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Recent trends in management of common glomerulopathy

Kamel El-Reshaid

Department of Medicine, Faculty of Medicine, Kuwait University

ABSTRACT

Diagnosis of glomerulopathy requires correlation between: (a) clinicopathological syndromes, (b) kidney histology for the abnormalities which are useful for the severity of disease, stage of activity and extent of chronicity. Subsequently, management dictates the choice of effective medications to avoid renal loss and long-term side effects. In this review article; we provide our practical experience with drug-therapy in common idiopathic and secondary glomerular diseases.

Keywords: glomerulopathy, kidney biopsy, nephrotic syndrome, Rituximab, treatment.

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***Address for Correspondence:**

Dr. Kamel El-Reshaid, Professor, Dept. Of Medicine, Faculty of Medicine, Kuwait University, P O Box 24923, 13110 Safat, Kuwait

Fax : (965) 5318454 Or E-mail : kamel@hsc.edu.kw

INTRODUCTION

Glomerulopthy (G) is an injury to the glomerulus. The latter is the first segment of the nephron which is responsible for filtration of blood received from the afferent arteriole and existing via the efferent one. The glomerulus is formed by the branching of the afferent arteriole which loses its muscular wall and left only with a glomerular basement membrane (BM) and an inner lining of endothelial cells. The latter arrangement is to provide an unhindered filtration process (Fig.1). The filtered fluid is collected in the first part of the urinary tubules which is the bowman space formed by an inner visceral and an out parietal layer of the bowman capsule.

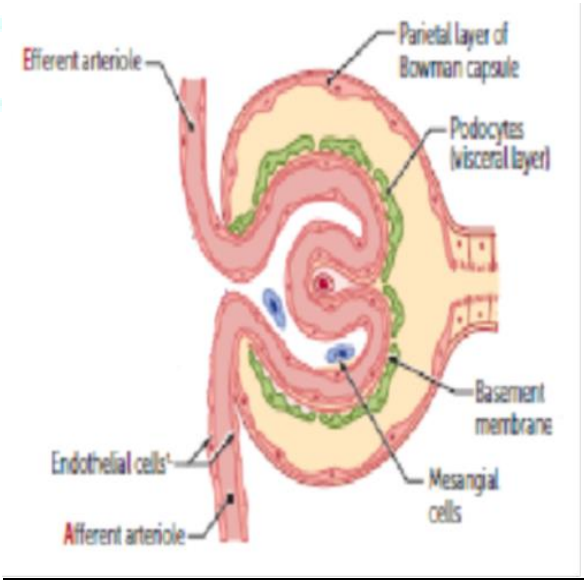

Figure 1: Showing ultrastructural features of normal glomerulus

MANIFESTATIONS OF G

G is a common cause of renal disease with an annual incidence rate 34.5 per 100,000 populations (PTP) [1]. In the latter study 21.1 PTP were non-diabetic G, of whom secondary lesions viz. lupus nephritis and vasculitis shared 4.8 PTP. G manifests as proteinuria caused by altered permeability of the BM, hematuria if BM ruptures, oliguria if reduced filtration of fluids leading to fluid overload, oedema and hypertension and lastly azotemia if impaired filtration of nitrogenous end-products of catabolism. The prognosis of G depends on nature of disease and its severity.

DIAGNOSIS OF G

It requires recognition of: (a) clinicopathological syndromes, (b) kidney histology for the abnormalities which are useful for the severity of disease, stage of activity and extent of chronicity. The clinicopathological abnormalities includes; clinical manifestations, routine laboratory tests and serological markers of disease. The latter serum tests include; complements (C3 & C4), ANA, anti-dsDNA, ANCA, anti-GBM antibodies, IgA level, SPEP, HBsAg and hepatitis C antibodies. Finally; the correlation between both is essential for final diagnosis. Kidney biopsy establishes the histological type and guides selection of its specific therapy of since some G are steroid-refractory. The next step is to assess if the histological diagnosis fits with the clinicopathological syndromes i.e. clinicopathological correlation since: (a) some histological diagnosis are secondary to systemic diseases, (b) superimposed G have been reported. An example of the latter is a case of acute nephrotic syndrome (NS) in a diabetic glomerulosclerosis (DGS) or an IgA histological features; can't rule out minimal change disease (MCD) superimposed on those G. Diagnosis of the latter may prove to be difficult even with the aid of electron microscopy to evaluate ultrastructual deposits and BM changes and an empiric trial of short-course of Prednisone may confirm diagnosis.

CLINICOPATHOLOGICAL SYNDROMES

Those with their corresponding histological lesions are summarized in Table 1. They include 4 clinical syndromes; (a) NS characterized by history of oedema and proteinuria ≥ 3.5 g/day, (b) advanced NS (with renal impairment) i.e. all diseases in the first group except pure MCD, (c) acute renal failure with hematuria and proteinuria which includes patients with proliferative and crescentic glomerular lesions, (d) asymptomatic hematuria with/without hematuria and renal impairment accidently disclosed during routine work up.

MECHANISMS OF G

1- MCD: The initial event starts by activation of T-lymphocyte leading to stimulation of B-lymphocyte to liberate a permeability factor [2]. The latter abolishes the negative charge on glomerular BM. Serum albumin is a negatively-charged small molecule that can easily pass through the fenestra of the BM yet is normally repelled by the negative charge on BM. Interestingly, such phenomenon prevents the attachment of the visceral layer of bowman capsule on the epithelial (outer) side of BM leading to a foot-process structure. Once the negative charge is lost; albumin can passes freely through the fenestra of BM and the visceral cells spread on the BM losing the foot-processes shape. Since the defect is loss of negative charge of BM rather than an inflammatory process; MCD is not associated with glomerulosclerosis. The initiating factor from T-lymphocyte is interleukins which can be blocked by Calcineurin inhibitors (CNI) and activated mature B-lymphocyte can be targeted with Rituximab [3, 4].

2- Certain immune complexes (IC) are bland and do not generate inflammatory response such as idiopathic membranous G (MG). Hence; treatment is only if severe NS and evidence of glomerulosclerosis [5]. Since deposits; with Rituximab therapy, improvement in MG may need 2 months compared to only few days in MCD since the latter is an electrical defect [6].

3- Slow deposition of IC may be associated with mild inflammation leading to mild G with limited glomerulosclerosis such as IgA nephropathy [7]. However, in genetically predisposed patients, high-load of such IC leads to abnormal mesangial cells reaction with subsequent progressive glomerulosclerosis and kidney loss. The G is the most common G in Far East and South East Asia and Europe and accounts for 25% of G. Since not a florid inflammation; such phenotype rarely benefits from chronic immunosuppression [8].

4- Idiopathic focal and segmental glomerulosclerosis (FSGS) is induced by a mixture of another form of permeability factor and IC disease [9]. The IC is IgM and starts segmentally leading to progressive sclerosis and subsequent hyperfiltration, hypertension and progressive G. If treated early; its acute NS can improve. However, it needs long-term maintenance therapy and if untreated; 50% can progress to end-stage kidney disease within 5 years [10].

5- Inflammatory lesions are initiated by antigens. Some are short-lived such as post-streptococcal glomerulonephritis or clear after treatment of infections such as post-infectious and membranoproliferative ones [11, 12]. However, high-load deposits as in lupus nephritis can initiate severe inflammatory response with endothelial cell proliferation, necrosis and rupture of BM leading to crescent formation by activation of podocytes of the visceral layer of bowman capsule [13]. Hence, an according to genetic predisposition, lupus nephritis can present as membranous G, proliferative G and IC crescentic G. The disease needs aggressive immunosuppressive therapy to stop the active process (induction phase) followed by an effective and safe long-term maintenance immunosuppressive treatment to prevent its relapse [14]. Vasculitis is another severe systemic vascular autoimmune disease [15]. Involvement of medium-sized vessels, in polyarteritis nodosa, leads to kidney infarctions and stripped fibrotic renal loss. Small-vessel disease can lead to glomerular BM damage with necrotizing G and/or crescentic one if vessel ruptures leading to podocyte disease. The latter presentation is common in Wegner's granulomatosis, microscopic polangiitis and anti-glomerular BM disease.

TREATMENT OF COMMON GLOMERULAR DISEASES:

Management of common glomerulopathy is summarized in table 2. Certain issues should be respected:

1- Nearly 90% of NS in children is due to steroid-responsive MCD. In adult population; the prevalence falls to 20% with nearly 40% are due to MG which is steroid-refractory G [16]. Hence, kidney biopsy; should be done in any adult with NS except for typical DGS.

2- The prevalence of DGS is 50% in type I DM and 20% in type II DM. The classic presentation of DGS is with 4 signs; slowly progressive NS, > 5 years after type II or > 10 years in type I, normal-sized kidneys and proliferative retinopathy. The latter findings should be associated with negative clinical, laboratory and serological markers of autoimmune diseases. Since type II DM is common and DGS is prevalent in 20% of those diabetics; kidney biopsy is rarely done if presentation is typical [17]. However, unexplained acute renal and sudden NS in an already accepted DGS

3- Clinically indicates kidney biopsy to rule out superimposed lesions or an initial misdiagnosis [18].

4- In rapidly progressive G; aggressive immunosuppressive induction therapy should be initiated till the final histopathological diagnosis is available.

5- Overall, immunosuppressive drugs should be efficacious and with minimal long-term side effects. Rituximab, if financially accessible, is preferred to long-term Corticosteroids, Alkylating agents and even CNI [6]. The latter drugs are efficacious alone or in combination with others in some cases of FSGS. However, caution should be exercised on long-term treatment and with doses > 3 mg/kg to avoid interstitial fibrosis [19].

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Table 1: Clinicopathological syndromes of common glomerulopathies

Nephrotic (oedema + proteinuria ≥ 3.5 g/day)	Advanced nephrotic	Nephritic (ARF+Proteiuria)		Asymptomatic hematuria (± proteinuria)
		Proliferative	Crescentic	
	All NS except	1- Post-infectious/strept	1- Anti-GBM disease	1- IgA nephropathy
1- Minimal change disease	pure MCD	2- Lupus nephritis	2- Immuncomplex mediated	2- Thin membrane disease
a- Primary			3- Pauci-immune deposits/vasculitis	3- Alport's syndrome
b- Secondary: Hodgkin, Leukemia				
2- Membranous glomerulopathy				
a- Primary				
b- Solid cancers, drugs (d-PNC, gold), SLE, infections				
3- Focal segmental glomerulosclerosis				
a- Primary				
b- Secondary: genetic, HIV, hyperfiltration, obesity, drugs				
4- Membranoproliferative:				
a- Rarely idiopathic (causes: infections including: Hepatitis C ± Cryoglobulinemia)				
b- C3 glomerulopathy				
5- Fibrillary/immunotactoid				
6- Nodular glomerulosclerosis:				
Diabetic GS				
Amyloidosis/Light chain				

Table 2. Immunosuppressive treatment of common primary glomerulopathy

Glomerulopathy	Treatment
A- Minimal change disease:	
I- Steroid-responsive:	Prednisone for 3 months*
1- No further relapse (10%)	None
2- Infrequent relapser (30%):	Repeat Prednisone course*
3- Frequent relapser/steroid-dependent (50%):	C-IH ± MMP for 1 year or yearly Rituximab (1-4 years)
II- Steroid-resistant (10%):	Rx as FSGS
B- Membranous glomerulopathy:	
1- Induction:	C-IH + MMP
2- Maintenance:	yearly Rituximab for 4-5 years
C- Focal segmental glomerulosclerosis:	
1- Induction:	C-IH + MMP
2- Maintenance:	Yearly Rituximab ± C-IH ± MMP
D- MPGN:	
1- Treat underlying infection:	1- If hepatitis + Cryglobulinemia: Solvady + yearly Rituximab (if NS)
2- C3-glomerulopathy:	2- No specific immunosuppressive Rx
E- Diabetic glomerulosclerosis:	Control hyperglycemia & ACEI/ARB (control hypertension and hyperfiltration): slows the disease
F- Amyloidosis/Light chain:	Treat the cause & if MM or Light chain: chemotherapy
G- Lupus nephritis (stage3 & 4 & NS with membranous):	
1- Induction phase (3 months):	Combination of 3 agents: Steroid ** + MMP + IV cyclophosphamide
2- Maintenance phase:	Rituximab yearly infusions or Prednisone 5 mg/day + MMP
H- Vasculitis/Crescentic glomerulopathy:	
1- Induction phase (3 months):	Combination of 3 agents: Steroid ** + MMP + IV cyclophosphamide
2- Maintenance phase (2 years):	Rituximab yearly infusions or Prednisone 5 mg/day + MMP
N.B.: if anti-GBM vasculitis: plasma exchange should be added	

Abbreviations & dosage of medications:

* Prednisone 2 mg/kg/day (< 60 mg/m2) for 4 weeks then taper down gradually till discontinuation by 3rd month

** 1 g of Solumedrol IV daily for 3 days followed by Prednisone 2 mg/kg/day (not > 60 mg/day) foe 4 weeks then to be tapered down till 5 mg/day

MMP: Mycophenolate mofetil; dose: 600 mg/m2 orally 2 times a day up to a maximum of 2 grams per day

Cyclophosphamide 750 mg/m2 IV monthly infusions in 200 ml of normal saline over 2 hours

C-IH: Calcineurin inhibitors:

A- Tacrolimus (Prograf): 0.1 mg/kg/day up to 2 mg twice daily

B- Cyclosporine A (Neoral): 5 mg/kg/day up to 100 mg twice daily