospective study carried out at the nephrology department of CHU Hassan II from December 2011 to 2024, covering 13 years.

All patients were collected from the department's renal biopsy archives. We identified 50 patients with MPGN pattern under the light microscope. After applying the exclusion criteria, 36 patients were retained. The omitted patients were: nine patients due to incomplete patient data, three patients due to SLE revealed as MPGN, and two underage patients.

The results revealed 22 cases of primary MPGN (61.1%) and 14 cases (38.9%) of secondary MPGN, based on the IF microscopy classifications, 19 IC-MPGN (52.8%), 13 C3-MPGN (36.1%), and 4 non-classified cases (11.1%).

This study aims to investigate the clinical, etiological, and histological characteristics and therapeutic differences between IC-MPGN and C3-MPGN, renal outcomes of patients, and prognostic factors.

INCIDENCE

The incidence of membranoproliferative glomerulonephritis (MPGN) has shown a dynamic evolution over the years. At the nephrology department of CHU Hassan II, the number of reported MPGN cases remained relatively stable between 2011 and 2018, with 1 to 3 cases annually. However, since 2019, there has been a marked increase, reaching 8 cases per year in 2023 and 2024. This trend may be attributed to the increased prescription of percutaneous renal biopsy, leading to a higher detection rate.

MPGN remains a rare cause of glomerulonephritis, with a reported incidence varying across populations. Studies from the United Kingdom and

Japan have shown a decline in MPGN cases over the past two decades, partly due to improved screening for secondary causes and changes in disease classification [87,88]

However, some recent reports suggest a resurgence of MPGN cases, particularly after the COVID-19 pandemic, potentially linked to viral infections or post-vaccination immune responses [89,90]. Although some studies have proposed a correlation, our findings do not provide substantial evidence to support this hypothesis, necessitating further research with larger cohorts.

AGE DISTRIBUTION

The mean age of our MPGN patients was 48.17 ± 15.36 years, with a majority (38.89%) being older than 55 years, followed by 27.78% in the 45-55-year age group. This suggests that MPGN predominantly affects middle-aged and older adults. Our findings are in agreement with those from a Japanese cohort, where the mean age ranged from 46.0 ± 13.3 years in adults to 73.4 ± 5.7 years in elderly patients [88]. Similarly, a Brazilian study reported a mean age of 53 ± 15.1 years [91], corroborating the observation that MPGN is frequently diagnosed in older individuals.

The age distribution also differs between immune-complex MPGN (IC-MPGN) and complement-mediated MPGN (C3-MPGN). In our series, the mean age at diagnosis was 52.2 ± 14.4 years for IC-MPGN and 45.2 ± 16.4 years for C3-MPGN. Which is in line with several reports showing that the age of onset of IC-MPGN in adults is relatively higher than that of patients affected

with C3-MPGN (Table 16). This trend suggests that IC-MPGN may be more frequently associated with chronic immune stimulation, whereas C3-MPGN, driven by dysregulation of the alternative complement pathway, may be present earlier.

Table 16:Average ages of IC-MPGN and C3-MPGN at onset

Cohort	Total No. of Patients (**IC-MPGN**/ C3-MPGN)	Age range (years)	IC-MPGN Median (range), years	C3-MPGN Median (range), years
Fes (Our Series)	36 (**19**/13)	18-77	56 (25 - 77)	48 (18 - 61)
United Kingdom [87]	38 (**28**/10)	40-67	64 (43-68)	55.5 (29-59)
Japan [92]	81(**67**/14)	20-64	62 (29 - 73)	19 (13 - 26)
Finland [93]	60 (**37**/ 23)	5-79	52 (5-78)	54 (16-79)

SEX DISTRIBUTION

In the literature, the sex ratio of MPGN is slightly in favor of the female population. In our study, the M/F ratio was 1:1.12; similar findings were reported in other studies [87,91-94]. Due to the omission of MPGN secondary to lupus (SLE), which predominantly affects women (with a male-to-female ratio of 1:12) [95]. Some studies suggest that hormonal differences, immune system variations, or genetic predispositions may play a role in the slight female predominance observed in some populations [2,5].

CLINICAL PRESENTATION OF MPGN

The clinical presentation of MPGN resembles that of other forms of glomerulonephritis. In patients with active disease, urinalysis typically

reveals hematuria with dysmorphic red blood cells (RBCs) and, in some cases, RBC casts. Proteinuria is present to a varying degree, and serum creatinine levels may be normal or elevated. In contrast, patients with a more insidious disease course may present at a later stage when active inflammation has resolved. In such cases, urinalysis may show a bland sediment with variable proteinuria and elevated serum creatinine. The definitive diagnosis is established through kidney biopsy [5].

The clinical manifestations in DDD and C3GN patients are similar [96] , with minor differences reported in a few studies [7,97,98].

In our study, clinical presentation at onset was heterogeneous (Figure 7) with proteinuria in all patients. Nephrotic syndrome (42%) was the major renal syndrome (Figure 11), this finding is consistent with that of Alchi B and Jayne D [4].

It is also worth noting that the results of this study are consistent with those reported by Iatropoulos et al. [99] and Servais et al.[64]. Specifically, the current findings indicate that nephrotic syndrome is more common in patients with IC-MPGN than in those with C3-MPGN.

Additionally, we observed a lower median eGFR in primary MPGN compared to secondary MPGN. Furthermore, primary MPGN patients had a higher prevalence of end stage renal disease (ERSD) (27.3%) than secondary MPGN patients (14.3%). These findings suggest that primary MPGN patients present with more severe kidney dysfunction at diagnosis.

Another noteworthy observation is the higher proteinuria in secondary MPGN (4.69 ± 3.49 g/24hr) compared to primary MPGN (3.57 ± 1.62

g/24hr). This suggests that secondary disease may be associated with greater glomerular injury.

Extrarenal Manifestations

Extrarenal signs typically reflect the underlying causative disease rather than the specific type of MPGN [100]. In C3-MPGN, these may include acquired partial lipodystrophy (affecting the face and upper limbs), C3 ocular deposits (Drusen), and thrombotic microangiopathy [24,64,97,101].

In our study, extrarenal manifestations were limited: two patients presented with polyarthralgia, and one had hemoptysis (associated with Goodpasture syndrome). However, no cases of arthritis, cutaneous lesions, alopecia, ophthalmological, digestive, or otorhinolaryngological symptoms were documented at diagnosis. This could be attributed to the fact that most patients were referred during the peak of renal symptoms. Additionally, conditions like SLE, which typically present with extrarenal signs, were excluded from our study [102–104].

Low C3 levels are frequently observed in both IC-MPGN and C3-MPGN, with no significant difference reported between the two [99,105,106]. However, in our cohort (Table VII), primary MPGN patients exhibited low C3 levels in 45.5% of cases, with a higher prevalence in C3-MPGN (53.8%) compared to IC-MPGN (26.3%).

Low C4 levels were more common in secondary MPGN (21.4%) than in primary MPGN (4.5%), suggesting that secondary MPGN may involve stronger

activation of the classical complement pathway, possibly due to autoimmune diseases or infections [107–109].

ETIOLOGY AND DIAGNOSIS

MPGN presents differently across age groups, with primary (idiopathic) forms being more common in children and typically related to complement abnormalities [2].

In adults, MPGN is more frequently secondary to various underlying conditions [3,12] including infectious diseases (viral like hepatitis B and C, bacterial, fungal, and particularly in developing regions, parasitic infections such as schistosomiasis and malaria), autoimmune disorders (SLE, Sjögren syndrome, rheumatoid arthritis), and monoclonal gammopathy [56–63] .

This distinction underscores the importance of conducting a comprehensive etiological workup when MPGN is identified on renal biopsy before concluding it is primary [12].

Current KDIGO (2021) guidelines recommend a systematic diagnostic approach for IC-MPGN [86]. First, infectious causes should be investigated, including hepatitis viruses, chronic bacterial infections (endocarditis, abscesses), and in appropriate settings, fungal or parasitic infections. Patients with recent infections should undergo streptococcal serology testing. Second, autoimmune diseases such as SLE must be considered. Additionally, malignancy-associated IC-MPGN may require age-appropriate cancer screening. For suspected monoclonal gammopathy-related MPGN, which becomes increasingly prevalent after age 50 [109,110], the evaluation should include serum and urine protein electrophoresis, immunofixation

studies to characterize monoclonal proteins, serum free light chain assessment, and bone marrow biopsy to identify clonal plasma cell or B-cell populations [12]. Notably, MPGN may sometimes represent the initial manifestation of an underlying lymphoproliferative disorder [12].

In cases where no secondary cause is identified, primary MPGN evaluation should focus on complement system abnormalities. This includes genetic testing for variants in complement-related genes (C3, CFB, CFHR5), assessment of acquired factors like C3 nephritic factor (C3NeF) and C5NeF, and testing for autoantibodies against complement regulatory proteins (Factor H, Factor B) [35,40]. Clinical history should be carefully reviewed as 28-54% of C3-MPGN cases follow infections and are often initially misdiagnosed as post-infectious glomerulonephritis (PIGN) [111-113].

In patients aged over 50 years, monoclonal gammopathy represents the predominant cause of MPGN [110,114]. The diagnostic evaluation in these cases should systematically include:

- Serum protein electrophoresis and immunofixation (SIFE) to characterize monoclonal proteins (light chains λ/κ, heavy chains) and assess for AL amyloidosis
- Bone marrow biopsy to evaluate for clonal plasma cell or B-cell proliferations[12].

For suspected primary MPGN, the diagnostic workup should focus on complement pathway abnormalities, Blood workup for primary MPGN includes comprehensive genetic testing for variants in complement-related

genes in C3, CFB, and CFHR5 [35,40], as well as testing for acquired factors like C3Nef and C5Nef and, less frequently, C4Nef, Factor H, and Factor B autoantibodies. [35,40].

Evidence of preceding infection is reported in 28–54% of C3-MPGN patients[112,113,115] which is usually misdiagnosed as PIGN [111].

At the Nephrology Department of CHU Hassan II, our standard diagnostic workup for secondary MPGN includes screening for hepatitis B and C, syphilis, HIV, urinary tract infections, and various systemic diseases including SLE, vasculitis, scleroderma, Sjögren syndrome, and rheumatoid arthritis. We also evaluate for hematologic malignancies such as lymphoma and multiple myeloma, as well as monoclonal gammopathies (MGUS/MGRS) (Tables IV). Notably, our protocol does not currently include testing for genetic or acquired complement abnormalities.

Patients with SLE were excluded from our study due to their established management protocols. Among our cohort, 28.6% of cases were secondary to hematologic malignancies, with affected patients having a mean age of 55.25 ± 15.26 years. This finding aligns with existing literature demonstrating that malignancy-associated MPGN predominantly occurs in older adults [116–118].

Viral infections were identified in 11.1% of cases, with hepatitis B and C being the most prevalent. These results are consistent with previous Moroccan studies from Marrakech and Casablanca, which reported hepatitis-associated MPGN in 6.5% (2 of 31) and 30% (6 of 20) of secondary cases respectively [94,118]. Bacterial infections – including syphilis, urinary tract

infections, and tuberculosis - accounted for 13.9% of secondary MPGN cases in our study.

BIOPSY AND HISTOLOGY

Our detection of the double contour sign in 52.8% of patients is consistent with studies describing its presence in membranoproliferative glomerulonephritis (MPGN) and C3 glomerulopathy. However, its absence in some cases reinforces the well-documented variability of this feature, particularly in dense deposit disease (DDD), where glomerular basement membrane (GBM) alterations may not always exhibit this hallmark [40].

However, its absence in some cases reinforces the well-documented variability of this feature, particularly in dense deposit disease (DDD), where glomerular basement membrane (GBM) alterations may not always exhibit this hallmark [75].

The presence of crescents in 16.7% of our patients correlates with their established role as a predictor of poor renal outcomes [119].

This frequency is slightly lower than in studies focusing on aggressive forms of MPGN (e.g., 20–30% in Huang et al., 2020 [120], possibly reflecting differences in disease severity or biopsy timing.

The majority of our patients (63.9%) lacked significant vascular lesions, contrasting with cohorts where hypertension or thrombotic microangiopathy predominated [129]. The observed onion-skin lesions (8.3%) and fibrinoid endarteritis (11.1%) suggest secondary vascular injury, resembling patterns seen in lupus nephritis or malignant hypertension[121].

The high prevalence of C3 deposits (96.9%) underscores the central role of complement dysregulation, as reported in C3 glomerulopathy [114]. The detection of immunoglobulins and fibrinogen aligns with mixed-pattern injury, as described in secondary MPGN [122]. Without electron microscopy, the definitive diagnosis of dense deposit disease (DDD) cannot be established, as ultrastructural analysis remains essential for identifying the characteristic intramembranous dense deposits.

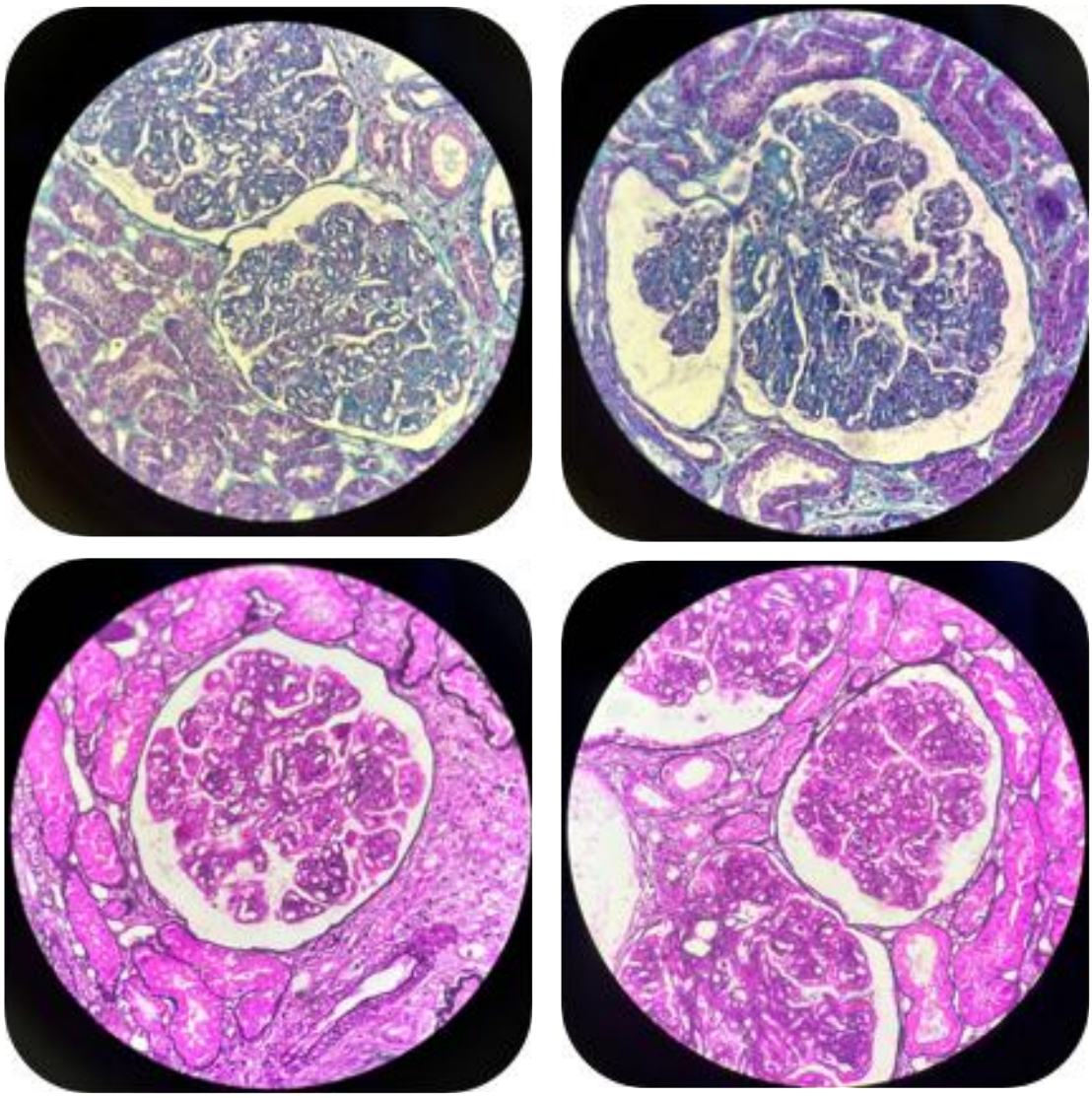


Figure 16:Membranoproliferative glomerulonephritis under light microscope from the Anapathological department of CHU Hassan II.

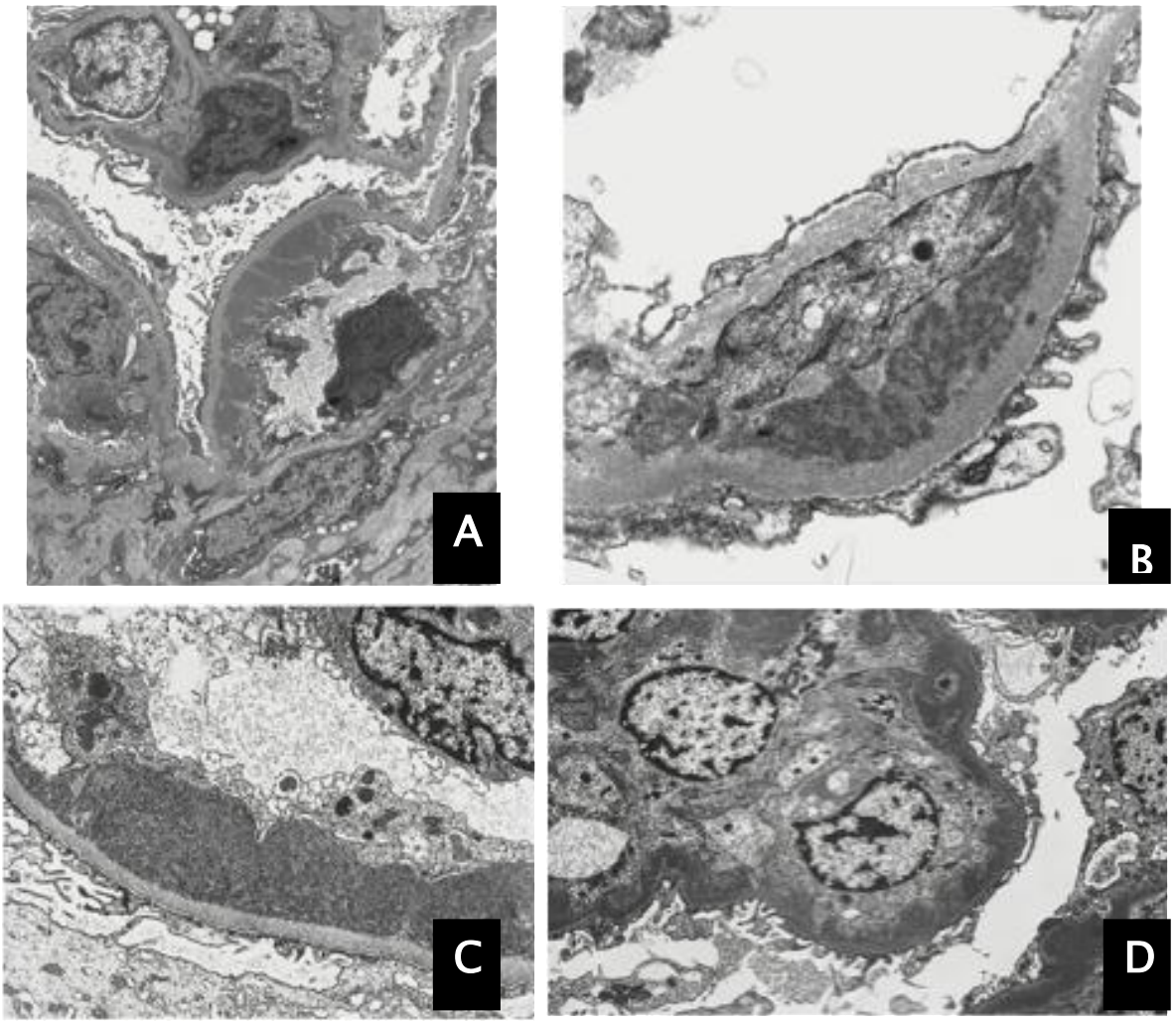


Figure 17: Membranoproliferative glomerulonephritis under Electron microscope [9]

Figure 16: A: MPGN with massive subendothelial deposits in the right loop, with minimal endocapillary hypercellularity, and small, sliver-like deposits on the left and top loops, with associated hypercellularity. Scattered mesangial deposits are also present. There is subtotal effacement of the overlying foot process (transmission electron microscopy, ×8000). **B:** MPGN, Subendothelial deposits are present, without attendant hypercellularity. The mottled, vaguely wormy substructure of the deposits suggests the possibility of a secondary etiology, such as cryoglobulin deposits. (transmission electron microscopy, ×11,250). **C:** MPGN, Subendothelial deposits are present, without attendant hypercellularity. The mottled, vaguely wormy substructure of the deposits suggests the possibility of a secondary etiology, such as cryoglobulin deposits (transmission electron microscopy, ×11,250).
D: MPGN with marked endocapillary hypercellularity, small subendothelial deposits, and a transmembranous deposit (lower right). The endocapillary hypercellularity is due to a mixture of

proliferation of endothelial cells, mesangial cells, and infiltrating mononuclear cells/macrophages (transmission electron microscopy, ×8000).

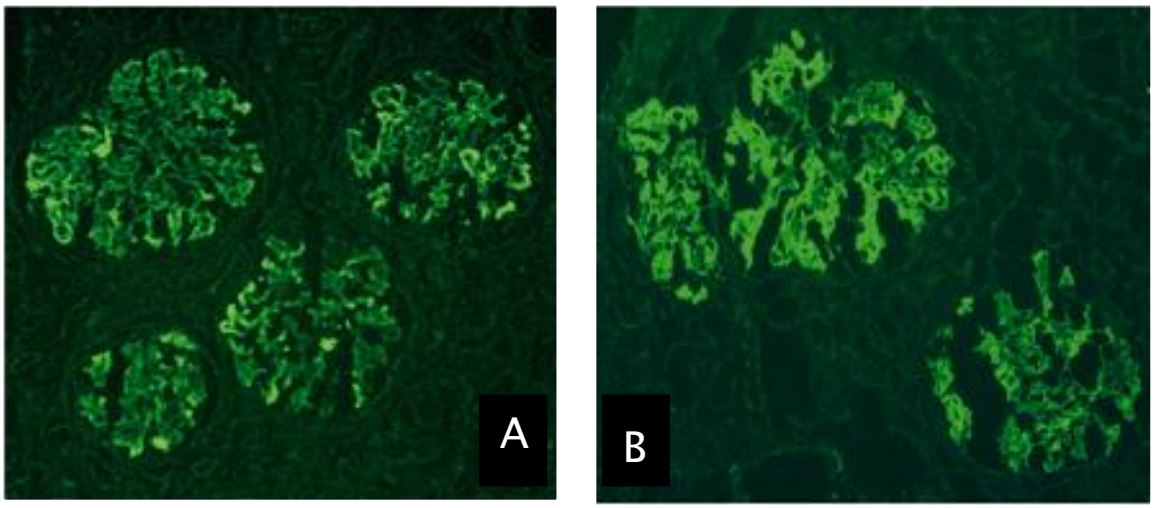


Figure 18:Membranoproliferative glomerulonephritis under immunofluorescent microscope [9]

Figure 17: A: There is an irregular, chunky capillary loop and mesangial staining in MPGN, with coarse, subendothelial deposits with a molded, smooth outer contour (anti-IgG immunofluorescence, ×100**).**
B: The smooth outline of the sausage-shaped, chunky peripheral loop deposits is evident along with the scattered mesangial deposits. The smooth outer contour of the peripheral loop deposits reflects their subendothelial location, with molding under the glomerular basement membrane (anti-C3 immunofluorescence, ×200).

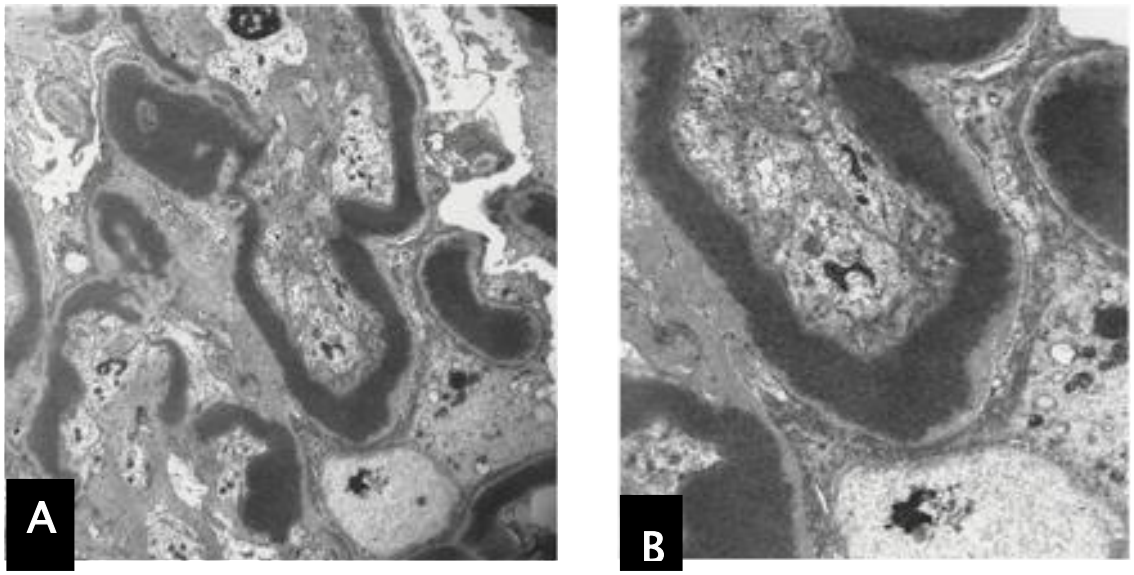


Figure 19:Dense Deposit Disease (DDD) under the electron microscope [9]

Figure 18: **A:** DDD, there is a dense transformation of the glomerular basement membrane, with associated endocapillary and mesangial hypercellularity and occasional large, globular mesangial densities (transmission electron microscopy, ×8000). **B**: DDD, There is a dense transformation of nearly the entire thickness of the glomerular basement membrane, with associated endocapillary hypercellularity. Overlying foot processes are extensively effaced. The transformed material contains complement components (transmission electron microscopy, ×20,250).

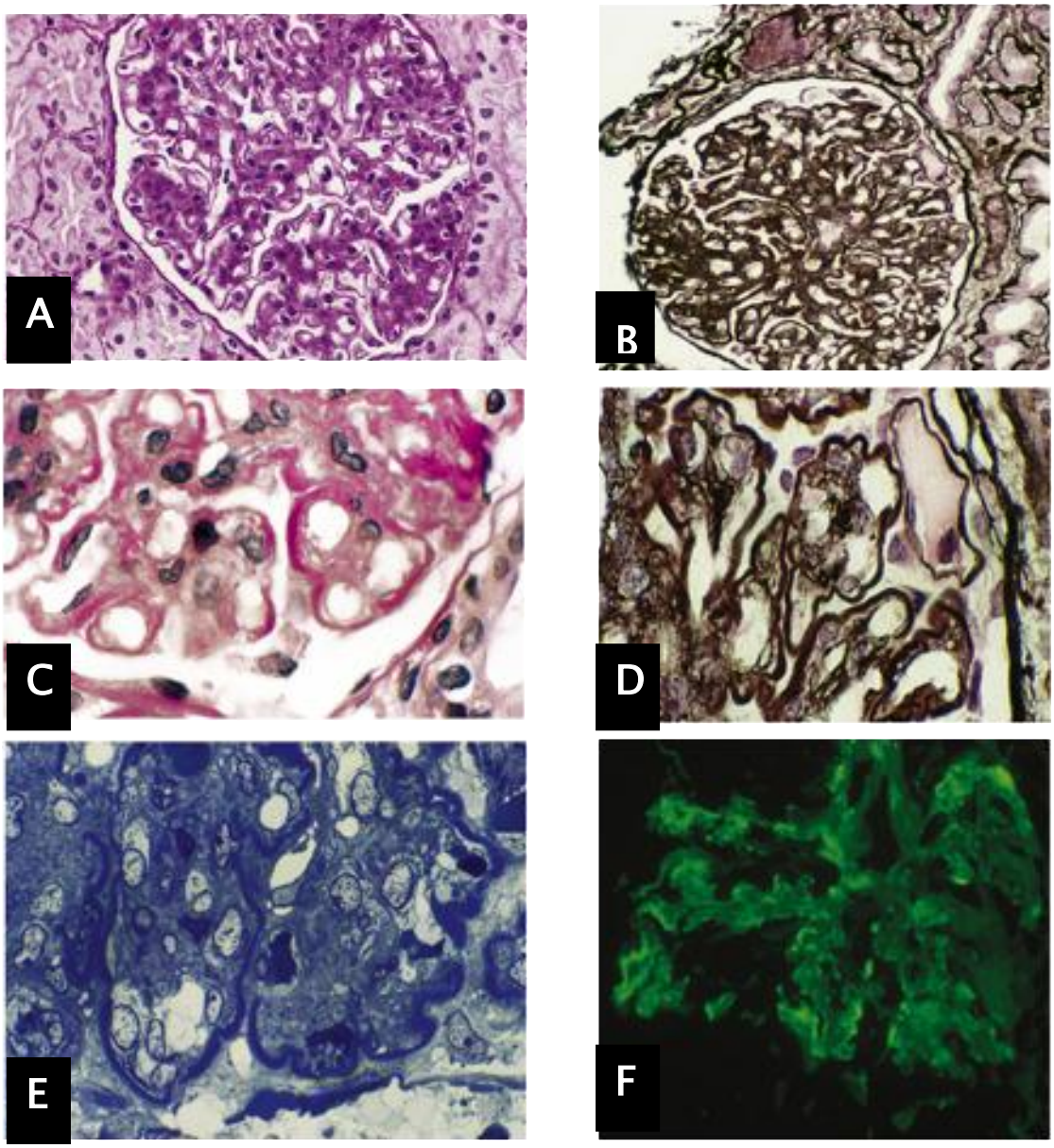


Figure 20:Dense Deposit Disease under light and immunofluorescent microscope [9]

Figure 19: A: DDD appearance under a light microscope, with diffuse, global mesangial, and often endocapillary hypercellularity and frequent glomerular basement membrane duplication (hematoxylin and eosin, ×400). **B:** DDD, with moderate mesangial and endocapillary hypercellularity and segmental glomerular basement membrane duplication with interposition. There are no large eosinophilic subendothelial deposits as typically seen in the idiopathic or immune complex–related membranoproliferative glomerulonephritis (Jones silver stain, ×200). **C:** DDD with an evident refractile, dense appearance of the glomerular basement membrane, along with mesangial and endocapillary hypercellularity. Note that the density is within the basement membrane itself and not in a subendothelial location (periodic acid–Schiff, ×1000). **D:** DDD with an apparent refractile, dense glomerular basement membrane of dense deposit disease is apparent. The basement membrane appears ribbon-like. There is associated mesangial and segmental endocapillary hypercellularity with occasional segmental interposition (Jones silver stain, ×1000). **E:** DDD with an apparent on plastic-embedded sections, the ribbon-like dense transformation of the entire glomerular basement membrane is apparent. There is associated mesangial and endocapillary hypercellularity (toluidine blue stain, ×1000). **F:** DDD, there is typically only complemented positivity in dense deposit disease, with chunky mesangial and coarse, irregular capillary loop positivity. Immunoglobulin staining is typically absent, indicating that there are no true immune complex–type (ie, antibody–antigen) deposits (anti-C3 immunofluorescence, ×400).

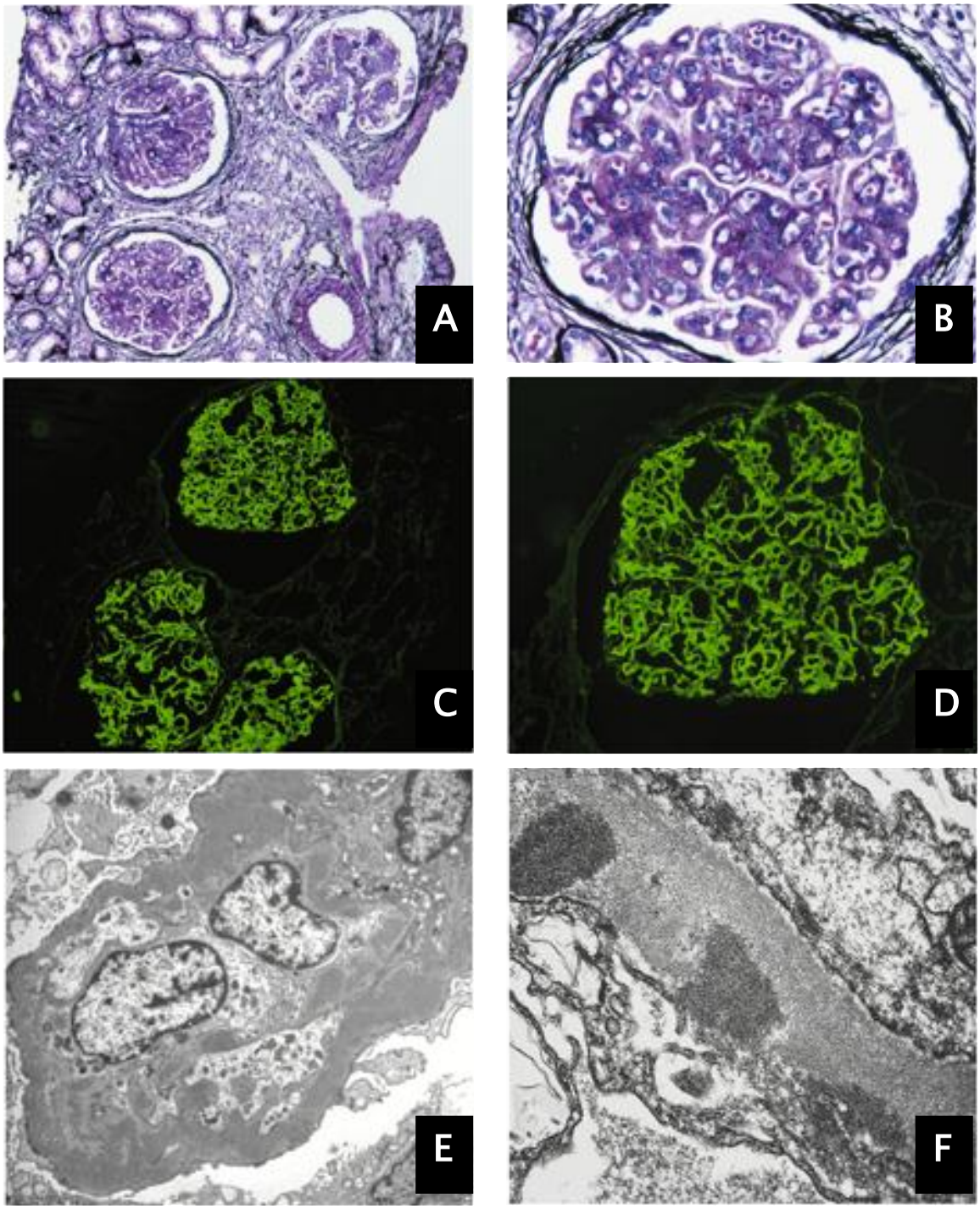


Figure 21:C3 Glomerulonephritis under Light Immunofluorescent And Electron Microscope[9]

Figure 20: A: C3 glomerulonephritis, is frequently associated with a membranoproliferative appearance as shown here, with endocapillary hypercellularity and occasional double contours of glomerular basement membranes. There is also proportional interstitial fibrosis and tubular atrophy (Jones silver stain, ×200). **B:** This case of C3 glomerulonephritis demonstrates mesangial proliferation and variable endocapillary hypercellularity with double contours of the glomerular basement membranes on Jones silver stain. Small adhesions are also present (Jones silver stain, ×400). **C:** C3GN, intense C3 by immunofluorescence, in a mesangial and chunky, irregular capillary loop pattern, with minimal or no immunoglobulin staining (anti-C3 immunofluorescence, ×200). **D:** C3GN with an irregular, chunky to granular capillary loop and mesangial staining evident with C3 with minimal or no staining by immunoglobulin (anti-C3 immunofluorescence, ×400). **E:** In C3 glomerulonephritis, mesangial and subendothelial deposits are apparent by electron microscopy. These differ from dense deposit disease (DDD) in that they are not replacing the lamina densa, nor do they have the unusual dense appearance of DDD (transmission electron microscopy, ×5000). **F:** C3GN. There may be occasional subepithelial or more frequently transmembranous deposits in cases that otherwise appear as MPGN. These lesions may meet morphologic criteria for the previously used diagnosis MPGN iii, which commonly has presence of C3 nephritic factor. Occasional transmembranous deposits may, however, be found in any type of MPGN lesion (transmission electron microscopy, ×17,125).

TREATMENT AND RENAL OUTCOME

For several reasons, the optimal treatment for primary C3G and IC-MPGN has not yet been established [86,123,124]. Some of the reasons reported in several studies include prior misclassification of secondary C3-MPGN or IC-MPGN as idiopathic and MPGN. The classification criteria have changed over time and the small numbers of patients limits the possibility of conducting randomized clinical trials [123]. Common management principles for primary C3G and IC-MPGN, commonly referred to as supportive care, are similar to those recommended for other proteinuric glomerulopathies. These principles include adopting a low-salt diet, managing hypertension, reducing proteinuria through angiotensin inhibition, and addressing dyslipidemia [86,123,124]. Prescription of immunosuppressive drugs is based on results from retrospective studies [86,123,124].

The management of secondary C3G and IC-MPGN primarily involves supportive care in conjunction with the treatment of the underlying etiology. This typically entails immunosuppression for autoimmune diseases, antiviral medications for viral infections, and antibiotics for bacterial infections [86,124].

Treatment of Primary MPGN

Making therapeutic decisions for patients with idiopathic immune complex-mediated MPGN is difficult given the lack of large, randomized, controlled trials or any other evidence clearly demonstrating the efficacy of any treatment regimen. Several parameters at the time of presentation may influence clinical decision-making, including the severity of kidney

dysfunction, degree of proteinuria, presence or absence of hematuria, and the histologic findings on kidney biopsy. Some patients with mild disease present with few abnormalities in these parameters, and aggressive treatment with immunosuppressive therapy is generally not indicated in this setting. Other patients present with more abnormalities in various combinations, and treatment with immunosuppressive agents may be appropriate even in the absence of high-quality evidence to support this approach [125].

In primary MPGN, the KDIGO guidelines 2021[86] recommend a combination of corticosteroids with MMF in **IC-MPGN patients** presenting with abnormal kidney function with active urine sediments, with or without nephrotic range proteinuria for a period of six to twelve months. This was the case for two out of three of IC-MPGN patients in our study with stages 3 and 5 CKD, associated proteinuria and active sediments. The other IC-MPGN patient with signs of activity was treated with a combination of corticosteroids with cyclophosphamide following the KDIGO 2021 guidelines for MPGN that suggest a combination of corticosteroids with cyclophosphamide or rituximab can be considered for patients with PBR showing active signs of glomerulonephritis [86].

In the absence of monoclonal gammopathy, MMF plus glucocorticoids for at least six months should be considered for patients with proteinuria > 1g/d and hematuria or who have had declining kidney function. In case of nonresponse, consider eculizumab[86].

Currently, in **Primary C3-MPGN** patients, no optimal treatment strategies have been established [86,123,124]. According to the KDIGO guidelines for MPGN (2021), the usual supportive measures and immunosuppressive therapy are indicated in moderate to severe disease cases, particularly with moderate-to-marked proliferation on biopsy and proteinuria greater than 2g/d[86]. Studies report that the use of only corticosteroids does not seem to reduce the progression of kidney failure compared to no treatment [7,64].

The combination of corticosteroids and MMF, however, has shown great success in some studies [126,127] with reduced or stabilized serum creatinine levels and lowered proteinuria. Nonetheless, other studies have also reported worsened outcomes in patients treated with corticosteroids and MMF[128,129]. 2 out of 3 patients (66.7%) treated with corticosteroids and MMF in our series showed complete remission. A combination of corticotherapy and cyclophosphamide was also used in our study to treat C3-MPGN patients and yielded complete remission in both patients. A patient with normal kidney function and non-nephrotic proteinuria was treated with only supportive care and had complete remission as well. The combination of Corticosteroids with MMF is the first line of treatment considered in our unit for C3-MPGN patients in our setting.

Treatment of SECONDARY MPGN

Most patients with immune complex-mediated MPGN have an identifiable underlying cause, such as chronic infection, autoimmune disease, or monoclonal gammopathy. Such patients should receive therapy

directed against the underlying cause of the MPGN since resolution of the MPGN usually occurs after successful treatment of the primary disease. Per the KDIGO (2021) guidelines, all patients with identified secondary MPGN are best treated with supportive care in conjunction with the treatment of the underlying cause [86].

Patients with hepatitis B and C treated with antiviral treatment with supportive care in a cohort study [130,131] showed improved renal function and complete remission. Immunosuppressive therapy is both unnecessary and potentially deleterious in patients with hepatitis, except in selected conditions such as severe HCV-associated mixed cryoglobulinemia or rapidly progressive glomerulonephritis[132].

Our patients who followed through with the treatment were treated with supportive care and appropriate antiviral drugs for hepatitis. One patient with cryoglobulinemia secondary to hepatitis B was put on a combination of Corticotherapy and MMF which yielded no remission. Urinary tract infection-induced MPGN patients showed complete remission after supportive care and antibiotheraphy (Table 11).

Patients with MPGN associated with a malignant hematologic disorder such as multiple myeloma or a lymphoproliferative disorder (eg: Waldenström macroglobulinemia, chronic lymphocytic leukemia) should be referred to an appropriate specialist and treated for the underlying malignancy. The treatment of MPGN in patients with a nonmalignant or premalignant plasma cell or B cell clone (monoclonal gammopathy of renal significance [MGRS]), such as proliferative glomerulonephritis with

monoclonal immunoglobulin deposits (PGNMID), should target the underlying pathogenic clone, whenever possible. The treatment of plasma cell clones is based on combinations including bortezomib, a drug that can be used without dose adjustment in renal impairment (RI), including in dialysis. Monoclonal anti-CD38 antibodies, which are increasingly used, are associated with high rates of deep hematologic response from the first cycle, with low toxicity. For lymphocytic or lymphoplasmacytic clones, the therapeutic strategy relies on anti-CD20 monoclonal antibody-based regimens[133].

RENAL OUTCOME

The analysis of treatment responses in our cohort revealed distinct patterns based on therapeutic approaches and MPGN subtypes. Patients receiving corticosteroid monotherapy uniformly demonstrated poor outcomes, with no observable therapeutic benefit and consistent deterioration of renal function as measured by rising serum creatinine levels. These findings corroborate previous reports by Servais et al. [64] and Medjeral-Thomas et al. [7], that established the limited efficacy of corticosteroid-only regimens in altering disease progression

In contrast, combination therapy with corticosteroids and mycophenolate mofetil (MMF) yielded more favorable but variable results. The overall cohort showed a 62.5% remission rate with this regimen, while 37.5% experienced treatment failure. Notably, response rates differed substantially between MPGN subtypes. Patients with C3-MPGN achieved a 50% remission rate, whereas those with IC-MPGN showed only a 25%

remission rate. This variability in treatment response echoes the conflicting outcomes reported in the literature, underscoring the current challenges in predicting therapeutic efficacy [114,126,127,129].

Supportive care combined with ACE inhibitor therapy proved particularly effective, producing an 86% remission rate. The single case of treatment failure in this group occurred in a patient with Churg-Strauss syndrome. Patients with MPGN secondary to hematologic malignancies demonstrated complete remission following completion of VCD protocol treatment.

Recent developments in management protocol for MPGN

IC-MPGN has a more concrete management guideline. Recently, due to the lack of substantial evidence on treatment guidelines for C3-MPGN patients, a few studies suggest the use of complement inhibitors [35,124].

A recent study published by Marina N. and Guiseppe R.[124] on the MPGN treatment standard emphasized the lack of progress in managing primary MPGN (IC-MPGN or C3-MPGN). It was discovered that;

A course of steroids plus MMF in patients with **antibody-mediated (C3Nef) or genetic causes** of MPGN yields a rather disappointing outcome, with remission only 36% of the time as reported in a case study [134].

Also, The anti-CD20 antibody, **Rituximab**, has little to no effect on primary C3-MPGN or IC-MPGN [135].

Moreover, **Eculizumab**, an anti-C5 monoclonal antibody, in a small retrospective series [136,137] and clinical trial (EAGLE), proved to stabilize

renal function with partial remission in the long term in about half of the patients. In contrast, the other half did not gain any therapeutic benefit from the treatment[138]. Responsiveness to Eculizumab may be evaluated by the elevated levels of soluble terminal complement complex (sC5b-9) [139] , but this is not always the case since another EAGLE trial in 10 patients with high levels of sC5b-9 documented a consistent decrease in proteinuria in only three patients despite normalized sC5b-9 levels [138]. Nonetheless, in-depth studies are required to recommend C5 inhibition as a treatment of primary C3-MPGN and IC-MPGN. There is no clear marker that predicts response to C5-inhibition [124]. C5 inhibition may be used in patients who present acute crescentic lesions [124].

Patients with severe proteinuria experience accelerated drug loss in the urine and, hence, may need close monitoring and individualized therapy [124]. This was the case in a boy whose clinical outcome improved after intensification of MMF and eculizumab [140].

Treatment of C3-MPGN suggested by Heiderscheit AK et al (Figure 16) [35]

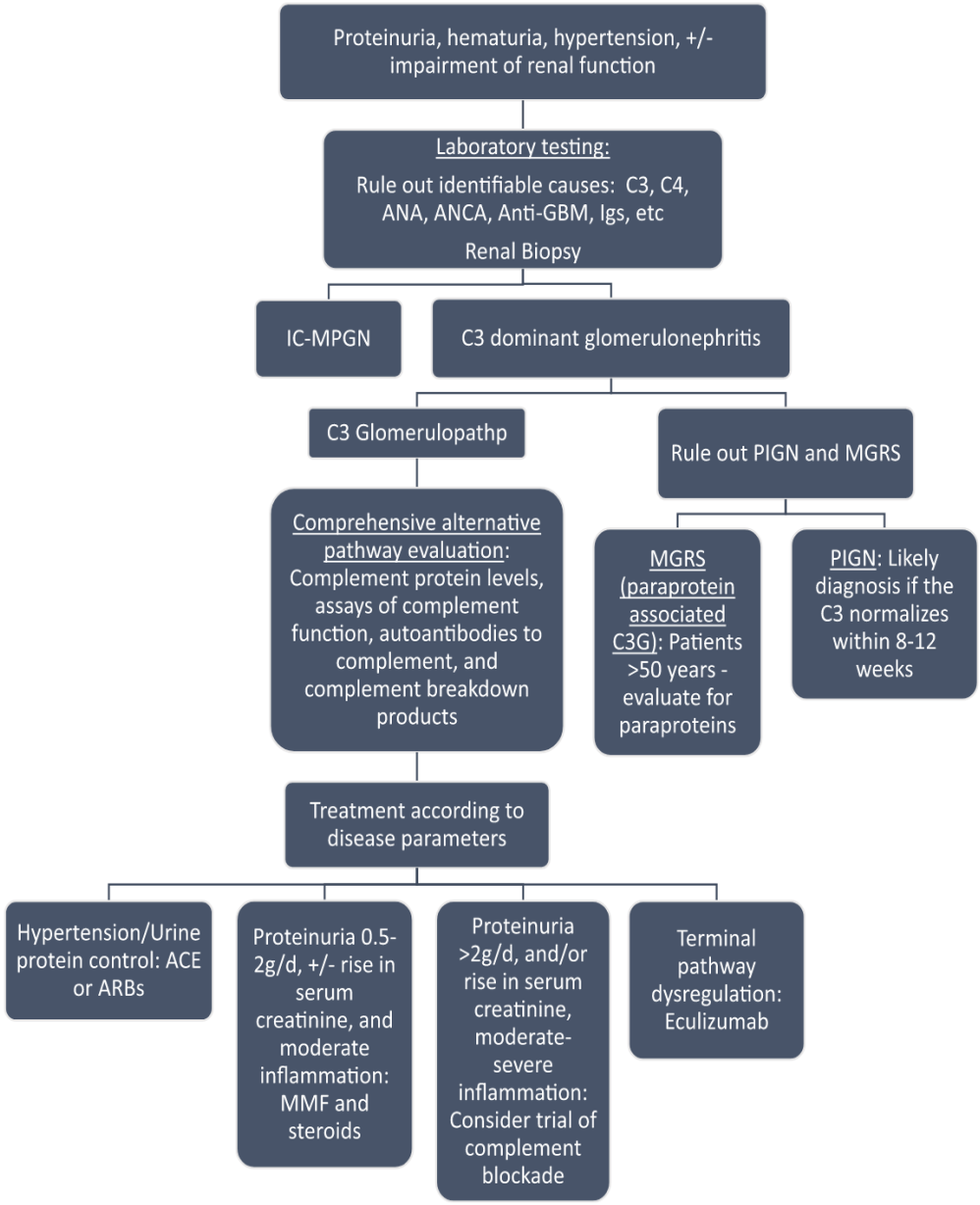


Figure 22:Diagnostic and therapeutic approach to C3-MPGN [35]

Renal Transplantation

MPGN is known to recur after renal replacement therapy in both IC-MPGN and C3-MPGN. The recurrence rate due to C3-MPGN is higher than IC-MPGN, and the overall recurrence rate varies between 19% and 48% [135]. In C3-MPGN, up to 50–55% and 43–67% for DDD and C3GN, respectively,

following transplantation in patients with C3-MPGN [105,141-143], of patients experiencing secondary graft loss, which reduces graft survival rates at 1, 5, and 10 years to 94%, 69%, and 28%, respectively[143].

Reported Risk factors for recurrence in the literature include living-related transplantation, female host, low complement levels, monoclonal gammopathy [144].

There is no optimal treatment for MPGNr; earlier reports suggesting the use of rituximab with or without plasmapheresis have a low level of evidence[145-147]. Some authors report a decline in MPGN recurrence after bone marrow transplant and plasmapheresis in patients presenting MPGNr secondary to monoclonal gammopathy [144].

None of our patients had a kidney transplant.

Plasmapheresis

Only a handful of clinical data supports the use of plasmapheresis in C3-MPGN [40]. Occasional case reports have yielded favorable outcomes in cases where the disease-causal mutated protein has been identified [148].

Plasmapheresis has demonstrated efficacy in patients with C3-MPGN who present with acute kidney injury [40]. In contrast, it has been found to be ineffective in cases involving C3 nephritic factors (C3Nef), as the production of these autoantibodies persists post-procedure. A notable case involved a 15-year-old patient who experienced recurrent MPGN following the cessation of plasmapheresis [149]. None of our patients had plasma exchange therapy.

New developments in treatment

The cluster approach to primary C3G and IC-MPGN might be helpful in therapeutically approaching the disease entity [124]. This approach uses mathematical unsupervised cluster analysis to group patients with commonalities close together so that the differences within the cluster are small[99]. The data included in the cluster are histologic, biochemical, genetic, and clinical parameters that were available at disease onset. In the study [99], they realized clusters better predicted renal survival than C3-MPGN (DDD, C3GN) and IC-MPGN classification.

Danicopan is a first-generation orally active inhibitor of Factor D (FD)[150]. It is an alternative pathway inhibitor. Two phase 2 studies (NCT03369236, NCT03459443) [151,152] that analyzed the pharmacokinetics/ pharmacodynamics showed that danicopan reduced alternative pathway activity shortly after administration. Nonetheless, the Alternative pathway activity recovered within a few hours, yet neither C3 nor sC5b-9 reached their normal levels. In vitro and in vivo studies indicated that more than 90% of FD inhibition is needed to block the alternative pathway efficiently [153].

A second-generation FD inhibitor, Venircopan, is in ongoing trials and showing promising outcomes with up to 98% suppression of the alternative pathway for over 24h post-dosing in C3-MPGN patients [154].

Iptacopan (LNP023) is a small orally active molecule that binds to factor B and Bb and specifically inhibits the enzymatic activity by blocking the cleavage of C3 and the activation of the amplification loop without

affecting the classical and the lectin pathways [155]. In an open-label phase 2 study (NCT03832114), the treatment was well tolerated with no emergent severe adverse events. It was associated with a 45% reduction in proteinuria in patients with native kidneys as well as a significant reduction of C3 deposits in the kidney grafts of patients with recurrent C3-MPGN transplant post-transplant [156]. Also, in a long-term extension study (NCT03955445) from 26 patients, preliminary results at 12 months showed that 53% of patients with native kidneys showed a ≥50% reduction from baseline in urine protein/creatinine ratio (uPCR) and ≥50% increase in serum C3, whilst patients with C3 deposits post renal transplant showed a stable eGFR with a 96% increment in C3 levels [156]. There are yet a few other ongoing trials like the multicenter, double-blind, placebo-controlled phase 3 study (APPEAR-C3, NCT04817618) on adolescents and adults (12-60 years) [157] and also a twin phase 3 trial in adults and adolescents with primary IC-MPGN[158].

Pegcetacoplan, an unselective C3 inhibitor, is a synthetic cyclic peptide conjugated to a polyethylene glycol polymer that binds to C3 and inhibits C3 activation from all three pathways. It also binds to C3b and prevents the activity of C3 and C5 convertases of the alternate pathway. Its safety and efficacity were evaluated in two open-label studies (DISCOVERY, NCT03453619), and the results from the C3G patients after 48 weeks of treatment showed a six-fold increase in serum C3 and a 57.3% decrease in plasma sC5b-9 levels. There was also a 50.9% reduction in proteinuria and an increase in serum albumin[159].

Recently, **RNA modifying therapies**, which could target the complement system, are undergoing studies and clinical trials. With its benefit of overcoming the challenge of frequent dosing and achieving massive inhibition of the target [124] . Among these RNA modifiers are **ARO-C3, an investigational RNA interference (RNAi)** treatment designed to silence liver-produced C3, **IONIS-FB-LRX**, an antisense oligonucleotide targeting factor B mRNA in the liver [160]

New complement targeting agents are moving to the clinic, expanding the therapeutic potential for C3G and IC-MPGN. Some of these include **KP104**, a monoclonal anti-C5 antibody linked to the FH regulatory domain, which simultaneously inhibits the common terminal pathway and the alternative pathway C3 convertase (NCT05517980), and the **anti-Bb humanized monoclonal antibody NM8074** (NCT05647811) [124].

Factors of progression to End stage renal disease

Many factors, including age, histology, clinical factors, advanced renal failure, genetic mutations, and treatments, can affect the progression of MPGN to ESRD. Older patients have a high risk of progression to ESRD [161]. Histological and clinical factors like the severity of interstitial fibrosis, crescentic formation, and mesangial proliferation are significant predictors of progression to ESRD [162]. Advanced renal failure at presentation and glomerulosclerosis are also associated with a higher risk of ESRD [161].

Genetic mutations in complement-regulating genes also influence disease progression, with some cases progressing to ESRD despite treatment[163,164]. Response to treatments such as immunosuppressants is

variable, with some patients achieving remission while others progress to ESRD[163,164].

In our study, neither age, histological or clinical factors, nor therapeutic factors significantly influenced the progression of MPGN to ESRD. The only factor associated with progression to ESRD was the use of corticosteroids alone in managing MPGN, with a P-value of 0.032 (Table 15). This correlation may be affected by the size of our cohort and, therefore, may not accurately represent what is found in the literature.

Recommendations and clinical implications of our study

With the continuous growth in the understanding of the etiopathology and management plan in MPGN, we will yield a high rate of remission if we;

- Sensitize the laboratories to use the IF-based classifications (IC-MPGN/ C3-MPGN) instead of the old ultrastructural classification (type I, II, III MPGN) since it gives a clearer therapeutic approach.
- Development of other reference centres for MPGN treatment, to decrease the number of patients lost to follow up due to distance.
- Broaden our etiological compass to encompass other emerging causes of MPGN like covid-19, quantification of other complement components, autoantibodies and genetic testing.

Limitations

- A retrospective observational study, as well as the small numbers. Given this study design, the results may not be generalizable to a broader population, and there is a risk of selection bias.
- Additionally, MPGN re-classification and change in management of MPGN throughout the study may mean there are cases that are unaccounted for.
- Also, there might have been under-appreciation of complement abnormalities or monoclonal gammopathies as the cause of MPGN earlier in the study timeframe.
- Quite a number of our patients were lost to follow-up due to their location; that is, 38.9% of our patients in the series come from rural origins far from our unit.
- Notwithstanding, the cost of investigative analysis was exorbitant and could have also contributed to the loss to follow-up.

CONCLUSION

CONCLUSION

Membranoproliferative glomerulonephritis (MPGN) represents a complex and heterogeneous renal disorder with significant clinical, etiological, and pathophysiological diversity. The recent reclassification into immune-complex mediated and complement-mediated forms has enhanced our comprehension of its underlying mechanisms, particularly the pivotal role of complement dysregulation in C3 glomerulopathy. However, despite advancements in diagnostic techniques, including immunofluorescence and genetic testing—challenges remain in accurately distinguishing between subtypes and establishing targeted therapeutic approaches.

This study, the first retrospective analysis of MPGN conducted in Morocco over a 13-year period, provides critical insights into its epidemiological, clinical, and pathological characteristics. Our findings reinforce the evolving understanding of MPGN, highlighting the importance of precise classification to inform therapeutic decision-making. Consistent with existing literature, our data indicate a predominance of MPGN among women and middle-aged adults, with a high burden of clinical and biological manifestations. The therapeutic regimen combining corticosteroids and mycophenolate mofetil (MMF) showed encouraging results in primary MPGN, despite the limited cohort size. Furthermore, the progression to end-stage renal disease (ESRD) within a mean duration of 55.67 ± 5.92 months underscores the aggressive nature of the disease, emphasizing the necessity of early diagnosis and intervention to mitigate renal function decline.

Given the rarity and complexity of MPGN, further collaborative research is imperative to refine diagnostic criteria, investigate novel therapeutic avenues, and optimize patient outcomes. The incorporation of molecular and genetic analyses into routine clinical practice holds transformative potential, paving the way for personalized and more effective management strategies.

In summary, while considerable progress has been achieved in elucidating the mechanisms of MPGN, numerous aspects remain to be clarified. A multidisciplinary approach, integrating nephrologists, pathologists, and immunologists, will be essential to advance our understanding and improve the management of this challenging disease in the years to come.

This work contributes to the growing body of knowledge on MPGN and lays the foundation for future research aimed at enhancing diagnostic precision and therapeutic efficacy in Morocco and beyond.

ABSTRACT

ABSTRACT

Introduction:

Membranoproliferative glomerulonephritis (MPGN) is a rare and chronic glomerular disease characterized by mesangial proliferation and capillary wall thickening, resulting from either immune complex deposition or complement dysregulation. The recent reclassification into immune complex-mediated MPGN (IC-MPGN) and complement-mediated MPGN (C3-MPGN) has provided new insights into its pathophysiology and clinical management.

objectives

This study aimed to describe the clinical, biological, and histological characteristics of MPGN and analyze renal outcomes and prognostic factors in patients followed at the Nephrology Department of Hassan II University Hospital.

Methods:

We conducted a retrospective analysis of adult patients diagnosed with MPGN between December 2011 and December 2024. Data were collected from medical records and the hosix.net database. Patients were reclassified according to current guidelines, excluding those with systemic lupus erythematosus. Statistical analysis used to analyze data were: Fischer exact test (qualitative variables), the non-parametric Mann-Whitney test (quantitative variables), and Kaplan Meier curve (renal survival).

Results:

Our cohort included 36 patients consisted of 19 women (52.8%) and 17 men (47.2%) with a mean age of 48.17 ± 15.36 years. Most patients (61.1%) were from urban areas. The main clinical presentations were nephrotic syndrome (41.7%) and acute kidney injury (41.7%), followed by isolated proteinuria (36%), nephritic syndrome (17%), and rapidly progressive glomerulonephritis (5%). Systemic manifestations were uncommon (5.6%).

Primary MPGN accounted for 61.1% of cases, while secondary forms (38.9%) were predominantly associated with hepatitis infections (28.6%). After reclassification, we recorded 19 IC-MPGN patients (52.7%) and 13 C3-MPGN patients (36.1%).

Histopathological analysis revealed characteristic double contour lesions in 52.8% of cases, with onion-skin lesions in 8.3% and fibrinoid endarteritis in 11.1%.

Treatment strategies varied according to disease subtype. Patients with primary MPGN received a combination of corticosteroids and mycophenolate mofetil (MMF), while secondary cases were managed with targeted therapies. Outcomes included complete remission in 52.2% of patients, partial remission in 13%, and disease progression in 34.8%. Statistical analysis identified corticosteroid therapy as the only significant prognostic factor for treatment response ($p=0.032$). The mean renal survival time was 55.67 ± 5.92 months, with a 58% probability of renal survival at 71 months.

Discussion

This study provides important insights into the characteristics and outcomes of MPGN in our population. The results underscore the need for accurate classification and personalized treatment approaches. While current therapies show efficacy in some patients, the progression to renal failure remains a significant concern. These findings highlight the importance of multidisciplinary collaboration and further research to improve diagnostic accuracy and therapeutic outcomes for patients with MPGN.

conclusion

The integration of advanced diagnostic tools, including genetic and molecular studies, along with the development of targeted therapies, will be crucial for advancing the management of this complex disease. Future studies with larger cohorts and longer follow-up periods are needed to validate these findings and optimize treatment strategies for MPGN patients.

RESUME

Introduction :

La glomérulonéphrite membranoprolifération (GNMP) est une maladie glomérulaire rare et chronique caractérisée par une prolifération mésangiale et un épaississement de la paroi capillaire, résultant soit d'un dépôt de complexes immuns, soit d'une dysrégulation du complément. La reclassification récente en GNMP à médiation par les complexes immuns (GNMP-CI) et GNMP à médiation par le complément (GNMP-C3) a permis de mieux comprendre sa physiopathologie et sa prise en charge clinique.

Objectifs

Cette étude visait à décrire les caractéristiques cliniques, biologiques et histologiques de la MPGN et à analyser les résultats rénaux et les facteurs pronostiques chez les patients suivis au service de néphrologie de l'hôpital universitaire Hassan II.

Méthodes :

Nous avons réalisé une analyse rétrospective des patients adultes diagnostiqués avec une GNMP entre décembre 2011 et décembre 2024. Les données ont été recueillies à partir des dossiers médicaux et de la base de données hosix.net. Les patients ont été reclassés selon les directives actuelles, en excluant ceux atteints de lupus érythémateux disséminé. Les analyses statistiques utilisées pour analyser les données étaient les suivantes

: Le test exact de Fischer (variables qualitatives), le test non paramétrique de Mann-Whitney (variables quantitatives), et la courbe de Kaplan Meier (survie rénale).

Résultats :

Notre cohorte comprenait 36 patients, dont 19 femmes (52,8 %) et 17 hommes (47,2 %), avec un âge moyen de 48,17 ± 15,36 ans. La plupart des patients (61,1 %) venaient de zones urbaines. Les principales présentations cliniques étaient le syndrome néphrotique (41,7 %) et l'insuffisance rénale aiguë (41,7 %), suivis par la protéinurie isolée (36 %), le syndrome néphritique (17 %) et la glomérulonéphrite rapidement progressive (5 %). Les manifestations systémiques étaient rares (5,6 %).

La MPGN primaire représentait 61,1 % des cas, tandis que les formes secondaires (38,9 %) étaient principalement associées aux infections hépatiques (28,6 %). Après reclassification, nous avons enregistré 19 patients IC-MPGN (52,7%) et 13 patients C3-MPGN (36,1%).

L'analyse histopathologique a révélé des lésions caractéristiques à double contour dans 52,8 % des cas, des lésions en bulbe d'oignon dans 8,3 % des cas et une endartérite fibreuse dans 11,1 % des cas.

Les stratégies de traitement variaient en fonction du sous-type de la maladie. Les patients atteints de GNMP primaire ont reçu une combinaison de corticostéroïdes et de mycophénolate mofétil (MMF), tandis que les cas secondaires ont été traités par des thérapies ciblées. Les résultats

comprenaient une rémission complète chez 52,2 % des patients, une rémission partielle chez 13 % d'entre eux et une progression de la maladie chez 34,8 %. L'analyse statistique a identifié la corticothérapie comme le seul facteur pronostique significatif pour la réponse au traitement (p=0,032). La durée moyenne de survie rénale était de 55,67 ± 5,92 mois, avec une probabilité de 58 % de survie rénale à 71 mois.

Discussion :

Cette étude fournit des informations importantes sur les caractéristiques et les résultats de la MPGN dans notre population. Les résultats soulignent la nécessité d'une classification précise et d'approches thérapeutiques personnalisées. Bien que les thérapies actuelles soient efficaces chez certains patients, la progression vers l'insuffisance rénale reste une préoccupation importante. Ces résultats soulignent l'importance d'une collaboration multidisciplinaire et d'une recherche plus poussée pour améliorer la précision du diagnostic et les résultats thérapeutiques pour les patients atteints de GNMP.

Conclusion :

L'intégration d'outils diagnostiques avancés, y compris des études génétiques et moléculaires, ainsi que le développement de thérapies ciblées, seront cruciaux pour faire progresser la gestion de cette maladie complexe. De futures études portant sur des cohortes plus importantes et des périodes

de suivi plus longues sont nécessaires pour valider ces résultats et optimiser les stratégies de traitement pour les patients atteints de GNMP.

ملخص

مقدمة:

التهاب كبيبات الكلى التكاثري الغشائي (GNMP) هو مرض كبيبي مزمن نادر ومزمن يتميز بتكاثر الأوعية الدموية المتوسطة وسماكة جدار الشعيرات الدموية، وينتج إما عن ترسب مركب مناعي معقد أو عن خلل في تنظيم المكملات. وقد أدت إعادة التصنيف الأخيرة إلى مرض التهاب الكبيبات الكبيبات الكبيبي بوساطة المركب المناعي المعقد (IC-GNMP) ومرض التهاب الكبيبات الكبيبيبي بوساطة المكملات (C3-GNMP) إلى فهم أفضل للفيزيولوجيا المرضية والإدارة السريرية.

الأهداف:

كان الهدف من هذه الدراسة هو وصف السمات السريرية والبيولوجية والنسيجية لمرض النانو الكلوي متعدد الكلى وتحليل النتائج الكلوية والعوامل المنذرة لدى المرضى الذين تمت متابعتهم في قسم أمراض الكلى في المستشفى الجامعي الحسن الثاني.

الطرق:

أجرينا تحليلاً بأثر رجعي للمرضى البالغين الذين تم تشخيص إصابتهم بمرض GNMP بين ديسمبر 2011 وديسمبر 2024. تم جمع البيانات من السجلات الطبية وقاعدة بيانات hosix.net. تم إعادة تصنيف المرضى وفقًا للمبادئ التوجيهية الحالية، باستثناء المرضى المصابين بالذئبة الحمامية الجهازية. كانت التحليلات الإحصائية المستخدمة لتحليل البيانات على النحو التالي: اختبار فيشر الدقيق (المتغيرات الفئوية)، واختبار مان-ويتني غير البارامترية (المتغيرات الكمية)، ومنحنى كابلان ميير (البقاء على قيد الحياة الكلوي).

النتائج:

ضمت مجموعتنا 36 مريضًا، 19 امرأة (52.8%) و17 رجلاً (47.2%)، بمتوسط عمر 48.17 ± 15.36 سنة. كان معظم المرضى (61.1%) من المناطق الحضرية. كانت المظاهر السريرية الرئيسية هي المتلازمة الكلوية (41.7%) والفشل الكلوي الحاد (41.7%)، تليها البيلة

البروتينية المعزولة (36%) وتلازمة التهاب الكلية (17%) والتهاب كبيبات الكلى سريع التقدم (5.6%). كانت المظاهر الجهازية نادرة (5%).

شكّلت حالات الإصابة بالتهاب كبيبات الكلى غير الكولي الأولي 61.1% من الحالات، بينما ارتبطت الأشكال الثانوية (38.9%) بشكل رئيسي بالتهابات الكبد (28.6%). بعد إعادة التصنيف، سجلنا 19 مريضاً مصاباً بالـ C3-GNMP (36.1%) و13 مريضاً مصاباً بالـ IC-GNMP (52.7%).

كشف التحليل المرضي النسيجي عن آفات مميزة مزدوجة الكفاف في 52.8% من الحالات، وآفات البصلة البصلية في 8.3% والتهاب الشرايين الليفي في 11.1%.

تباينت استراتيجيات العلاج وفقاً للنوع المرضي. تلقى المرضى المصابون بالتهاب الشرايين الليفية الليفية الأولية مزيجاً من الكورتيكوستيرويدات الفموية والميكوفينولات موفيتيل (MMF)، بينما عولجت الحالات الثانوية بالعلاجات الموجهة. تضمنت النتائج هدوءاً تاماً لدى 34.8%. أشار 52.2% من المرضى، وهو جزئياً لدى 13% من المرضى، وتطور المرض لدى 13% من المرضى. التحليل الإحصائي إلى أن العلاج بالكورتيكوستيرويدات هو العامل الوحيد المهم للتنبؤ بالاستجابة للعلاج (p=0.032). كان متوسط مدة بقاء الكلى على قيد الحياة 55.67 ± 5.92 شهرًا، مع احتمال بقاء الكلى على قيد الحياة بنسبة 58% عند 71 شهرًا.

المناقشة:

توفر هذه الدراسة معلومات مهمة عن خصائص نتائج مرض التصلب المتعدد الأغشية المتعددة الناخعية لدى سكاننا. تسلط النتائج الضوء على الحاجة إلى تصنيف دقيق ونهج علاج شخصي. على الرغم من أن العلاجات الحالية فعالة في بعض المرضى، إلا أن تطور المرض إلى الفشل الكلوي لا يزال مصدر قلق كبير. تُسلط هذه النتائج الضوء على أهمية التعاون متعدد التخصصات وإجراء المزيد من الأبحاث لتحسين تقنية التشخيص والنتائج العلاجية للمرضى الذين يعانون من اعتلال الغدد الصماء الكلوي المتعدد.

الخلاصة

سيكون دمج أدوات التشخيص المتقدمة، بما في ذلك الدراسات الوراثية والجزيئية، بالإضافة إلى تطوير علاجات مستهدفة، أمرًا حاسمًا في تطوير إدارة هذا المرض المعقد. هناك حاجة إلى إجراء دراسات مستقبلية تشمل مجموعات أكبر وفترات متابعة أطول للتحقق من صحة هذه النتائج وتحسين استراتيجيات العلاج للمرضى الذين يعانون من GNMP.

ANNEXE

FICHE D'EXPLOITATION

DEMOGRAPHIQUE

Nom du patient :

Identification du Patient (IP) :

Age :

Origine :

Habitat :

Statut Familial : ☐ Célibataire ☐ Marié(e) ☐ Divorcé(e) ☐ Veuf(ve)

Profession : ☐ sans profession ☐ ouvrière ☐ Fonctionnaire ☐ Profession Libérale

Autre ; Précisez :

Sexe : ☐ Homme ☐ Femme

Couverture sociale : ☐ Aucune ☐ CNSS ☐ CNOPS ☐ AMO ☐ Ramed ☐ Mutuelle

MOTIF DE HOSPITALISATION :

☐ Syndrome Œdémateux ☐ Insuffisance rénale ☐ Hématurie

☐ Syndrome Néphrotique

ANTECEDENT PERSONNEL

Diabète ☐ Oui ☐ Non

Cardiopathie ☐ Oui ☐ Non

Tuberculose ☐ Oui ☐ Non

Asthme ☐ Oui ☐ Non

HTA ☐ Oui ☐ Non

Prise médicamenteuse ☐ Oui ☐ Non

Si oui, précisez :

Hémopathie Maligne

- Lymphome Non Hodgkin ☐Oui ☐Non
- Lymphome Hodgkin ☐Oui ☐Non
- Myélome ☐Oui ☐Non
- Leucémie ☐Oui ☐Non

Maladie Auto-immune

- Lupus ☐Oui ☐Non
- Purpura Rhumatoïde ☐Oui ☐Non
- Syndrome d'Antiphospolipides (SAPL) ☐Oui ☐Non
- Connectivite indéterminé ☐Oui ☐Non
- Syndrome de Sjögren ☐Oui ☐Non

Maladie Infectieuse pré-diagnostic

- Virale : ☐Hépatite C ☐Hépatite B ☐VIH
- Bactérienne : ☐Syphilis ☐Endocardite ☐Dérivation Ventriculo-atriale infectée, ☐Abcès Viscéraux ☐Lèpre, ☐Méningite à méningocoques
- Parasitaire : ☐paludisme, ☐schistosomiase,☐ mycoplasme, ☐Leishmaniose
- Autres, Précisez :

Maladie Rénale

- Insuffisance Rénale Chronique ☐Oui ☐Non

Si oui ; Précisez DFG selon MDRD :

☐DFG > 60

☐30< DFG < 60

☐DFG< 30

☐DFG<15

ANTECEDENT TOXIQUE

Tabagisme ☐Oui ☐Non

Si oui, précisez (Paquet) : ……. / (années)…….

Alcoolisme ☐Oui ☐Non

Toxicomanie ☐Oui ☐Non

Prise de Plantes ☐Oui ☐Non

Autres ;

ATCD CHIRURGICAUX

Transplantation Rénale ☐Oui ☐Non

Autres, Précisez ;

ATCD FAMILIAUX

- Néphropathie ☐Oui ☐Non
- Hémopathie Maligne ☐Oui ☐Non
- Maladie Auto immune ☐Oui ☐Non

  Autres, Précisez ;

MANIFESTATIONS CLINIQUES

Signes généraux

- PA (mm Hg) :
- Température :
- Poids (Kg) :
- Alteration de l'état général ☐Oui ☐Non
- Diurèse/ 24h : ☐Conservé ☐Oligurie ☐ Anurie
- Asthénie ☐Oui ☐Non
- Déshydratation ☐Oui ☐Non
- Ictère ☐Oui ☐Non
- État Hémodynamique ☐Conservé ☐Choc
- Vomissements ☐Oui ☐Non
- Ascite ☐Oui ☐Non

- Œdème ☐Oui ☐Non
- Dyspnée ☐Oui ☐Non

Signes Uro- Néphrologiques

- Hématurie Macroscopique ☐Oui ☐Non
- Hématurie Microscopique ☐Oui ☐Non
- OMI ☐Oui ☐Non
- Oligurie ☐Oui ☐Non
- Anurie ☐Oui ☐Non
- Douleurs Lombaires ☐Oui ☐Non
- Syndrome Néphrotique ☐Oui ☐Non

Autres, Précisez :

Signes Cutanés ☐Oui ☐Non

Si Oui, précisez :

☐Urticaire ☐Nodosités sous cutanées ☐Livedo ☐Gangrène ☐ Vésicules

☐ Ulcérations ☐Bulles ☐Purpura Vasculaires

Autres signes, précisez :

Signes Neurologiques ☐Oui ☐Non

Si oui, précisez :

☐Accident vasculaire cérébral ☐Méningite ☐Thrombophlébite cérébrale

☐Encéphalopathie ☐Mononévrite ☐Multinévrite ☐convulsion ☐Déficit Focal

Autres signes, précisez

Signes Cardiaques

Si oui précisez

☐Insuffisance cardiaque ☐HTA ☐Anévrysmes coronariens ☐Péricardite

☐ Infarctus du myocarde

Autres signes, précisez

Signes Rhumatologiques

Si oui, précisez :

☐Arthralgies ☐ Polyarthrite ☐Mono-arthrite ☐ Myalgies

Autres signes, précisez

BILAN BIOLOGIQUE INITIALE

Paramètres	valeur
Urée sanguine (g/l)	
Créatininémie (mg/l)	
Protidémie (g/l)	
Albuminémie (g /l)	
Natrémie (mmol/l)	
Kaliémie (mmol/l)	
Calcémie (mg/l)	
Acide urique (mg/l)	
Diurèse (cc/j)	
Protéinurie 24h (mg/j)	
ECBU: Nombre de GB (/mm3) Nombre de GR (/mm3) Culture	
CRP (mg/l)	
GOT/ GPT (UI/L)	
Bilirubine directe / indirecte / totale (µmol/l)	
Taux de prothrombine / Temps de céphaline activée (TP/TCA)	
C3 bas (Oui/Non)	
C4 bas (Oui/Non)	
c ANCA (taux)	
p ANCA (taux)	

Anti MBG (taux)	
ANN (taux)	
Anti DNA (taux)	

INDICATION DE PBR :

☐Sd Néphrotique Pur ☐Sd Néphrotique Impur ☐Hématurie ☐Sd Néphritique

☐Insuffisance Rénale

Autre, Précisez :

Date de réalisation de la PBR :

Lieu/ centre de réalisation de la PBR :

Résultat de la PBR :

- Nombre de Glomérules :

Modifications Focales

Glomérule	Atteinte tubulo-interstitielle	Atteintes Vasculaire	Immunofluorescence (dépôts)

ETIOLOGIE

- ☐Monoclonal
- ☐Polyclonal
- ☐Autres
  - ☐Complement mediated(C3 / C4) MPGN
  - ☐Microangiopathie Thrombotique (MAT)

DIAGNOSTIC RETENU :

TRAITEMENT

Traitement non specifique :

- ☐ Antiprotéinuriques (IEC / ARAII)
- ☐ Corticoïde
- ☐ Mycophenolate mofetil (MMF)
- ☐ Inhibiteur de calcineurine (CNI)
- ☐ Rituximab (Anti CD20)
- ☐ Cyclophosphamide

Traitement étiologique :

EVOLUTION

Suivi clinique

- Fonction rénale
- Protéinurie
- Hématurie
- Leucocyturie

Suivi Globale

☐Rémission ☐Décès ☐Perdue de vue

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