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Acute Idiopathic Immune Complex Mesangioproliferative Glomerulopathy in an Adult; Resurge of the Fallen

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Abstract

Background: Idiopathic form of mesangioproliferative glomerulopathy (MesPGP) was excluded by the standardized classification and reporting of glomerulonephritis (Mayo clinic consensus) in 2016 aiming to limit such group only to IgA nephropathy, IgA vasculitis, infection-related GP, lupus nephritis, and fibrillary GP with polyclonal Ig deposits in an attempt to aid in treatment. **The case:** A 32-year-old man presented with severe hypertension that was associated with progressive renal failure (serum creatinine at 358 umol/L), proteinuria and hematuria. Clinical assessment and laboratory testing did not show evidence of infection and autoimmune disease. Kidney biopsy showed MesPGP with 39% glomerulosclerosis and 60% interstitial fibrosis. Immunohistochemical studies showed 2(+) IgG and IgA deposits over the peripheral capillary loops not mesangium. C3 and C1q were negative. Electron microscopy scanning showed subepithelial, subendothelial and mesangial electron dense deposits. Hence, diagnosis of idiopathic MesPGP was established. He improved after intravenous Solumedrol followed by a tapering dose of Prednisone with Mycophenolate mofetil for 3 months. Subsequently, he remained in remission up to 1 year with Rituximab alone and will be using it for a minimum of 2 years. **Conclusion:** Acute idiopathic immune complex MesPGP should be re-included in classification of glomerulopathy and was amenable to immunosuppressive therapy.

Keywords

Prednisone, Rituximab, Mycophenolate, Immune Complex, Mesangioproliferative Glomerulopathy, Idiopathic, Mayo Clinic Consensus of Glomerulonephritis

1. Introduction

Glomerulopathies (GPs) are among the leading causes of chronic kidney disease (CKD). Excluding diabetic nephropathy, GPs account for 25% of the cases of CKD worldwide [1]. Moreover, they are the third most common cause of end-stage renal disease after diabetes mellitus and hypertension and with an annual incidence at 8.6% [2]. In general, development of GPs involves a complex interplay of genetic predisposition and triggers viz. infections, autoimmune diseases, neoplasia, drug-exposure and environmental factors [3]. Kidney biopsy, aided by clinical, laboratory and serological data, is an essential tool in disease definitions and hence, subsequent treatment and prognosis [4]. Unfortunately, even the most recent KDIGO guideline to date, covering a large array of diseases, fell short of addressing certain GP [5]. In 2016, a standardized classification and reporting of glomerulonephritis (Mayo clinic consensus) was established to classify GP according to etiology/pathogenesis aiming to assist in its management [6]. Based on their tentative mediators, GPs were divided into 5 groups viz., immune complex, antineutrophil cytoplasmic antibody, anti-glomerular basement membrane, monoclonal immunoglobulin and C3. In their consensus, immune complex mediated GPs were limited to: IgA nephropathy, IgA vasculitis, infection-related GP, lupus nephritis, and fibrillary GP with polyclonal Ig deposits. In our case report, we present an adult patient with an acute idiopathic mesangioproliferative glomerulopathy (MesPGP) that is unspecified by the latest Mayo clinic consensus in an attempt to expand our knowledge in its diagnosis, management and prognosis.

2. The Case

A 32-year-old man presented to with persistent headache for 1 week. At that time, his blood pressure was 180/120 mm Hg. The patient did not have past history of other significant medical illness, surgery, allergy or chronic intake of medications. Work up at that time revealed serum creatinine at 156 umol/L, albumin at 35 g/L, hematuria and proteinuria at 2.4 g/day. Blood pressure was controlled with Amlodipine 10 mg daily. Serum complements (C3 & C4), IgA, ASOT and protein electrophoresis were normal. ANA, anti-ds DNA, ANCA, anti-GBM antibodies, RF, HIV, hepatitis B surface antigen and anti-HCV antibodies were negative. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound did not show abnormality except for normal-sized kidneys with increase cortical echogenicity. One month later, his serum creatinine had increased to 195 umol/L and by 2 months later, it reached 358 umol/L. At the latter time, he sought our medical advice. He was short of breath and had bilateral lower limbs as well as sacral edema. He was afebrile and with body weight at 62 kg and blood pressure at 160/100 mm Hg. Systemic examination did not show abnormality except for bilateral basal chest rales. Laboratory investigations and follow up are summarized in **Table 1**. He had normal peripheral leucocytic and platelets counts. Hemoglobin was 84 g/L with normal transferrin saturation% and vitamin B12. Serum sugar, electrolytes and liver functions were normal except for albumin at 26 g/L. LDL-cholesterol was at 5

Table 1. Flow chart of demographical data and biochemical changes of a treated patient with idiopathic immune-complex glomerulonephritis.

	Time (months)					
	-2	0	1	3	6	12
Age, gender & race: 32 years, male, White						
Clinical data:						
Nephrotic state	3(+)	3(+)	3(+)	(-)	(-)	(-)
Blood pressure (120-80 mm Hg)	180/120	160/100	120/80	120/80	120/80	120/80
Body weight (Kg)	56	62	63	56	57	57
Laboratory tests*:						
Hemoglobin: (130-160 g/L)	90	84	95	110	118	122
Serum:						
Serum urea (4-6 mmol/L)	14	20	23	18	12	6
Serum creatinine (60-120 umol/L)	156	358	210	185	160	120
Serum Albumin (35-50 g/L)	35	26	29	34	39	43
Serum LDL-Cholesterol (< 3 mmol/L)	3	5	6	4	2	2
Urine routine (protein/blood) (- / -)	3(+)/ excess	3(+)/ excess	4(+)/ excess		-- / few	-- / few
24-hour urinary protein: (< 150 mg)	2.4	4 g	2.8 g	1.9 g	< 150 mg	< 150 mg
Drug therapy:						
Corticosteroids						
Mycophenolate mofetil						
Rituximab						
Lisinopril dose				5	5 10	20 20
Amlodipine dose		10 mg		5	5 5	
Furosemide		40 mg				
Atorvastatin		40 mg				
Darbepoetin alfa		40 ug/ 2 weeks				

mmol/L. Urine routine and microscopy showed excess RBCs/HPF and proteinuria. Stool testing was negative for ova and parasites. Procalcitonin and blood cultures were negative. Viral studies were negative, especially Parvovirus B19, CMV and EBV. Results of repeat serological tests for autoimmune diseases remained within normal limits. Moreover, serum cryoglobulins were negative. Chest x-ray showed pulmonary venous congestion. Abdominal and pelvic ultrasound showed the same previous findings in addition to moderate ascites. Echocardiogram did not show valvular vegetations. After control of hypertension and excluding bacterial infection, percutaneous kidney biopsy was done 2 days later. It showed a total of 38 glomeruli of which 15 (39%) were globally sclerotic while the rest showed mesangial cell proliferation and focal segmental glomerulosclerosis (**Figure 1**). The interstitium showed tubular atrophy and severe fibrosis (60% of the sampled cortex). The arteries showed mild sclerosis without thrombi or vasculitis. Immunohistochemical stains showed 2(+) IgG and IgA at peripheral capillary loops (**Figure 2**). C3c and C1q were negative. On electron microscopic scans (EMS), dense deposits were evident in sub-epithelial, sub-endothelial and mesangial areas without tubuloreticular inclusions and organized deposits (**Figure 3**). Hence, diagnosis of "idiopathic" MesPGP was established. His immunosuppressive therapy was daily Solumedrol 1 g intravenously for 3 days followed by Prednisone 60 mg

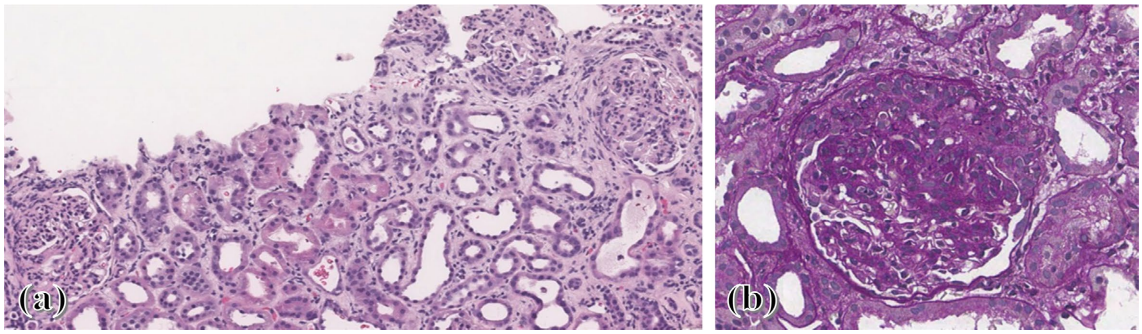

Figure 1. Photomicrograph of a kidney biopsy showing extensive mesangioproliferative glomerulopathy with interstitial fibrosis (H&E at ×200 in (a) and 400 in (b)).

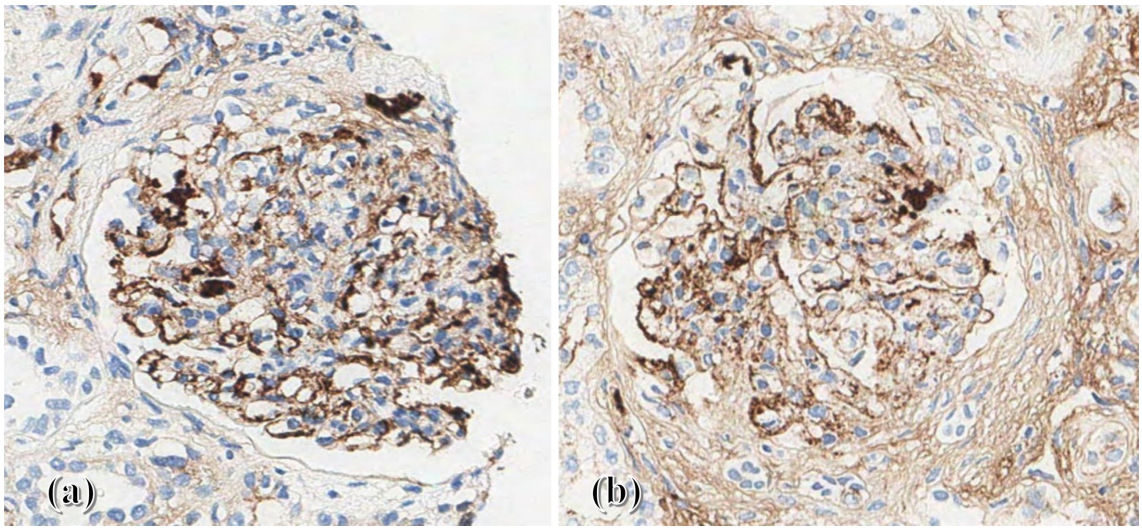

Figure 2. Photomicrograph of kidney biopsy showing (a) 2(+) positive peripheral immunoperoxidase staining for IgG and (b) for IgA.

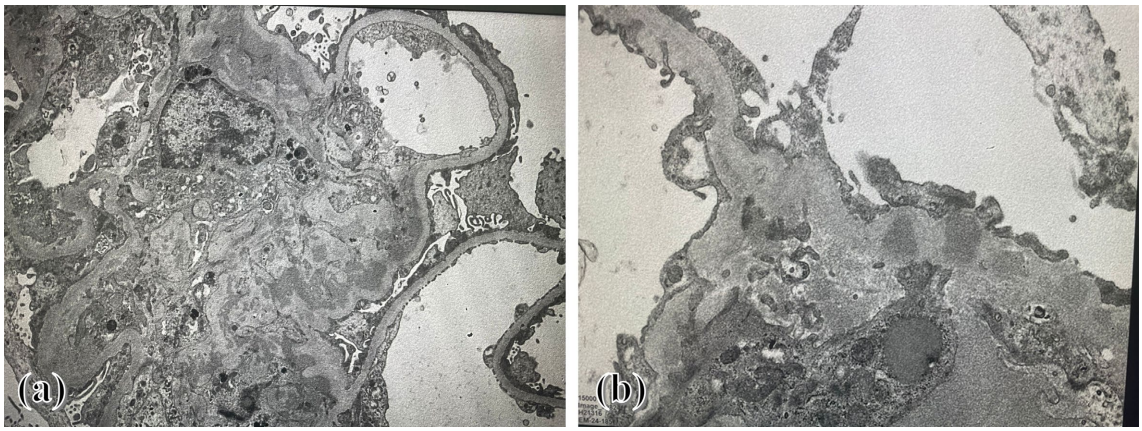

Figure 3. Photomicrograph of an electron microscopic sections of a kidney biopsy showing mesangial and subendothelial deposits in (a) and subepithelial in (b).

daily that was tapered gradually to 5 mg/day by the 3rd month. He also had received Mycophenolate mofetil (MMF) 1 g twice daily on day 1. Antihypertensive therapy was maintained in addition to Furosemide 80 mg daily to control his fluid

overload and Atorvastatin 40 mg daily for his high LDL-cholesterol. Moreover, he received Darbepoetin alfa, 40 ug subcutaneously every 2 weeks, to improve his symptomatic anemia to hemoglobin between 110 - 120 g/L. As shown in Table 1, the patient improved after 1 month of such therapy. After 3-months of such induction immunosuppressive-therapy; Rituximab was added, as a maintenance therapy, at a yearly dose of 1 g infusion over 4 hours followed by another 1 g infusion 2 weeks later. By the 3rd month; Prednisone was discontinued and MMF was withdrawn 1 month later. The patient remained in remission up to 1 year with Rituximab alone and will be using it for a minimum of 2 years.

3. Discussion

MesPGP is a non-specific GP characterized by capillary wall thickening associated with endothelial and mesangial cell proliferation with matrix expansion. It manifests with an acute renal injury associated with acute renal injury, fluid overload, proteinuria, and hematuria. It results from immune complex formation due to: 1) antigenemia of chronic infections (hepatitis B and C as well as endocarditis and malaria), autoimmune disorders (systemic lupus erythematosus and sarcoidosis), monoclonal gammopathies, cryoglobulinemia and cancer (chronic lymphocytic leukemia and lymphoma) or, 2) activation of the alternative pathway of complement [7]. As seen in Table 2, its etiology can be established by a combination of;

Table 2. Differential diagnosis of different types of mesangioprolifertive glomerulopathy (MesPGP).

Type	Light microscopy	Special stains	Imunostains	Electron microscopy	Serological tests
Idiopathic	Classic	NC	Capillary IgG+IgA	Subepithelial, subendothelial and mesangial deposits	NC
Poststrept/ infectious	Classic with neutrophils	NC	Starry (small & few) IgG & C3 along capillary walls & mesangium	Large (humps) subepithelial	High ASOT
Lupus	Classic + sclerosis + wire loops + necrosis + crescents		All immunoglobulins & C3	Subendothelial deposits & endothelial cells tubuloreticular inclusions	High ANA, antidsDNA + low C3 & C4
C3 glomerulopathy	Classic + sclerosis + wire loops	NC	Dense C3	None	Low C3
Dense deposit disease	Classic	NC	Dense C3	Dense deposits	Low C3
IgA	Classic + segmental sclerosis	NC	Mesangial IgA	Mesangial and subendothelial	High serum IgA
Cryoglobulinemic	Classic + cry	PAS (+) cryo capillary plugs	Mesangial IgM + monoclonal (kappa or lambda)		High serum cryoglobulins

Abbreviations: Classic MesPGP: capillary wall thickening and mesangial cellular proliferation, NC: non-contributary, PAS: Periodic acid-Schiff stain.

clinical manifestations, laboratory and serological testing and kidney biopsy. It should be noted that MesPGP without immune deposits and electron-dense deposits was reported in; late stage of thrombotic microangiopathies resulting from injury to the endothelial cells viz. thrombotic thrombocytopenic purpura or hemolytic–uremic syndrome, atypical hemolytic-uremic syndrome associated with complement abnormalities, the antiphospholipid antibody syndrome, drug-induced thrombotic microangiopathies, nephropathy associated with bone marrow transplantation, radiation nephritis, malignant hypertension, and connective-tissue disorder [8]. According to the Mayo clinic consensus; our patient presented with an "idiopathic" form of immune-complex of MesPGP since he had; typical light microscopic picture, IgG deposits on immunostains, and pericapillary deposits on EMS as well as negative clinical and serological evidence of systemic disorders [8]. Postinfectious MesPGP was excluded by the normal level of ASO and lack of large subepithelial deposits "humps" by EMS. The pericapillary deposits may suggest lupus nephritis, but he lacked lupus features in biopsy (light microscopy and immunostains) as well as clinical manifestations and serological markers. IgA nephropathy was another possibility; yet he did not have mesangial deposition of IgA and C3 [9]. C3 MesPGP and dense deposit disease were excluded since immunostains were negative for C3 [10]. Other causes of infection related GP, are not in keeping with the clinical and histological findings as well as immmunostains [11]. Lack of cryoglobulinemia as well as histological light chain capillary plugs and vasculitis; excluded cryoglobulinemia as an etiology [12]. Though transplant GP may show similar microscopic features, it was not the case of our patient [13]. Prognosis of MesPGP depends on its underlying etiology and efficacy of its treatment. Despite its rarity; idiopathic MesPGP is associated with poor outcome since; 1) Up to 50% - 60% of untreated patients will progress to end-stage kidney disease within 10 - 15 years, 2) spontaneous remission or improvement occurs in less than 10% of cases, 3) those presenting, as in our patient, with nephrotic syndrome, kidney insufficiency, hypertension and crescents have worse prognosis, and 4) worse kidney graft survival and a higher risk of relapse in kidney transplantation [14]. Previous treatment options were empirical and were based on case series and non-randomized clinical trials. They included: corticosteroids and antiproliferative agents (mycophenolate mofetil, cyclophosphamide), monoclonal antibodies (rituximab, bortezomib) or plasmapheresis [15]. In our case report, the choice of induction and maintenance therapy was based on the role of early cellular events in the development of glomerular and interstitial fibrosis [16]. In the antithymocyte serum model of MesPGP; mesangial cell proliferation is initiated by processes involving complement and platelets and may involve basic fibroblast growth factor. Mesangial cell proliferation is maintained by an autocrine mechanism involving upregulation of mesangial cell platelets derived growth factor and its receptors. Mesangial cells also change phenotype with expression of a smooth muscle actin and production of type I collagen leading to glomerular sclerosis. Moreover, such an acute GP is accompanied by upregulation

of mRNA and protein for osteopontin which is a macrophage chemotactic/adhesive factor expressed by cortical tubules that induces interstitial disease and subsequent fibrosis. Hence, we used a potent induction therapy with Mycophenolate mofetil and high-dose Corticosteroids followed by Rituximab; a potent and safe drug to block T-cells mediators. Fortunately, such intervention was safe and efficacious.

4. Conclusion

Idiopathic MesPGP should be reincluded in the classification of immune complex mediated GP and was amenable to our therapy protocol.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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