

REVIEW

Novel Insights into the Pathogenesis, Diagnosis and Treatment of Glomerular Diseases

Marielena Papadaki, MD, Theofanis Apostolou, MD, PhD

Department of Nephrology,
Evangelismos General Hospital, Athens,
Greece

KEY WORDS: *glomerular diseases; glomerulonephritis; minimal change disease; membranous nephropathy; IgA nephropathy; Lupus nephritis; systemic vasculitis; ANCA vasculitis; corticosteroids; cyclosporine; cyclophosphamide; rituximab; plasmapheresis; focal segmental glomerulosclerosis*

ABBREVIATIONS

ANCA = anti-neutrophil cytoplasm antibodies
ANGPTL4 = angiotensin-like 4 protein
CD80 = cluster of differentiation 80
FSGS = focal segmental glomerulosclerosis
GD = glomerular disease(s)
HIV = human immunodeficiency virus
IgAN = IgA nephropathy
KDIGO = Kidney Disease Improving Global Outcomes (Foundation)
MCD = minimal change disease
MMF = mycophenolate mofetil
MN = membranous nephropathy
NEP = neutral endopeptidase
NSAID = non-steroidal anti-inflammatory drugs
PLA2R = phospholipase A2 receptor
RAAS = renin-angiotensin-aldosterone system
RTA = renal tubular acidosis
SLE = systemic lupus erythematosus
TLR = Toll-like receptor

Correspondence to:

Theofanis Apostolou MD,
PhD, Nephrology Department
Evangelismos General Hospital,
Athens, Greece, Tel.: 213-204 5267;
E-mail: tapostolou@ath.forthnet.gr
*Manuscript received April 10, 2013;
Revised manuscript received October 4,
2013; Accepted November 23, 2013*

ABSTRACT

Glomerular diseases (GD) are characterized by lesions of the glomerular basement, which may be or may not be accompanied by inflammation and cellular hyperplasia. They are mainly classified as primary or secondary to a systemic disease. They are also classified as proliferative or non-proliferative diseases depending on the cellular infiltrate. Minimal change disease, focal segmental glomerulosclerosis and thin membrane disease are non-proliferative, usually primary, glomerular diseases. Nephrotic syndrome is mainly the clinical syndrome that accompanies these GD. Proliferative GDs comprise IgA and IgM nephropathy, and crescentic GDs with or without immunodeposits. Secondary proliferative GDs include systemic lupus erythematosus GD, vasculitides, and post-infection GDs. Non proliferative secondary GDs encompass diabetic nephropathy, amyloidosis, HIV nephropathy. Recent data on many aspects of GDs, i.e. pathogenesis and pathophysiology, diagnosis, therapy and other are briefly discussed in the present review.

INTRODUCTION

Glomerulopathies or glomerular diseases (GD) are renal diseases that affect both kidneys and are characterized by lesions of the glomeruli often accompanied by inflammation of the mesangium and/or the glomeruli. Glomerular diseases have various clinical presentations (Table 1) that vary from the asymptomatic individual who is diagnosed at a routine medical assessment, to a patient with a fulminant illness with acute kidney injury. Patients can present with hematuria and/or proteinuria (nephritic syndrome), or as a nephrotic syndrome (heavy proteinuria), and/or acute or chronic renal injury.¹

There are different types of glomerular syndromes that are categorized into several different pathological patterns. One classification divides the GD into primary and secondary. Primary GD is a disease confined to the kidney, while secondary GD is usually due to a systematic disease, such as diabetes, systemic lupus erythematosus (SLE), or vasculitis, or may be caused by drugs or certain infections that also affect the kidneys² (Table 2). In this brief review we will describe the new developments in glomerular diseases related mainly to their pathogenesis, diagnosis and treatment.

Conflict of Interest: none declared.

Authors' statement: The manuscript is original and has never been published before except in abstract form. It was presented as an oral presentation at the 17th Seminar of Evangelismos General Hospital, Athens, Greece in February 2013.

TABLE 1. Classification of Glomerulonephritis According to Clinical Presentation

Common Glomerular Diseases Presenting as Nephrotic Syndrome in Adults
Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Membranoproliferative glomerulonephritis I
Membranoproliferative glomerulonephritis II
Cryoglobulinemic membranoproliferative glomerulonephritis
Amyloid
Diabetic nephropathy
Common Glomerular Diseases Presenting as Nephritic Syndrome
Poststreptococcal glomerulonephritis
Other postinfectious glomerulonephritis
IgA nephropathy
Lupus nephritis
Common Glomerular Diseases Presenting as Rapidly Progressive Glomerulonephritis
Goodpasture's syndrome
Vasculitis
Granulomatosis with polyangiitis (Wegener's)
Microscopic polyangiitis
Pauci immune crescentic glomerulonephritis
Immune complex disease
Systemic lupus erythematosus
Poststreptococcal glomerulonephritis
IgA nephropathy/Henoch Schonlein purpura

MINIMAL CHANGE DISEASE (Fig. 1)

Minimal change disease (MCD) is the main cause of nephrotic syndrome in children younger than 10 years, in about 50% to 70% of older children, and 10% to 15% of adults. It is thought to be a T-cell disorder mediated by a circulating factor that alters podocyte function resulting in proteinuria. In renal pathology and in light microscopy there is absence of histologic glomerular abnormalities, other than evidence of epithelial cell foot process fusion which is evident in electron microscopy. Corticosteroid-sensitive nephrotic syndrome is the term used to describe the disease occurring in children with nephrotic syndrome who respond to corticosteroids but who have not had a renal biopsy to provide the histologic

TABLE 2. Types of Glomerular Disease

Primary Glomerular Diseases
Minimal change disease
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
Focal segmental glomerulosclerosis
Mesangial proliferative glomerulonephritis (IgA Nephropathy, Henoch Schönlein purpura)
Anti GBM glomerulonephritis
ANCA associated glomerulonephritis, renal limited)
Secondary Glomerular Diseases
Diabetes mellitus
SLE, systemic vasculitis
Lymphoma, solid tumors
Amyloidosis, multiple myeloma
Post-infectious glomerulonephritis (Malaria, endocarditis, HIV, HBV, HCV, other viruses)
Poststreptococcal glomerulonephritis

ANCA = anti-neutrophil cytoplasmic antibodies; GBM = glomerular basement membrane; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus

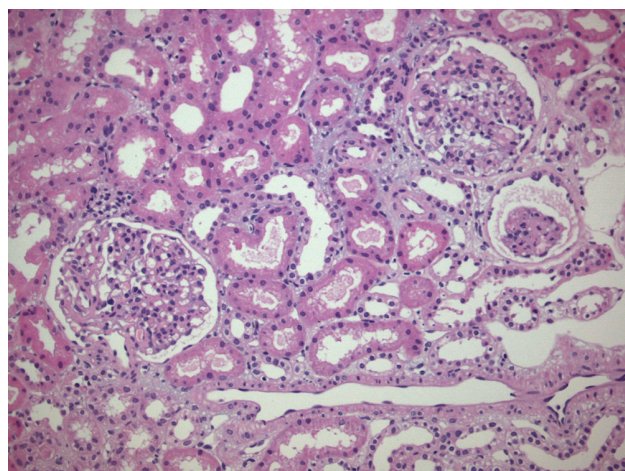


FIGURE 1. Minimal Change Disease (MCD). Glomeruli with no lesions. H-Ex200.

proof of MCD. Several times MCD appears to overlap with a variety of histologic variants that have a tendency to be less corticosteroid responsive. These conditions include focal segmental glomerulosclerosis (FSGS) and IgM nephropathy.

It is possible that both MCD and FSGS have similar initial histological appearances. Most cases are idiopathic, but they can also be secondary to neoplasias, such as Hodgkin's disease, or secondary to administration of drugs (non-steroidal anti-inflammatory drugs-NSAIDs, interferon alpha, etc.).¹

With regards to the new developments concerning MCD, there are some new insights into its pathogenesis. There is evidence that MCD is associated with a defect in the expression of cluster of differentiation 80 or CD80, a co-stimulatory molecule also known as B7.1, in the podocytes. This molecule (CD80) is expressed on all antigen-presenting cells and is also present on podocytes, as a number of experimental models of nephrotic syndrome suggest. This results in persistent defect of CD80 expression and persistent proteinuria. CD80 is also present in the urine during active nephrotic syndrome. CD80 expression is known to be induced by Toll-like receptor (TLR) ligands in dendritic cells. For some authors, urinary excretion of CD80 is thought to be a useful marker to differentiate MCD from FSGS. In addition, studies have also shown that relapse of MCD is associated with a significant increase in measured urinary CD80, while patients in remission have no significant differences when compared to patients with FSGS.²⁻⁴ Other recent studies on the molecular basis of MCD pathogenesis claim that overproduction of angiopoietin-like 4 protein (ANGPTL4) in podocytes in MCD, causes binding of this molecule to the glomerular basement membrane, leading to the development of diffuse effacement of foot processes, and loss of glomerular basement membrane charge and as consequence nephrotic-range selective proteinuria.⁵ If everything is correct, these findings may lead to both new diagnostic tests and potential therapeutics for this important renal disease.

There are no new guidelines for the treatment of MCD in children or adults. Corticosteroids remain the mainstay of

therapy in both cases and they are used both for initial therapy and for relapses. In frequent relapses and steroid-resistant MCD, or when corticosteroids are not well tolerated or not indicated, then cyclophosphamide or calcineurin inhibitors (CNIs) are the next therapeutic option in adults, while other alkylating agents such as chlorambucil can be given in children. Mycophenolate mofetil (MMF) can also be used, while rituximab, a monoclonal antibody against B cell proliferation, is considered only in children with frequent relapses after optimal therapy with combinations of corticosteroids and corticosteroid sparing agents and/or in those who have serious adverse effects from previous therapies.^{1,6,7}

MEMBRANOUS NEPHROPATHY (Fig. 2)

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. Clinically it is characterized by high-grade proteinuria with usually well preserved renal function. When renal biopsy is performed, there are typical immune deposits of IgG and complement components that develop predominantly or exclusively beneath podocytes in the subepithelial surface of the glomerular capillary wall. The disease occurs in association with a variety of conditions (Table 3). However, most of the cases of MN (about two thirds) are without obvious initiating events and are thought to be idiopathic. The rest may be caused by infections, drugs, autoimmune diseases or neoplasms.

Novel insights from experimental studies have been recently translated into substantial advances in understanding the pathogenesis of human membranous nephropathy. These include identification of neutral endopeptidase (NEP), a membrane associated podocyte antigen that digests peptides, as the target

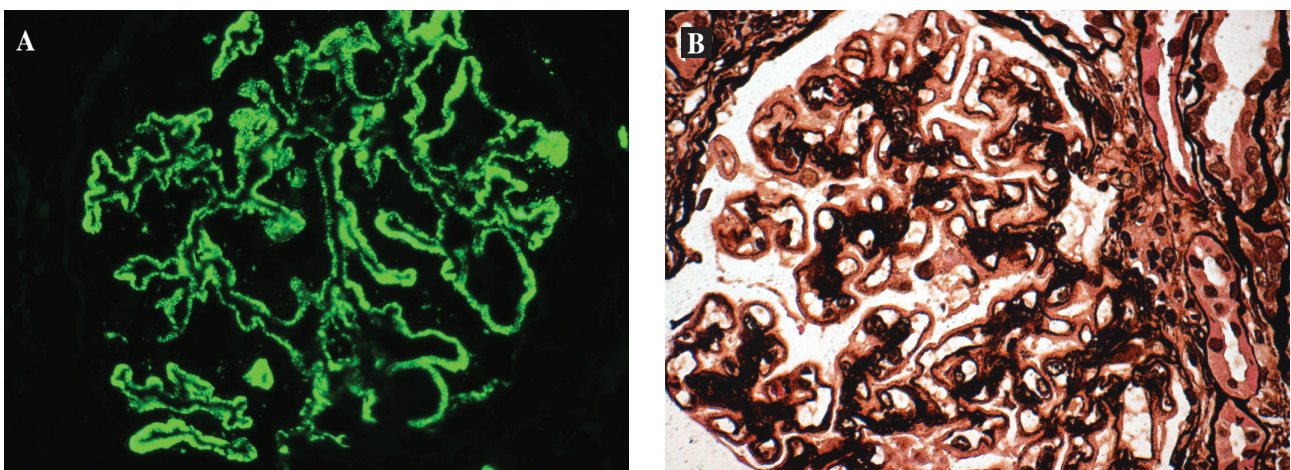


FIGURE 2. Membranous Nephropathy (MN). A) Immunofluorescence: granular deposition of IgG along capillary walls. B) Membranous nephropathy stage II, visible spikes of glomerular basement membrane (PASM ×600).

TABLE 3. Conditions and Agents Associated with Membranous Nephropathy

Immune diseases	SLE, diabetes, rheumatoid arthritis, Hashimoto disease, etc.
Infectious diseases	Hepatitis B or C, syphilis
Drugs and toxins	Gold, penicillamine, NSAIDs
Miscellaneous	Tumors, sarcoidosis, sickle cell disease

NSAID = non-steroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus

antigen in alloimmune MN resulting from feto-maternal immunization in NEP-deficient mothers, and the demonstration that a high proportion of patients with idiopathic MN have circulating antibodies to the M-type phospholipase A2 receptor (PLA2R), a transmembrane protein located on podocytes.⁸⁻¹⁰ Given that the sensitivity and specificity of anti-PLA2R for idiopathic MN are >75% and 100%, respectively, there is hope that a widely available assay for anti-PLA2R will prove to be valuable for diagnosing idiopathic MN, distinguishing it from secondary MN, and evaluating response to therapy.

Newer data regarding the treatment of idiopathic membranous nephropathy relate to the fact that immediate immunosuppressive therapy is reserved for patients with severe or life threatening symptoms associated with the nephrotic syndrome, while for those with a moderate disease, this therapy can be applied at a later stage, i.e. 6-8 months after its diagnosis following a conservative treatment.¹¹ This first line of conservative treatment consists of antihypertensive agents which block the renin-angiotensin-aldosterone system (RAAS), while waiting for a possible spontaneous remission of the nephrotic syndrome which may happen in about 1/3 of cases.

When the criteria for immunosuppressive therapy are met (persistent nephrotic syndrome, hypoalbuminemia, etc.), the initial therapy that the new Kidney Disease Improving Global Outcomes (KDIGO) Foundation guidelines recommend, consists of a 6-month course of alternating monthly cycles of oral and intravenous corticosteroids and oral cyclophosphamide. Alternative regimens include calcineurine inhibitors (CNIs, cyclosporine or tacrolimus). Monotherapy with MMF is not recommended as initial therapy for idiopathic membranous nephropathy.¹² Rituximab, which selectively depletes B-cells, has been examined as an alternative option in the therapy of idiopathic MN and a clinical trial is running and soon there will be results of such treatment. Only case reports and case series have been published until now, with promising results in controlling proteinuria and achieving total or partial remission. Rituximab-induced depletion of PLA2R autoantibodies may play a critical role in predicting response to treatment. More large controlled studies are still needed to prove the effectiveness of this agent in the treatment of idiopathic MN.¹²⁻¹⁵

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) (Fig. 3)

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome in children and adolescents, as well as an important cause of renal failure in adults. It defines a number of clinico-pathological syndromes that may be primary (idiopathic) or secondary to diverse etiologies. Genetic, toxic, infectious and inflammatory mediators have been identified.¹ The most common causes of secondary FSGS are virus induced (HIV1, parvovirus B19), drug induced (heroin, interferon, lithium, sirolimus) and postadaptive (reduced renal mass, hypertension, obesity, anabolic steroids).

The genetic forms of FSGS can be part of a syndrome or can manifest as kidney limited disease. Mutations that are responsible for syndromic FSGS may include mutations in glomerular basement membrane proteins (Alport syndrome) and transcription factors that are important in podocyte differentiation or metabolic disorders (Fabry's disease). In renal limited disease the genetic mutations encode for proteins in the actin based cytoskeleton complex or the slit diaphragm complex and adhesive proteins (mutations in nephrin, podocin, actin, phospholipase C1, or in transient receptor potential cation 6 channel). Some of these familial FSGS syndromes are listed here.

FAMILIAL FSGS

a. Autosomal recessive: Mutations in genes NPHS1 (coding for nephrin), NPHS2 (coding for podocin) and PLCE1 (coding for PLC epsilon1), LAMB2 (coding for Laminin beta 2 chain). b. Autosomal dominant: Mutations in genes ACTN1 (coding for alpha actinin4), TRPC6 (coding for transient re-

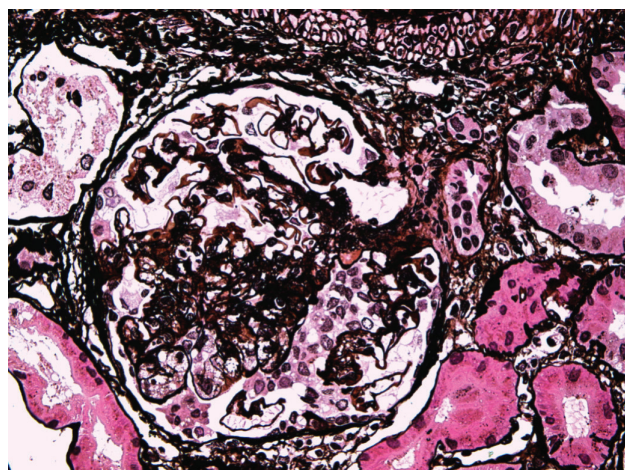


FIGURE 3. Focal segmental glomerulosclerosis (FSGS): Adhesion of lobular part with Bowman capsule. Hypertrophy of podocytes (PASM ×400).

ceptor potential cation 6 channel), INF2 (coding for INF2), WT1 (coding for WT1). All the mutations that are found in FSGS involve genes that are expressed in podocytes and this highlights the association between FSGS and podocyte injury.

With regards to renal pathology, histologic variants of idiopathic focal segmental glomerulosclerosis may have prognostic value. A recent classification system (Columbia Classification system) has distinguished five variants depending on the appearance of histology¹⁶⁻¹⁸:

- Cellular
- Collapsing (affects younger and more often black patients)
- Tip lesion
- Perihilar
- Not otherwise specified

Irreversible podocyte stress leading to podocyte depletion through apoptosis or detachment is a critical mechanism in most forms of FSGS. In the collapsing variant, podocyte dysregulation leads to podocyte dedifferentiation and glomerular epithelial cell proliferation.

Primary focal segmental glomerulosclerosis has long been attributed to a circulating permeability factor. Indirect evidence is the ability to modulate proteinuria through immunoadsorption, the potential disease recurrence soon after renal transplantation and therapeutic reduction in proteinuria by plasmapheresis. In addition serum samples from patients with FSGS cause increased permeability to albumin in isolated glomeruli and induce foot process effacement and proteinuria when injected to rats. Several plasma factors have been proposed. Elevated serum levels of soluble urokinase receptor have been identified in more than two thirds of patients with primary focal segmental glomerulosclerosis but not in those with minimal change disease or other glomerular diseases. Also increased levels of soluble urokinase receptor have been

associated with higher probability of recurrent disease in the renal allograft.¹⁹ Circulating soluble urokinase receptor induces foot process effacement through the activation of podocyte $\beta 3$ integrin, and its effect can be blocked in animal models by neutralizing antibodies targeting soluble urokinase receptor.^{20,21} The cellular source and stimulants of the receptor in individuals with primary FSGS are unknown.

Therapy of idiopathic FSGS has not significantly changed over the last several years with corticosteroids remaining the initial recommended therapy. For steroid-resistant FSGS or if steroids cannot be used, cyclosporine or tacrolimus is an alternative therapy, while MMF and high dose dexamethasone is reserved for patients who are intolerant to cyclosporine. Plasma exchange, which is successful in treating some patients with recurrent FSGS in the renal allograft, has not proved useful in patients with disease in their native kidneys.

Another area of active research is the use of agents to prevent renal fibrosis in patients with FSGS. Pirfenidone, an oral TGF- β inhibitor, was used in 21 patients with FSGS and a declining glomerular filtration rate (GFR).²² The drug halted the decline of kidney function over time without altering either blood pressure or proteinuria. A study using an antibody to TGF- β is also ongoing in FSGS patients²³.

IgA NEPHROPATHY (Fig. 4)

IgA nephropathy (IgAN) is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA. IgAN is the most common primary glomerulonephritis in the world. The prevalence rate varies across different geographical regions. In Europe this is about 30-40%. The classic presentation (in 40-50% of the cases) is episodic

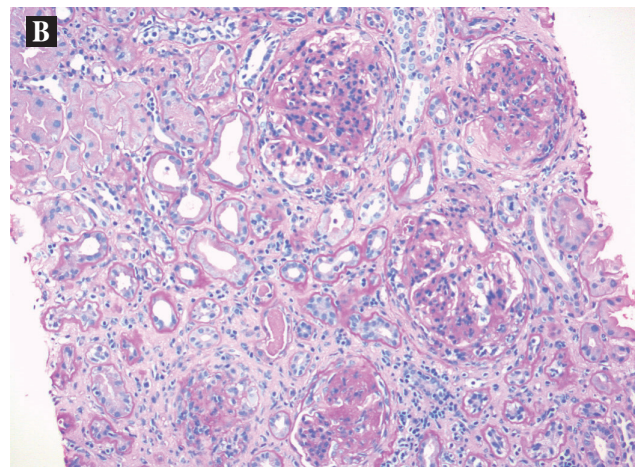
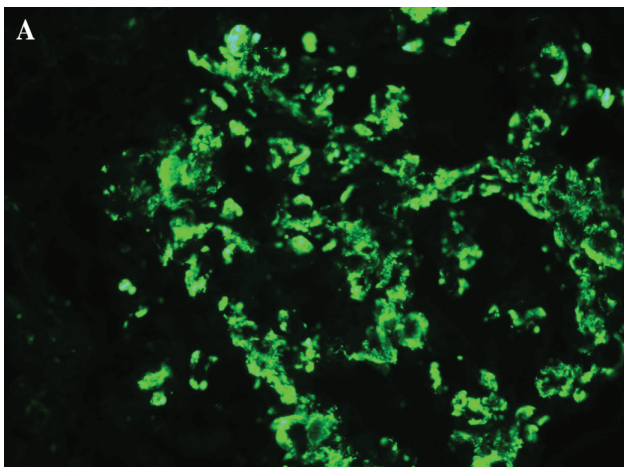


FIGURE 4. IgA Nephropathy. A) Diffuse and severe deposition of IgA in the mesangium. (IgA X 600). B) Light microscopy. IgA Nephropathy: Diffuse hyperplasia of the mesangium (PAS×200).

frank hematuria which usually starts within a day or two of a non-specific upper respiratory tract infection as opposed to post-streptococcal glomerulonephritis which occurs some time (weeks) after initial infection. Less commonly, gastrointestinal or urinary infection can be the inciting cause. Secondary IgAN is uncommon. Cirrhosis, celiac disease, and HIV infection are all associated with a high frequency of glomerular IgA deposition. IgAN has been infrequently associated with a variety of other diseases, including dermatitis herpetiformis, seronegative arthritis (particularly ankylosing spondylitis), small-cell carcinoma, lymphoma (Hodgkin lymphoma and T-cell lymphomas, including mycosis fungoides), disseminated tuberculosis, bronchiolitis obliterans, and inflammatory bowel disease (Crohn's disease and ulcerative colitis). These are usually clinically evident at the time of biopsy.

With regards to novel findings in IgA nephropathy, it has been recognized for some time that one of the most consistent features of IgA nephropathy is an alteration in the complement of serum IgA1 O-glycoforms, with an overrepresentation of poorly galactosylated IgA1 O-glycoforms both in the serum and mesangial deposits of patients with IgA nephropathy.²⁴ New data suggest that poorly galactosylated IgA1 O-glycoforms might act either as autoantigens driving the formation of glycan-specific antibodies, or antigens for cross-reactive antimicrobial antibodies.²⁵ Formation of these circulating and mesangial IgA-containing immune complexes appears pivotal to the pathogenesis of IgA nephropathy and there are strong in vitro data to support their role in activation of mesangial cells, induction of podocyte injury, and activation of proximal tubular epithelial cells.

The Oxford classification for IgA Nephropathy (2009) is a new pathological classification system that identifies six pathologic variables that could be used to interrogate prognostic significance independent of the clinical data in IgA nephropathy.²⁶ These variables are (1) mesangial cellularity score; (2) percentage of glomeruli showing segmental sclerosis; (3) endocapillary hypercellularity; or (4) cellular/fibrocellular crescents; (5) percentage of interstitial fibrosis/tubular atrophy; and finally (6) arteriosclerosis score.

Taking into consideration the results of clinical trials published over the past 10 years and taking into account the history of IgAN, the following therapeutic approach is now proposed.²⁷⁻³²

- Patients with micro-macrohematuria alone: annual check-ups with urine evaluation.
- Patients with proteinuria >1g/day: RAAS blockers, starting with a minimal dose, and then increasing up to the highest tolerated dose. The purpose is to suppress proteinuria or to keep it <1g/day. In cases of persistent proteinuria >1 g/d, at least a six-month course of corticosteroids is needed.
- Immunosuppressants (cyclophosphamide and azathioprine) should be reserved for patients with rapidly progressive renal failure or with vasculitic lesions (other than crescents)

at histological examination.

Further studies are required to determine the effectiveness of tonsillectomy, MMF and Omega 3 fatty acids in the therapeutic treatment of patients with IgAN.²⁷⁻³²

LUPUS NEPHRITIS (Fig. 5)

Lupus nephritis is a common and serious feature of systemic lupus erythematosus (SLE). From 30% to 50% of SLE patients will have clinically evident renal disease at presentation. During follow-up, renal involvement will occur in 60% of young adults and a greater percentage of young children. Renal involvement is manifested by proteinuria, active urinary sediment with microhematuria, dysmorphic erythrocytes and erythrocyte casts, and hypertension. In many cases with major renal involvement, the nephritic syndrome develops in association with proliferative glomerulonephritis and a decline in glomerular filtration rate (GFR). Infrequently, renal disease in SLE patients presents with tubular disorders such as renal tubular acidosis (RTA) with hypokalemia (type 1 RTA) or hyperkalemia (type 4 RTA), thrombotic disorders associated with a secondary antiphospholipid syndrome and fibrillary glomerulonephritis.

Although lupus nephritis may affect all structures of the kidney, glomerular involvement has been the best studied component, and it has been well correlated with the presentation, course, and treatment of the disease. For many years, the World Health Organization (WHO) classification of lupus nephritis was used. The 2003 modifications in the current International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification refine and clarify some of the deficiencies of the WHO classification. As in the WHO classification, the ISN

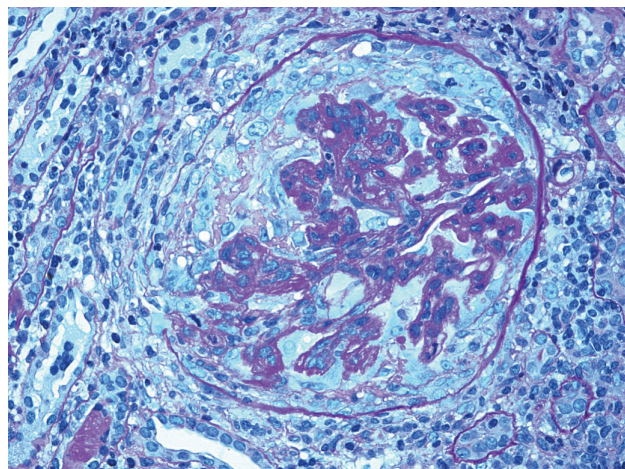


FIGURE 5. Systemic Lupus Erythematosus (SLE) Nephritis. Diffuse hyperplastic nephritis. Development of crescents. (PAS ×200).

classification is based on light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM) findings.³³

Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis 2003:³³

- Class I Minimal mesangial lupus nephritis
- Class II Mesangial proliferative lupus nephritis
- Class III Focal lupus nephritis
- Class IV Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
- Class V Membranous lupus nephritis
- Class VI Advanced sclerosing lupus nephritis

While therapies such as corticosteroids, cyclophosphamide and mycophenolate mofetil have improved outcomes in lupus nephritis, some patients have refractory disease or are unable to tolerate these agents.³⁴⁻³⁷ These limitations along with the better understanding of the immunopathogenesis of SLE have resulted in the development of new immunosuppressive and immunomodulatory treatments for lupus nephritis. Novel strategies include B cell depletion by the monoclonal antibodies rituximab and epratuzumab, “immunomodulation” of pathologic antibodies to dsDNA by abetimus, blockade of T-cell costimulation of B cells by abatacept, belatacept, IDEC131 and BG9588 and blockade of B cell stimulation by belimumab.^{38,39} Goals for new therapies of lupus nephritis are: (1) prevention of relapse, (2) improved side effect profile, (3) treatment of refractory disease, and (4) prevention of the development of chronic interstitial fibrosis and progressive renal failure or end-stage renal disease. Preliminary results are promising but large controlled trials are needed before there can be safe widespread use of these agents.³⁴⁻³⁹

SYSTEMIC VASCULITIS (Fig. 6)

The primary systemic vasculitides are a group of inflammatory diseases of unknown cause, which are usually fatal if untreated. Various attempts have been made to create a universally accepted classification scheme but still the classification of the vasculitides remains a matter of controversy. Some classification systems have focused on the size of the vessels, while several other classification schemes have been based on histologic findings.⁴⁰ The most recent classification schema proposed by the American College of Rheumatology (ACR) uses both vessel size and type of inflammatory infiltrate. It classifies vasculitis as follows: polyarteritis nodosa (PAN), Churg-Strauss syndrome, granulomatosis with polyangiitis (former Wegener’s), hypersensitivity vasculitis, Henoch-Schönlein purpura, giant cell arteritis, Takayasu’s arteritis, granulomatous angiitis of the central nervous system, Berger’s disease, and Kawasaki disease.^{40,41}

In 1994, the Chapel Hill Consensus Conference (CHCC)

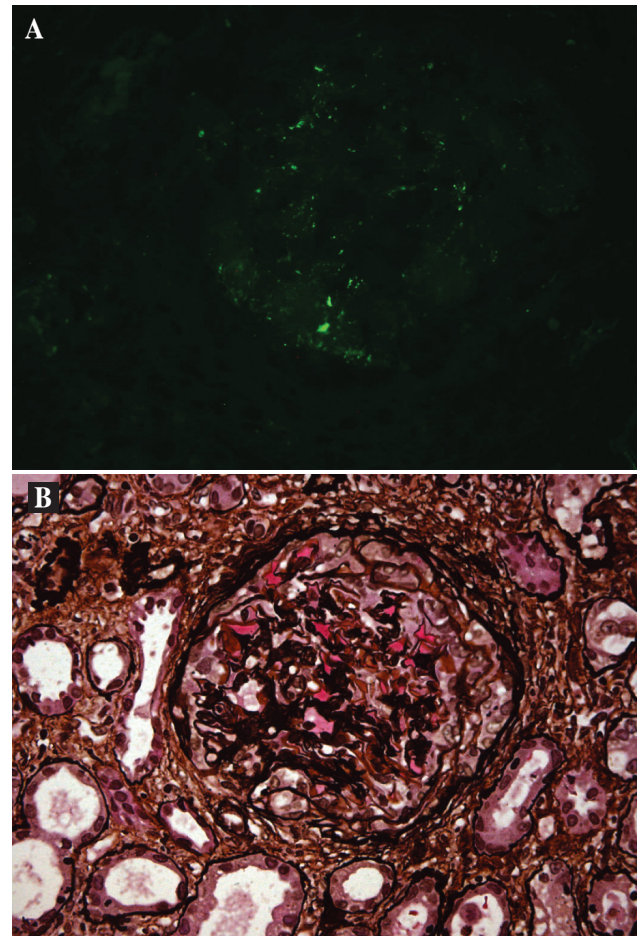


FIGURE 6. A) Immunofluorescence in a vasculitic lesion: Rare immune deposition of C3 in the mesangium (C3 x 600). B) Light microscopy. Fresh hypercellular crescent. (PASM x 400).

created an alternative schema for classification of the major types of vasculitis. According to the CHCC, the vasculitides are divided into large, medium, and small-vessel vasculitis. The largest subgroup comprises syndromes associated with circulating anti-neutrophil cytoplasm antibodies (ANCA)-ANCA-associated systemic vasculitides (AASV). These include granulomatosis with polyangiitis (Wegener’s, GPA) microscopic polyangiitis (MPA), Churg-Strauss angiitis and renal limited vasculitis. The kidneys are targets for a variety of systemic vasculitides, especially those that affect small vessels, due to the large number and variety of renal vessels.⁴⁰⁻⁴³

The targets for small-vessel vasculitides are the glomeruli, and therefore the most common clinical renal manifestations are those of glomerulonephritis and include hematuria, proteinuria, and renal failure. Renal failure often has the characteristics of rapidly progressive glomerulonephritis in patients with granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis but usually is less severe in those

with Churg-Strauss syndrome. The glomerulonephritis usually has necrosis and crescent formation and an absence or paucity of immunoglobulin deposition and is often designated pauci-immune crescentic glomerulonephritis. When pauci-immune crescentic glomerulonephritis occurs in the apparent absence of systemic vasculitis, it is sometimes referred to as renal vasculitis, renal-limited vasculitis, or idiopathic rapidly progressive glomerulonephritis. The most common antigen specificities of ANCA in patients with vasculitis and glomerulonephritis are for proteinase 3 (PR3) and myeloperoxidase (MPO). In addition to ANCA, the cellular immune system contributes to the pathogenesis of the disease. ANCA-mediated degranulation of neutrophils causes vasculitic damage; T cells drive granuloma formation, promote vasculitic damage by several different pathways, and enhance autoantibody production by B cells. Recently, complementary PR3 and lysosomal membrane protein-2 (LAMP-2) were suggested as novel autoantigens in vasculitides.⁴³ New findings also indicate the importance of complement and dendritic cells.

The treatment of systemic and renal vasculitis is based on the use of steroids in combination with immunosuppressive agents, most commonly cyclophosphamide and recently MMF to induce remission. In the presence of severe renal disease, plasma exchange is often used as an adjunct to the pharmacological treatment. When remission is achieved, maintenance therapy with lower doses of steroids and less potent agents such as azathioprine is suggested.⁴³⁻⁴⁵

Two of the most important studies for the use of rituximab (an anti CD-20 monoclonal antibody that depletes B lymphocytes) in ANCA-associated vasculitis were conducted in 2010.^{44,45} The RAVE trial compared rituximab to commonly used cytotoxic agents for induction of complete remission by six months in patients with severe ANCA associated vasculitis. The data provided by this large multicenter trial suggest that the regimen containing rituximab plus corticosteroids is not inferior to the standard regimen of cyclophosphamide and corticosteroids and it may even be superior for induction of remission in severe relapsing disease.⁴⁴ The RITUXIVAS trial tried to assess the treatment response and rates of associated adverse events with the rituximab based regimen as compared with the cyclophosphamide based regimen. The researchers concluded that rituximab was not associated with a reduction in early severe adverse effects and both regimens were associated with the same frequency of mortality (18%).⁴⁵

CONCLUSION

New insights into the pathogenesis, diagnosis and treatment of glomerular diseases comprise the following developments.

a) Minimal change disease (MCD): New data with regards to its pathogenesis relate to a defect in the expression of CD80, a co-stimulatory molecule (also known as B7.1) in the

podocytes, which seems to represent a possible new marker of disease activity and a new target for therapy. Similarly, overproduction of angiopoietin-like 4 protein (ANGPTL4) in podocytes in MCD causes binding of this molecule to the glomerular basement membrane, diffuse effacement of foot processes, and loss of glomerular basement membrane charge and as a consequence nephrotic-range selective proteinuria, findings that could also lead to new targets of disease activity and treatment.

b) Membranous nephropathy. Regarding its pathogenesis, the demonstration that a high proportion of patients with idiopathic membranous nephropathy have circulating antibodies to the M-type phospholipase A2 receptor (PLA2R), a transmembrane protein located on podocytes will prove to be valuable for diagnosing idiopathic membranous nephropathy, distinguishing it from secondary membranous nephropathy, and evaluating response to therapy. With regards to its treatment, the new development concerns mainly the possible use of rituximab not only for persistent nephrotic syndrome but also as for first line treatment (studies are on-going). In any case, immunosuppressive therapy is limited to non-responders to strict conservative treatment with a follow up of more than 6-8 months.

c) FSGS. There are ongoing studies concerning the pathogenesis of genetic forms. As for the primary FSGS and its pathogenesis, high levels of circulating soluble urokinase receptor have been identified in more than two thirds of patients with FSGS including those with recurrence in renal allograft, inducing foot process effacement through the activation of podocyte $\beta 3$ integrin, and this effect can be blocked in animal models by neutralizing antibodies targeting soluble urokinase receptor. This seems to be a fascinating target for disease activity and therapy.

d) In IgA nephropathy new data regarding its pathogenesis suggest that poorly galactosylated IgA1 O-glycoforms might act either as autoantigens driving the formation of glycan-specific antibodies, or antigens for cross-reactive antimicrobial antibodies leading to activation and injury of mesangial cells and podocytes. The Oxford Classification system helps to classify the disease, whilst, as far as therapy is concerned, it is now concluded that patients with proteinuria > 1 g/d with or without renal impairment need corticosteroid treatment.

e) Lupus nephritis. There no concrete new developments regarding its pathogenesis but with regards to its treatment, new immunosuppressive and immunomodulatory treatments for lupus nephritis are now under investigation (B cell depletion, blockade of B and T stimulation etc).

f) In systemic vasculitides, concerning their pathogenesis, recently, complementary PR3 and lysosomal membrane protein-2 (LAMP-2) were suggested as novel autoantigens in these diseases. New findings also indicate the importance of complement and dendritic cells in their pathogenesis. As for their treatment, the use of Rituximab has been proved not

inferior to the standard cytotoxic therapy with cyclophosphamide, whilst MMF takes its position as a potential treatment modality of ANCA associated vasculitides both as induction or maintenance therapy.

ACKNOWLEDGMENT

The photos included in this review are part of the archive of Christina Vourlakou, MD, Consultant in Pathology, Evagelismos General Hospital, Athens, Greece. The images were derived from cases hospitalized in our Nephrology Department. We would like to thank Dr Vourlakou for her continuous assistance in our work and for the excellent histopathological reports she offers to our Department and our patients.

REFERENCES

- Floege J, Johnson R, Feehally J (eds). Glomerular Disease. In Comprehensive Clinical Nephrology, 4th Edition-Section IV. Elsevier 2010, p. 193-355.
- Ishimoto T, Shimada M, Araya CE, Huskey J, Garin EH, Johnson RJ. Minimal change disease: a CD80 podocytopathy? *Semin Nephrol* 2011; 31:320-325.
- Shimada M, Araya C, Rivard C, et al. Minimal change disease: a “two-hit” podocyte immune disorder? *Pediatr Nephrol* 2011; 26:645-649.
- Garin EH, Diaz LN, Mu W, et al. Urinary CD80 excretion increases in idiopathic minimal-change disease. *J Am Soc Nephrol* 2009; 20:260-266.
- Chugh SS, Clement LC, Macé C. New insights into human minimal change disease: lessons from animal models. *Am J Kidney Dis* 2012; 59:284-292.
- Oh J, Kemper MJ. Minimal change (steroid sensitive) nephrotic syndrome in children: new aspects on pathogenesis and treatment. *Minerva Pediatr* 2012; 64:197-204.
- Takei T, Nitta K. Rituximab and minimal change nephrotic syndrome: a therapeutic option. *Clin Exp Nephrol* 2011; 15:641-647.
- Debiec H, Guignon V, Mougnot B, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med* 2002; 346:2053-2060.
- Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; 361:11-21.
- Stanescu HC, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA2R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011; 364:616-626.
- Polanco N, Gutierrez E. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2010; 21:697-704.
- Bombardieri A, Derebail V, McGregor JG, Kshirsagar AJ, Falk RJ, Patrick H. Rituximab therapy for membranous nephropathy: a systematic review. *Clin J Am Soc Nephrol* 2009; 4:734-744.
- KDIGO Clinical Practice Guidelines for Glomerulonephritis. *Kidney Int* 2012; 2:140-274.
- Branten A, du Buf-Vereijken PW. Mycophenolate mofetil in idiopathic membranous nephropathy: a clinical trial with comparison to a historic control group treated with cyclophosphamide. *Clin J Am Soc Nephrol* 2007; 2:932-937.
- Dusso B, Morange S, Burtsey S. Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. *Am J Kid Dis* 2008; 52:699-705.
- D’Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004; 43:368.
- Sanchez-Ares M, Garcia-Vidal M, Antucho EE, et al. A novel mutation, outside of the candidate region for diagnosis, in the inverted formin 2 gene can cause focal segmental glomerulosclerosis. *Kidney Int* 2013; 8:153-159.
- D’Agati VD. Pathobiology of focal segmental glomerulosclerosis: new developments. *Curr Opin Nephrol Hypertens* 2012; 21:243-250.
- Shimizu A, Higo S, Fujita E, Mii A, Kaneko T. Focal segmental glomerulosclerosis after renal transplantation. *Clin Transplant* 2011; 25(Suppl. 23):6-14.
- Wei C, Hindi S, Li J, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 2011; 17:952-960.
- Wei C, Trachtman H, Li J, et al. Circulating suPAR in two cohorts of primary FSGS. *JASN* 2012; 23:2051-2059.
- Cho ME, Smith DC, Branton MH, et al. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2007; 2:906-913.
- Trachtman H, Fervenza FC, Gipson DS, et al. A phase 1, single-dose study of fresolimumab, an anti-TGF-beta antibody, in treatment-resistant primary focal segmental glomerulosclerosis. *Kidney Int* 2011; 79:1236-1243.
- Novac J, Julian B, Tomana M, Mestecky J. IgA glycosylation and IgA immune complexes in the pathogenesis of IgA Nephropathy. *Semin Nephrol* 2008; 28:78-87.
- Coppo R, Fonsato V, Balegno S, et al. Aberrantly glycosylated IgA1 induces mesangial cells to produce platelet-activating factor that mediates nephrin loss in cultured podocytes. *Kidney Int* 2010; 77:417-427.
- A working group of the international IgA nephropathy network and the renal pathology society: Cattran DC, Coppo R, Cook HT, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009; 76:534-545.
- Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol* 2004; 15:157-163.
- Cheng J, Zhang X, Zhang W, et al. Efficacy and safety of glucocorticoids therapy for IgA nephropathy: a meta analysis of randomized controlled trials. *Am J Nephrol* 2009; 30:315-322.
- Tumlin JA, Lohavichan V, Hennigar R. Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide. *Nephrol Dial Transplant* 2003; 18:1321-1329.

30. Pozzi C, Andrulli S, Pani A, et al. Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. *J Am Soc Nephrol* 2010; 21:1783-1790.
31. Donadio JV, Grande JP. The role of fish oil/omega-3 fatty acids in the treatment of IgA nephropathy. *Semin Nephrol* 2004; 24: 225-243.
32. Komatsu H, Fujimoto S, Hara S, et al. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. *Clin J Am Soc Nephrol* 2008;3:1301-1307.
33. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15:241-250.
34. Appel GB, Contreras G, Dooley MA, et al; Aspreva Lupus Management Study Group. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; 20:1103-1112.
35. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; 353:2219-2228.
36. Houssiau FA, D'Cruz D, Sangle S, et al; MAINTAIN nephritis trial group. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010; 69:2083-2089.
37. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004; 350:971-980.
38. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Results From the Randomized, Double-Blind Phase III LUNAR Study. *Arthritis Rheum* 2012; 64:1215-1226.
39. Mok CC. Update on emerging drug therapies for systemic lupus erythematosus. *Expert Opin Emerg Drugs* 2010; 15:53-70.
40. Falk RJ, Nachman PH, Hogen SL, Jennette JC. ANCA glomerulonephritis and vasculitis: A Chapel Hill perspective. *Semin Nephrol* 2000; 3:233-243.
41. Franssen CFM, Stegeman CA, Kallenberg CG. Antiproteinase-3 and antimyeloperoxidase-associated vasculitis. *Kidney Int* 2000; 57:2195-2206.
42. Salama AD, Pusey CD. Shining a LAMP on pauci-immune focal segmental glomerulonephritis. *Kidney Int* 2009; 76:15-17.
43. Wilde B, van Paassen P, Witzke O, Tervaert JW. New pathophysiological insights and treatment of ANCA-associated vasculitis. *Kidney Int* 2011; 79:599-612.
44. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363:221-232.
45. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363:211-220.