Two Years Comparative Study of the Pattern of Kidney Injury and the Different Therapeutic Modalities in the Acute Haemodialysis Unit in Kasr Al-Eini

Thesis

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By

Khaled Marzouk Sadek

M.B.B.CH, M.Sc.

Supervised by

Prof. Dr: Dawlat Mohamed Abd-El Hamid Belal

Professor of Internal Medicine and Nephrology
Faculty of Medicine
Cairo University

Prof.Dr: Manal Mohamed Nabeh Eldeeb

Professor of Internal Medicine and Nephrology
Faculty of Medicine
Cairo University

Prof.Dr. Bahaa El Den Mostafa Abd El Moaty

Assistant Professor of Internal Medicine and Nephrology
Faculty of Medicine
Cairo University

Prof.Dr. Dina Hesham Ahmed

Assistant Professor of Chemical Pathology
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
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Khaled Marzouk Sadek

Dedication

I dedicate this work to

*My beloved **family** especially*

*My **father**, My **mother***

&

*My **wife** who always show so much care,*

aid, support and patience.

I dedicate this work also to all dear professors from whom I learned as well as my sincere friends who support me.

Contents

Glomerular Disease

DEFINITION

Glomerular disease has clinical presentations that vary from the asymptomatic individual who is found to have hypertension, edema, hematuria, or proteinuria at a routine medical assessment to a patient with a fulminant illness with AKI possibly associated with life-threatening extrarenal disease.

In many patients the AKI improved and the kidney functions regress to normal level but in many patients this will progress to chronic kidney disease which many finally progress to end stage renal disease for regular haemodialysis .

The most dramatic symptomatic presentations are uncommon. Asymptomatic urine abnormalities are much more common but less specific; they may also indicate a wide range of non-glomerular urinary tract disease ***(Mundel et al., 2002).***

CLINICAL EVALUATION OF GLOMERULAR DISEASE

The history, physical examination, and investigations are aimed at excluding non-glomerular disease, finding evidence of associated multisystem disease, and establishing renal function ***(Machuca et al, 2009).***

Table (1-2): Clinical Presentations of Glomerular Disease

I) Asymptomatic	II) Macroscopic hematuria
1. Proteinuria 150 mg to 3 g per day. 2. Hematuria >2 red blood cells per high- power field in spun urine or >10 × 106 cells/liter (red blood cells usually dysmorphic).	1. Brown/red painless hematuria (no clots); typicallycoincides with intercurrent infection. 2. Asymptomatic hematuria ± proteinuria between attacks.
III) Nephrotic syndrome	**IV) Nephritic syndrome**
1. Proteinuria: adult >3.5 g/day; child >40 mg/h per m2. 2. Hypoalbuminemia <3.5 g/dl. 3. Edema. 4. Hypercholesterolemia. 5. Lipiduria.	1. Oliguria. 2. Hematuria: red cell casts. 3. Proteinuria: usually <3 g/day. 4. Edema. 5. Hypertension. 6. Abrupt onset, usually self-limiting.
V) Rapidly progressive glomerulonephritis	**VI. Chronic glomerulonephritis**
1. Hypertension. 2. Renal insufficiency. 3. Proteinuria often > 3 g/day. 4. Shrunken smooth kidneys.	1. Renal failure over days/weeks. 2. Proteinuria: usually < 3 g/day. 3. Hematuria: red cell casts. 4. Blood pressure often normal. 5. May have other features of vasculitis.

Hinkes et al., (2006)

History

The majority of glomerular diseases do not lead to symptoms that patients will report. However, specific questioning may reveal edema, hypertension, foamy urine, or urinary abnormalities during prior routine testing (e.g., during routine medical examinations). Multisystem diseases associated with glomerular disease include diabetes, hypertension, amyloid, lupus, and vasculitis. Apart from the individual history suggestive of these diseases, a positive family history may also be obtained in some cases ***(Sheerin et al., 2008).***

Other causes of familial renal disease may include Alport's syndrome (especially if it is associated with hearing loss), uncommon familial forms of IgA nephropathy, focal segmental glomerulosclerosis (FSGS), hemolytic-uremic syndrome (HUS), and other rare conditions. Morbid obesity can be associated with FSGS ***(Wolf et al., 2005).***

Certain drugs and toxins may cause glomerular disease; these include minimal change disease (MCD; nonsteroidal anti-inflammatory agents [NSAIDs] and interferon), membranous nephropathy (penicillamine; NSAIDs; mercury, for example, in skin-lightening creams), FSGS (pamidronate, heroin), and HUS (cyclosporine, tacrolimus, mitomycin C, oral contraceptives). Recent or persistent infection (especially streptococcal infection, infective endocarditis, and certain viral infections) may also be associated with a variety of glomerular diseases ***(Couser, 1998).***

Various malignant neoplasms are associated with glomerular disease. These include lung, breast, and gastrointestinal carcinoma (membranous nephropathy); Hodgkin's disease (MCD); non-Hodgkin's lymphoma (membrane oproliferative glomerulonephritis [MPGN]); and

renal carcinoma (amyloid). Patients will occasionally present with the renal disease as the first manifestation of a tumor ***(Atkins et al., 2006).***

Physical Examination

The presence of dependent pitting edema suggests the nephrotic syndrome, heart failure, or cirrhosis. In the nephrotic subject, edema is often periorbital in the morning, whereas the face is not affected overnight in edema associated with heart failure (because of orthopnea resulting from pulmonary congestion) or cirrhosis (because the patient cannot lie flat owing to pressure on the diaphragm from ascites). As it progresses, edema of genitals and abdominal wall becomes apparent, and accumulation of fluid in body spaces leads to ascites and pleural effusions. Yet surprisingly, edema may become massive in nephrotic syndrome before patients seek medical help; fluid gains of 20% of normal body weight are by no means unusual. The edema becomes firm and stops pitting only when it is long-standing. In children, fluid retention may also be striking with nephritic syndrome ***(Wolf et al., 2005).***

Chronic hypoalbuminemia is also associated with loss of normal pink color under the nails, resulting in white nails or white bands if the nephrotic syndrome is transient (Muehrcke's bands). Xanthelasmas may also be present as a result of the hyperlipidemia associated with the nephrotic syndrome ***(Reiser et al., 2004).***

The presence of pulmonary signs should suggest one of the pulmonary-renal syndromes. Palpable purpura maybe seen in vasculitis, systemic lupus, cryoglobulinemia, or endocarditis ***(Wolf et al., 2005).***

Laboratory Studies

Assessment of renal function and careful examination of the urine are critical. The quantity of urine protein and the presence or absence of dysmorphic red cells and casts will help classify the clinical presentation ***(Atkins et al., 2006).***

Certain serologic tests are also helpful. These include antinuclear and anti- DNA antibodies (lupus), cryoglobulins and rheumatoid factor (both suggestive of cryoglobulinemia), anti-glomerular basement membrane (anti-GBM) antibodies (Goodpasture's disease), anti-neutrophil cytoplasmic (ANCA) antibodies; vasculitis, and anti-streptolysin O titer or streptozyme test (poststreptococcal glomerulonephritis [GN]) ***(Wolf et al., 2005).***

Serum and urine electrophoresis will detect monoclonal light chains or heavy chains (myeloma-associated amyloid or light-chain deposition disease). Testing for the presence of ongoing bacterial or viral infections is also useful. This includes blood cultures and testing for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infection ***(Kaufman et al., 2010).***

Measurement of systemic complement pathway activation by testing for serum C3, C4, and CH50 (50% hemolyzing dose of complement) is particularly helpful in limiting the differential diagnosis ***(Sheerin et al., 2008).***

Imaging

Ultrasound scanning is recommended in the workup to ensure the presence of two kidneys, to rule out obstruction or anatomic abnormalities, and to assess kidney size. Renal size is often normal in GN, although large kidneys (>14 cm) are sometimes seen in

nephrotic syndrome as sociated with diabetes, amyloid, or HIV infection. Large kidneys can also occasionally be seen with any acute severe GN. The occurrence of small kidneys (<9 cm) suggests chronic renal disease and should limit enthusiasm for renal biopsy or aggressive immunosuppressive therapies ***(Wolf et al., 2005).***

Renal Biopsy

Renal biopsy is generally required to establish the type of glomerular disease and to guide treatment decisions. There are some situations, however, in which renal biopsy is not performed ***(Reiser et al., 2004).***

- If there are no unusual clinical features in nephrotic children.
- The probability of MCD is so high that corticosteroids can be initiated without biopsy.
- In acute nephritic syndrome, if all features point to poststreptococcal GN, especially in an epidemic, biopsy can be reserved for the minority who do not show early spontaneous improvement.
- In anti-GBM disease, the presence of lung hemorrhage and rapidly progressive renal failure with urinary red cell casts and high titers of circulating anti-GBM antibody establishes the diagnosis without the need for a biopsy, although a biopsy may still provide prognostic information ***(Machuca et al., 2009).***
- In patients with systemic features of vasculitis, a positive ANCA titer, negative blood cultures, and a tissue biopsy specimen from another site showing vasculitis are sufficient to secure a diagnosis of renal vasculitis.

Again, however, renal biopsy may provide important clues to disease activity and chronicity. Biopsy is also not generally performed in long-standing diabetes with characteristic findings suggestive of diabetic nephropathy and other evidence of microvascular complications of diabetes. Biopsy may also not be indicated in many patients with mild glomerular disease presenting with asymptomatic urine abnormalities as the prognosis is excellent and histologic findings will not alter management ***(Machuca et al., 2009).***

HISTOLOGIC CLASSIFICATION

Glomerular disease may have a wide variety of causes and clinical presentations. Some glomerular diseases are given the generic title of glomerulonephritis (GN), which implies an immune or inflammatory pathogenesis. Although there are some situations in which specific diagnosis can be made on the basis of clinical presentation and laboratory tests, a renal biopsy is useful for both classification and prognosis in most cases ***(Machuca et al, 2009).***

Ideally, the renal biopsy specimen should be examined by light microscopy, immunofluorescence, and electron microscopy. By use of this approach, a histologic pattern can be diagnosed. Some histologic patterns can be coupled with other laboratory test results to identify a specific etiology, but the condition is idiopathic in many cases. However, because treatments are often developed for specific histologic patterns, this approach is currently favored in the management of these disorders.

HISTOPATHOLOGY

The full assessment of a renal biopsy specimen requires light microscopy, electron microscopy, and examination for deposits of complement and immunoglobulin by immunofluorescence or immunoperoxidase techniques.

1) Light Microscopy

In GN, the dominant but not the only histologic lesions are in glomeruli **(Fig. 1.5).** GN is described as focal (only some glomeruli are involved) or diffuse. In any individual glomerulus, injury may be segmental (affecting only part of any glomerulus) or global. There is a potential for sampling error in a renal biopsy: the extent of a focal lesion may be misjudged in a small biopsy specimen, and sections through glomeruli may miss segmental lesions ***(Machuca et al., 2009).***

Lesions may also be hypercellular due to either an increase in endogenous endothelial or mesangial cells (termed proliferative) or an infiltration of inflammatory leukocytes (termed exudative). Severe acute inflammation may produce glomerular necrosis, which is often segmental ***(Reiser et al., 2004).***

The walls of the glomerular capillaries can also be thickened by a number of processes, which include an increase in glomerular basement membrane (GBM) material and immune deposits. Segmental sclerosis and scarring may also occur and are characterized by segmental capillary collapse with the accumulation of hyaline material and mesangial matrix and often with attachment of the capillary wall with Bowman's capsule (synechiae or adhesion formation) ***(Machuca et al., 2009).***

The classic stains used in light microscopy include hematoxylin and eosin and the periodic acid–Schiff (PAS) reaction, which is particularly good for evaluating cellularity and matrix expansion. More specific stains include methenamine silver, which stains GBM and other matrix black. It may, for example, reveal a double contour to the GBM because of the interposition of cellular material, or it may show increased mesangial matrix not easily seen with other techniques. Trichrome staining is also useful to show areas of scarring (stains blue), whereas immune deposits stain red ***(Reiser et al., 2004).***

Crescents are inflammatory collections of cells in Bowman's space. Crescents develop when severe glomerular injury results in local rupture of the capillary wall or Bowman's capsule, allowing plasma proteins and inflammatory material to enter into Bowman's space. Crescents consist of proliferating parietal and visceral epithelial cells, infiltrating fibroblasts, and lymphocytes and monocytes-macrophages, often with local fibrin deposition. They are called crescents because of their appearance when the glomerulus is cut in one plane for histology. They are destructive and rapidly increasing in size and may lead to glomerular tuft occlusion **(see Fig. 1.5).** If the acute injury is stopped, the crescents may either resolve with restitution of normal morphology or heal by fibrosis, causing irreversible loss of renal function. Crescents are most commonly observed with vasculitis, in Goodpasture's disease, and in severe acute GN of any etiology ***(Atkins et al., 2006).***

Tubulointerstitial injury and fibrosis can also accompany GN and may play an important role in the prognosis.

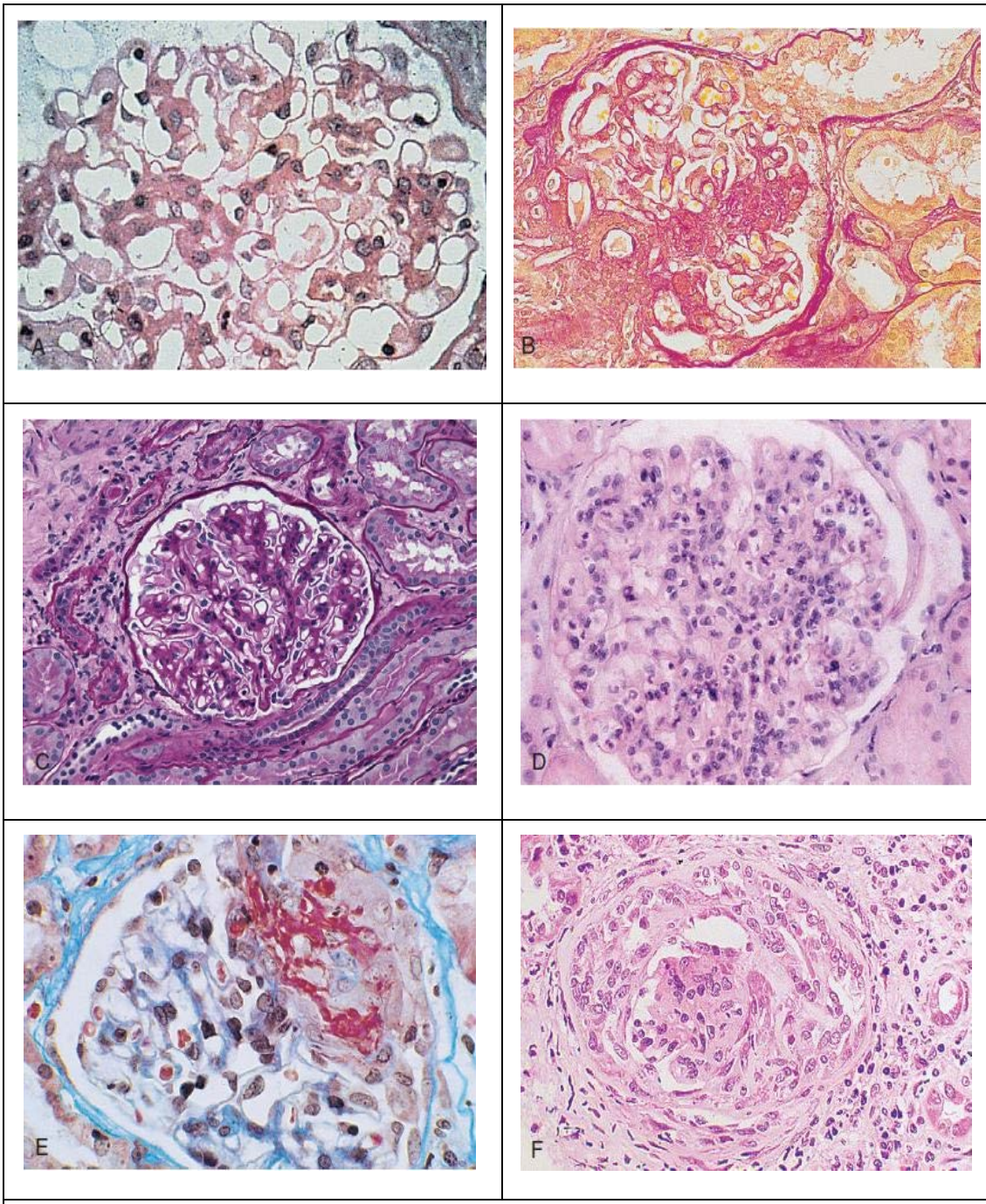

Fig. (1.5): Pathology of glomerular disease: light microscopy (Atkins et al., 2006). Characteristic patterns of glomerular disease illustrating the range of histologic appearances and the descriptive terms used. **A,** Normal glomerulus: minimal change disease. **B,** Segmental sclerosis: focal segmental glomerulosclerosis. **C,** Diffuse mesangial hypercellularity: IgA nephropathy. **D,** Diffuse endocapillary hypercellularity: poststreptococcal glomerulonephritis. **E,** Segmental necrosis: renal vasculitis. **F,** Crescent formation: anti–glomerular basement membrane disease. (**A** and **B,** Hematoxylin-eosin; **C, D,** and **F,** periodic acid–Schiff; **E,** trichrome.)

2) Immunofluorescence and Immunoperoxidase Microscopy

Indirect immunofluorescence and immunoperoxidase staining are both used to identify immune reactants **(Fig. 1.6).** Examination consists of staining for immunoglobulins IgG, IgA, and IgM; for components of the complement system (usually C3, C4, and C1q); and for fibrin, which is commonly observed in crescents and in capillaries in thrombotic disorders (such as hemolytic-uremic syndrome and the antiphospholipid syndrome) ***(Machuca et al., 2009).***

Immune deposits may occur along the capillary loops or in the mesangium. They may be continuous (linear) or discontinuous (granular) along the capillary wall or in the mesangium.

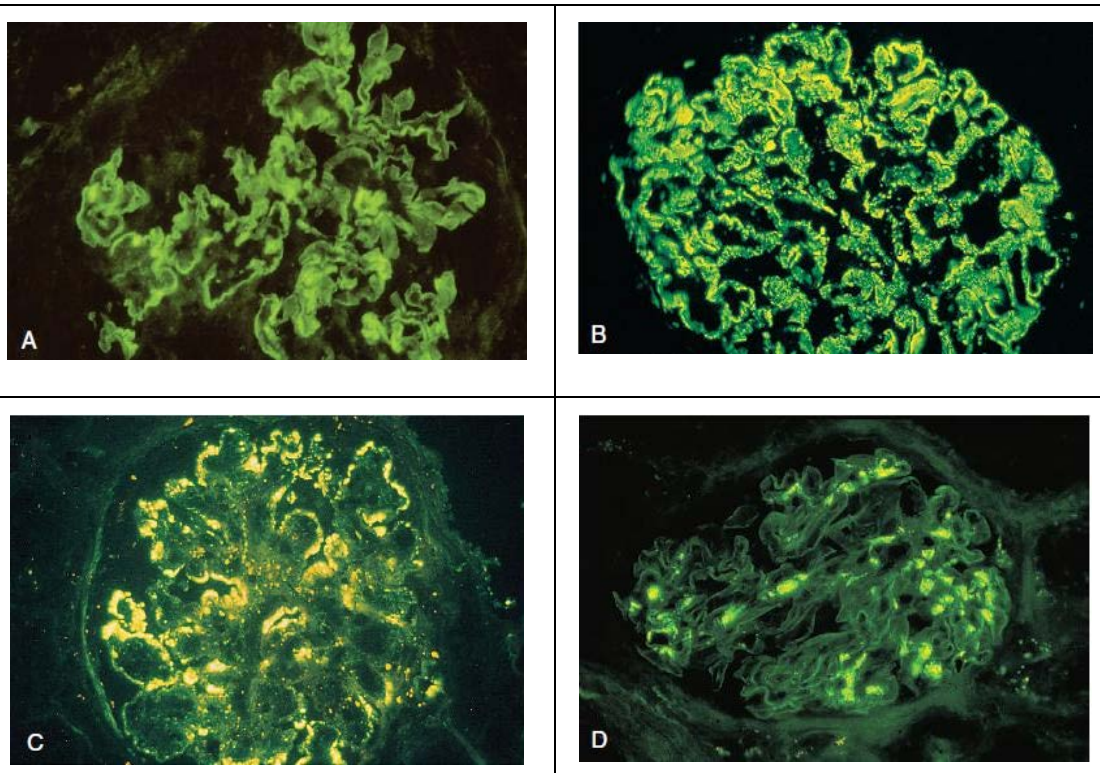

Figure (1.6): Pathology of glomerular disease: immunofluorescence microscopy. Common patterns of glomerular staining found by immunofluorescence. **A,** Linear capillary wall IgG: anti–glomerular basement membrane disease. **B,** Fine granular capillary wall IgG: membranous nephropathy. **C,** Coarse granular capillary wall IgG: membranoproliferative glomerulonephritis type I. **D,** Granular mesangial IgA: IgA nephropathy. **(Machuca et al., 2009)**