APPROACH TO GLOMERULAR DISEASE: CHRONIC GLOMERULONEPHRITIS, NEPHROTIC SYNDROME

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LEARNING OBJECTIVES

- List the history and physical examination findings, blood and urine testing results, that distinguish between the various syndromes by which glomerular disease may present
- List the common causes of primary nephrotic syndrome and common causes of secondary nephrotic syndrome; describe the pathophysiology and recognize the typical clinical presentation of each
- List and fully describe the characteristics of each stage of diabetic nephropathy
- List the mechanisms by with blocking the renin-angiotensin system provide a benefit in slowing the progression of diabetic nephropathy
- Distinguish the differences between microalbuminuria and overt proteinuria
- List the laboratory testing that is indicated in the evaluation of a patient with nephrotic syndrome

I. Initial Approach to Patients Glomerular Disease

As previously mentioned intrinsic renal injury can be categorized into disease states that primarily affect the glomerulus and those that target non-glomerular structures. In this lecture, the focus will be on glomerular disease and the syndromes by which glomerular disease may present.

Diseases of the glomerulus can present as one of five clinical syndromes: 1). chronic glomerulonephritis, 2). nephrotic syndrome, 3). acute glomerulonephritis, 4). rapidly progressive glomerulonephritis, and 5). asymptomatic hematuria and proteinuria. In approaching a patient with suspected glomerular disease determining which syndrome is present aids in narrowing the differential diagnosis. The clinical characteristics of the patient and urinalysis are useful tools in making this distinction.

Diseases that cause active inflammation within the glomerulus are typically associated with clinical features referred to as the ***nephritic syndrome***. This syndrome is characterized by signs and symptoms suggestive of *primary salt retention* by the kidney resulting in volume overload and circulatory congestion. Manifestations include hypertension, congestive heart failure, and peripheral edema. The urinalysis also reflects active glomerular inflammation and is described as nephritic in nature. A nephritic urinary sediment is characterized by a variable number of red blood cells, white blood cells, and red blood cell casts. *The finding of red blood cell casts is pathognomonic of active glomerulonephritis*. Protienuria is usually modest in degree ranging from 2-6 grams in a twenty four hour urine collection and the glomerular filtration rate is often severely reduced.

The ***nephrotic syndrome*** refers to a constellation of findings resulting from diseases that produce little in the way of active glomerular inflammation. The clinical characteristics of this syndrome result from the massive leakage of protein across the glomerular basement membrane. The development of hypoalbuminemia and subsequent decline in oncotic pressure cause intravascular fluid to translocate into the extravascular compartment giving rise to a contracted EABV.

The decline in EABV results in *secondary* renal salt retention. Unlike the nephritic syndrome hypertension is less prominent and findings of circulatory congestion are absent. Typically, the GFR is only mildly reduced. The urinalysis also reflects the lack of inflammation in the glomerulus. Characteristic findings include free fat droplets, oval fat bodies, fatty casts and only minimal amounts of cellularity. These findings along with large amounts of protein in the urine constitute a nephrotic urinary sediment.

Nephritic urinary sediment	Nephrotic urinary sediment
RBC casts RBC's WBC's Variable proteinuria in range of 2-6 gms	Heavy proteinuria >3.5 gms Oval fat bodies Fatty casts Free fat droplets

Nephritic syndrome	Nephrotic syndrome
Primary Na^+ retention Low urinary [Na^+] Hypertension common Edema Circulatory congestion resulting in congestive heart failure Severe reduction in GFR	Secondary Na^+ Retention Low urinary [Na^+] Hypertension may or may not be present Edema Less severe reduction in GFR

II. Overview of the Clinical Syndromes by which Glomerular Disease Can Present

A. Chronic glomerulonephritis

Chronic glomerulonephritis is a form of chronic kidney disease with characteristics suggesting some degree of glomerular involvement. The condition is characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in the glomerular filtration rate (GFR) and retention of uremic toxins. If disease progression is not halted with therapy, these patients develop progressive chronic kidney disease (CKD) and eventually end-stage renal disease (ESRD). The urinalysis demonstrates a few red cells and white cells but is mostly non-specific. A variable amount of proteinuria is present. Kidney size is typically small reflecting the presence of advanced fibrosis and glomerulosclerosis. Patients who present with this syndrome presumably have a glomerular disease (such as membranous glomerulopathy, focal and segmental glomerulosclerosis, membraboproliferative glomerulonephritis) that has progressed to end stage leaving the kidney irreversibly damaged. At the later stages of glomerular injury, biopsy results are not able to help distinguish the primary disease since fibrosis and sclerosis are the dominant findings.

B. Nephrotic syndrome

The nephrotic syndrome describes a patient who presents with a nephrotic clinical picture and a nephrotic urinary sediment. In addition to edema, hypoalbuminemia, and large amounts of urinary protein excretion, a number of other findings are typical of the nephrotic syndrome. These include hyperlipidemia, hypercoagulability, and a predisposition to infection with encapsulated gram positive organisms due to hypogammaglobulinemia. As with other clinical syndromes, the underlying cause of the nephrotic syndrome can be a primary renal disease or a systemic disorder that involves several organ systems to include the kidney.

Since the kidney can respond to injury in only a certain number of ways, systemic disorders often cause the same histologic picture as seen when the disease is primary to the kidney. For example, membranous glomerulopathy can be a primary renal disease or this same histologic pattern can develop in the setting of systemic lupus erythematosus or after exposure to gold as in the treatment of rheumatoid arthritis. The approach to the patient with nephrotic syndrome is directed toward distinguishing primary from secondary causes. Routine clinical evaluation may be sufficient to make this distinction but in many cases, additional laboratory tests are required.

C. Acute glomerulonephritis

Acute glomerulonephritis describes a patient who presents with the abrupt onset of a nephritic clinical syndrome accompanied by a nephritic urinary sediment. There is evidence of circulatory congestion manifested by hypertension and occasionally pulmonary congestion. Examination of the urine demonstrates red cells, white cells, and *red blood cell casts*. The GFR is relatively stable in contrast to the rapid fall in GFR seen with the syndrome of rapidly progressive glomerulonephritis. Acute glomerulonephritis is often associated with a preceding infection and can occasionally spontaneuously resolve. The work up is designed to determine whether the underlying disorder is a primary renal disease or a systemic disorder affecting the kidney.

D. Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis should be considered in patients who present with a nephritic clinical picture and who have a nephritic urinary sediment. What distinguishes these patients from those with acute glomerulonephritis is a rapid loss of renal function. Rapid loss of renal function is defined as a rise in the serum creatinine concentration of >2.0 mg/dl over a three-month period. Diseases that present in this manner have a much more inconsistent temporal relationship with infection and there is little tendency for spontaneous recovery. This syndrome needs to be recognized early as renal biopsy is indicated so that therapy can be instituted immediately. In a patient with renal biopsy evidence of a crescentic glomerulonephritis, immunofluorescent studies provide a useful classification of the diseases that most commonly give rise to this clinical syndrome.

E. Asymptomatic hematuria and or proteinuria

This syndrome describes a patient who is found to have hematuria or proteinuria but who is otherwise without clinical symptoms. Such patients may initially come to clinical attention on a routine physical examination when abnormalities are detected on a routine urinalysis. IgA nephropathy and thin basement membrane disease commonly present in this fashion.

With the above overview in mind, a more detailed discussion of the glomerular clinical syndromes will now be presented.

III. Chronic Glomerulonephritis

A patient with chronic glomerulonephritis presents with features of glomerular disease but have findings indicative of irreversible chronic kidney disease. The kidney size is typically small reflecting extensive fibrosis and glomerulosclerosis. The urinalysis may demonstrate a minimal amount of activity (few WBC's and a few RBC's) but is mostly non-specific. A variable amount of proteinuria is present. Patients who present with this syndrome presumably have a glomerular disease that is no longer active. The kidney is left irreversibly damaged.

There is no specific therapy to offer at this stage of the disease other than conservative management to include strict blood pressure control.

IV. Nephrotic Syndrome

This syndrome describes an individual who presents with a nephrotic clinical picture and a nephrotic urinary sediment. The hallmark of the nephrotic syndrome is proteinuria greater than 3.5 g/24 hr. It is very unusual for proteinuria of this magnitude to be caused by a condition other than glomerular disease. In the absence of a 24-hour urine collection, a spot urine collection can be used to estimate the degree of proteinuria. A normal urinary protein-to-creatinine ratio (mg/mg) is less than 0.15 predictive of a 24 hour urine collection of approximately 150 mg/day. A ratio of .750 is predictive of 750 mg of total protein in a 24 hour collection, a ratio of 4 is predictive of 4 grams total protein in a 24 hour collection, and so forth. A standard urine dipstick is merely a screen for proteinuria and only registers positive when urinary protein excretion typically exceeds 300 to 500 mg/day.

In addition to edema, hypoalbuminemia, and large amounts of urinary protein excretion, a number of other findings are typical of the nephrotic syndrome. These include hyperlipidemia, hypercoagulability, and a predisposition to infection. There is typically evidence of secondary Na^+ retention by the kidney.

Patients who present with the nephrotic syndrome may have a systemic disorder that is affecting the kidney or the disease may be primary to the kidney. The most common primary glomerular diseases causing nephrotic syndrome in adults are minimal change disease, focal and segmental glomerulosclerosis (FSGS), membranous nephropathy, and occasionally membranoproliferative GN. Although these histologic patterns are usually idiopathic when the disease is primary to the kidney, each histology can also develop secondary to an underlying systemic disease. For example, minimal change disease can lead to development of nephrotic syndrome in the absence of an identifiable systemic disorder or this same histology can develop as a complication of Hodgkins lymphoma. Two other systemic disorders that commonly affect the kidney and give rise to nephrotic syndrome are diabetes (diabetic nephropathy) and amyloidosis.

A. Minimal change disease (MCD; also called nil disease or lipoid nephropathy) is the most common cause of idiopathic nephrotic syndrome in children, accounting for 90 percent of cases under the age of 10 and more than 50 percent in older children. It is generally under-appreciated that this disorder also accounts for 15 to 20 percent of cases in adults of all ages. The plasma creatinine concentration is usually normal. The terms minimal change and nil disease reflect the observation that light microscopy in this disorder is either normal or reveals only mild mesangial cell proliferation. Immunofluorescence and light microscopy typically show no evidence of immune complex deposition. The characteristic histologic finding in minimal change disease is diffuse fusion of the epithelial cell foot processes on electron microscopy.

While most cases of MCD are idiopathic some patients may have an identifiable secondary cause. Non-steroidal anti-inflammatory drugs (NSAID), particularly fenoprofen, can give rise to nephrotic syndrome with histologic findings of MCD. Most, but not all, patients with this disorder have a concurrent acute interstitial nephritis. A similar combined disorder has been reported with ampicillin, rifampin, and interferon. Discontinuation of drug therapy leads to spontaneous resolution of the nephrotic syndrome.

MCD may be associated with hematologic malignancies, particularly Hodgkin's disease and less often other lymphomas or leukemias. In contrast, solid tumors usually produce an immune complex-mediated disease such as membranous nephropathy. The activity of the renal disease in this setting typically parallels that of the malignancy, with the proteinuria disappearing when remission is induced by radiation or chemotherapy.

B. Focal glomerulosclerosis (FGS; also called focal segmental glomerulosclerosis, FSGS) is becoming an increasingly important cause of the nephrotic syndrome in adults and remains a frequent cause in children and adolescents. It is the most common cause of idiopathic nephrotic syndrome in adult black patients.

FGS is characterized on light microscopy by the presence in some but not all glomeruli (hence the name focal) of segmental areas of mesangial collapse and sclerosis. Mild mesangial hypercellularity and partial occlusion of the capillary lumens by hyaline deposits are commonly seen. The focal nature of the sclerotic lesions means that some mild cases of FGS will be missed due to sampling error and misclassified as minimal change disease. Immunofluorescence microscopy usually reveals no immune deposits, except for what is thought to represent *nonspecific* binding of IgM and complement in sclerotic lesions. Electron microscopy in primary FGS shows diffuse fusion of the epithelial cell foot processes, similar to that seen in minimal change disease. *In secondary forms of FGS effacement of the epithelial cells is less continuous.* It is important to recognize that focal segmental sclerosis can occur as a primary renal disease or develop in a variety of secondary settings.

Primary FGS is an idiopathic (primary) disease that, in many cases, is thought to be etiologically related to but more severe than minimal change disease. In addition to the histologic similarities, some patients with biopsy-proven minimal change disease later progress to FGS, while occasional patients with FGS follow a frequently relapsing, steroid-responsive course similar to that in minimal change disease. Although the vast majority of cases of primary FGS are idiopathic, familial forms of FGS have also been described. It should be emphasized that, because of the focal nature of the glomerular lesions, sampling error on renal biopsy can cause minimal change disease to be diagnosed in a patient with underlying FGS. In the absence of sclerotic lesions in the glomeruli, the only potential clue to the presence of FGS is areas of tubular atrophy and interstitial fibrosis, features not typically seen in minimal change disease.

Injury to the visceral epithelial cell or podocyte appears to be the primary problem in most forms of FSGS. Research is focusing on the role of circulating factors that may be mediating this injury. In addition, a number of genetic forms of FSGS have been described and may account for a significant proportion of patients with steroid-resistant disease. In general, the genes involved encode for proteins that are integral for proper glomerular basement membrane formation and/or glomerular podocyte differentiation and function. These include the gene(s) for podocin, nephrin, alpha-actinin-4, and the TRPC6 ion channel.

Individuals with recent African ancestry carry an excessive burden of CKD and ESKD compared with individuals of other ancestries, even after adjusting for socioeconomic status and lifestyle and clinical factors (eg, diet and hypertension). Many of these patients are labeled as having kidney disease related to effects of mild to moderate hypertension. However, recent trials reveal that aggressive blood pressure control using angiotensin-converting enzyme inhibitors fails to slow nephropathy progression in patients with kidney disease attributed to hypertension and that nonhypertensive causes of kidney disease are often present.

There is evidence to suggest that many of these individuals with nondiabetic causes of ESKD have nephropathy caused by the G1 and G2 renal-risk variants in the apolipoprotein L1 gene (APOL1). Renal histology reveals lesions in the spectrum of focal segmental glomerulosclerosis (FSGS) and solidified (global) glomerulosclerosis, often with pronounced vascular and interstitial changes, particularly among the African American population. APOL1 renal-risk alleles have been reported only on African-derived chromosomes, including individuals from Africa and recently admixed individuals from the United States or Caribbean. The G1 and G2 variants are believed to have reached these high frequencies in West Africa due to recent events of positive selection. The driving force for the high frequency is thought to be the African Trypanosoma parasites, which are transmitted by the tsetse fly and are responsible for African sleeping sickness or trypanosomiasis. Both G1 and G2 can restore in vitro APOL1 trypanolytic activity against Trypanosoma brucei (Tb) rhodesiense, the parasite distributed across East and Central Africa and causing the acute form of the disease (2% of all trypanosomiasis cases) and delay its parasitemia in vivo in mouse models.

Focal glomerulosclerosis can develop as a secondary complication of other conditions. Secondary focal glomerulosclerosis may be induced by the adaptive response to nephron loss as occurs with many causes of chronic kidney disease, including non-glomerular disorders such as reflux nephropathy and ischemia in benign hypertensive nephrosclerosis. Nephron loss leading to glomerulosclerosis can also occur when there is a marked reduction in renal mass due to congenital absence or surgical removal. In these settings, compensatory intra-glomerular hypertension and hypertrophy in the remaining glomeruli lead to an increase in the nephron filtration rate that will initially tend to maintain the total GFR. Over a period of years, however, high intraglomerular pressure may lead to focal glomerulosclerosis. Segmental areas of glomerulosclerosis can be induced by intra-glomerular hypertension resulting from primary renal vasodilatation as occurs in diabetic nephropathy and sickle cell anemia. It has been proposed that hemodynamic changes are also responsible for the development of FGS in occasional patients with massive obesity. Finally, FGS can also be seen in a number of other disorders in which the pathogenesis is uncertain including HIV infection, heroin abusers, and cyanotic heart disease.

Up to 50% of patients with FGS and persistent nephrotic range proteinuria develop end-stage renal disease within 5 years. The renal prognosis is directly related to the amount of proteinuria. The presence of massive proteinuria (>10 gm/24h) is, in particular, associated with a poor prognosis.

Collapsing variant of FSGS:

A variant of FGS, called collapsing focal glomerulosclerosis, is being increasingly reported. It is distinguished from primary FGS by collapse and sclerosis of the entire glomerular tuft, rather than segmental injury. This more severe disorder, which may be idiopathic or induced by HIV infection, generally is resistant to therapy and follows a rapid downhill course.

HIV-Associated nephropathy (HIVAN)

HIVAN accounts for the majority of biopsy-proven glomerular disease in patients with HIV infection. This condition particularly affects black patients with HIV infection. HIVAN is not associated with a particular opportunistic infection or stage of infection with HIV. Patients with this condition have evidence of direct viral infection of glomerular visceral epithelial cells. HIVAN is characterized by the nephrotic syndrome, decreased kidney function, and rapid progression to ESRD. Patients with HIVAN usually do not have edema or hypertension. On ultrasonography, the kidneys are typically large and highly echogenic.

Kidney biopsy in patients with HIVAN may reveal segmental glomerulosclerosis, more commonly the collapsing variant, but tubular cystic lesions are characteristic of this condition. The presence of tubuloreticular bodies seen on electron microscopy of a biopsy specimen further supports the diagnosis. Many patients initially diagnosed with HIVAN already have advanced disease, but better screening practices are causing earlier detection of HIV-related kidney disease. Use of highly active antiretroviral therapy (HAART) can lead to a beneficial effect on renal outcomes as measured by decreases in proteinuria and a reduction in new-onset ESRD.

C. Membranous Glomerulopathy

Membranous nephropathy derives its name from the characteristic thickening of the GBM that is the hallmark of this disease. Membranous nephropathy is the most common cause of the nephrotic syndrome in white adults and is the leading cause of the nephrotic syndrome in persons older than 60 years. In adults, 80% of cases are idiopathic; the remaining 20% are due to secondary causes. The most common secondary causes are systemic lupus erythematosus, hepatitis B infection, drugs (e.g., gold, penicillamine), and solid tumors in the elderly. The term membranous nephropathy reflects the primary histologic change noted on light microscopy: basement membrane thickening with little or no cellular proliferation or infiltration. Electron microscopy reveals electron dense deposits across the glomerular basement membrane (GBM) in the subepithelial space. The immune nature of these deposits is confirmed by immunofluorescence microscopy, which usually demonstrates the presence of IgG, other immunoglobulins, and complement.

Membranous nephropathy is characterized by deposits that develop on the subepithelial surfaces of the glomerular capillary wall, mainly on the podocytes. An autoantibody targeting the M-type phospholipase A_2 receptor (PLA2R), an antigen normally expressed on the surface of podocyte-cell membranes, has been discovered. It has been suggested that cases of idiopathic membranous nephropathy may actually be cases of an autoimmune disease targeting podocytes with autoantibodies to PLA2R. Approximately 75 to 80% of cases of primary membranous nephropathy are associated with a positive test for antibodies to PLA2R at the time of diagnosis. Because the PLA2R allele is particularly overrepresented in those of European descent, studies cite membranous nephropathy as the most common cause of nephrotic syndrome in the white population.

D. Membranoproliferative Glomerulonephritis (MPGN)

Membranoproliferative glomerulonephritis (MPGN; also called mesangiocapillary or lobular glomerulonephritis) is an uncommon cause of glomerular disease that can either be a primary disorder or develop in the setting of a systemic disease. The idiopathic form of the disease generally occurs between the ages of 8 and 30. Secondary MPGN is most often associated with autoimmune diseases such as SLE or Sjogren syndrome, infections such as hepatitis C virus or poststreptococcal or infective endocarditis, or certain malignancies.

The name of this disorder is derived from the characteristic histologic changes seen on light microscopy: thickening of the glomerular basement membrane (GBM), due to immune complex deposition and to interposition of the mesangial cell cytoplasm between the GBM and the endothelial cell; and hypercellularity, often leading to a lobular appearance of the glomerular tuft. The increased cellularity results from both proliferation of the mesangial cells and influx of circulating monocytes. This activity in the glomerulus accounts for why some patients with MPGN may exhibit a urinary sediment with more activity than other primary glomerular diseases that cause nephrotic syndrome.

Three histologic forms of MPGN have been identified on electron microscopy, with type 1 being by far the most common:

- *Type 1* (common) is characterized by discrete immune deposits in the mesangium and subendothelial space. However, these findings are not specific for idiopathic MPGN, since they are thought to reflect the deposition of circulating immune complexes. Thus, patients with type 1 MPGN should be evaluated for secondary causes such as lupus, hepatitis C virus infection, subacute bacterial (infective) endocarditis or infection of a ventriculo-atrial shunt, and mixed cryoglobulinemia.

- *Type 2* is also called dense deposit disease, because it is characterized by continuous, dense ribbon-like deposits along the basement membranes of the glomeruli, tubules, and Bowman's capsule. This condition is usually diagnosed in children between 4 and 15 years of age who present with hematuria accompanied by proteinuria, acute nephritic syndrome, or the nephrotic syndrome. The origin of these deposits is at present not well understood but recent evidnce suggest genetic or acquired dysregulation of the alternative complement system. Immunofluorescence microscopy is generally negative for immunoglobulins but occasionally can be positive for C3 nephritic factor. Type 2 MPGN can also be seen in association with partial lipodystrophy.

- *Type 3* is an immune complex disease, similar to type 1. However, subepithelial deposits are prominent in type 3 and there is complex disruption of the glomerular basement membrane with large lucent areas. How this occurs is not well understood.

Based on a recent proposal, MPGN can also be classified as either **immune complex-mediated** or **complement-mediated**. Immune-complex mediated MPGN shows immunoglobulin and/or complement factors on IF studies. Complement-mediated MPGN shows complement factors but significant immunoglobulin staining is absent on IF studies. Immune complex-mediated MPGN results from chronic infections, autoimmune diseases and monoclonal gammopathies. Complement-mediated MPGN is caused by genetic or acquired dysregulation of the alternative pathway of complement and can be further classified into C3 glomerulonephritis and Dense Deposit Disease (DDD). On electron microscopy, C3 glomerulonephritis can be differentiated from DDD by the presence of electron-dense, osmophilic deposits, replacing the lamina densa and producing a smooth, ribbonlike thickening in patients with DDD.

Immune-complex mediated MPGN due to an infection is mainly secondary to hepatitis C virus (HCV). This infection can lead to development of circulating cryoglobulins and result in cryoglobulinemic glomerulonephritis. The clinical presentation is variable and can include nephrotic and nephritic features. In patients with cryoglobulinemic MPGN, the levels of C3, C4, and CH50 are persistently low, reflecting activation of both complement pathways (classical and alternative). On the other hand, patients with C3 glomerulonephritis or DDD may have persistently low levels of C3 but a normal level of C4. A C3 nephritic factor is present in some cases of DDD. C3 nephritic factor is an autoantibody to the alternative pathway C3 convertase, resulting in persistent breakdown of C3.

The absence of well-designed studies hinging on the current knowledge of the multiple pathogenic processes that impart a MPGN pattern of injury to the kidney make it impossible to give strong treatment recommendations. From a practical point of view, patient with MPGN secondary to chronic infections (e.g. hepatitis C, endocarditis), autoimmune disease and plasma cell dyscrasias should undergo treatment of the underling disease.

Hepatitis Associated Kidney Disease

In the evaluation of patients with nephrotic syndrome, hepatitis B and C serology is typically obtained. Hepatitis C virus-associated kidney disease most often manifests as membranoproliferative glomerulonephritis either with or without cryoglobulinemia. Hypertension is commonly present and edema is present in most patients. Nephrotic range proteinuria and a mildly nephritic urinary sediment is commonly present. Rapidly progressive glomerulonephritis develops in 20% of patients with membranoproliferative glomerulonephritis and cryoglobulinemia, but terminal kidney disease is rare. The treatment of this disorder is centered on treatment of the underlying hepatitis C infection. Less commonly hepatitis C virus infection may cause a secondary membranous glomerulopathy.

Patients with hepatitis B surface antigenemia are at risk to develop a secondary membranous lesion and nephrotic syndrome. Much less commonly, Type I membranoproliferative glomerulonephritis can develop in patients with hepatitis B antigenemia. Hepatitis B surface antigenemia is also commonly present in patients with the classical from of polyareritis nodosa.

E. Other Secondary Causes of the Nephrotic Syndrome

1. Amyloidosis

Amyloidosis refers to numerous conditions caused by deposition of abnormal fibrillary structures that are composed of precursor proteins. Manifestations of amyloidosis vary with the organ or site involved. In patients with kidney amyloidosis, proteinuria and kidney dysfunction are typically severe, but mild disease may occur. More than 25% of these patients have the nephrotic syndrome at the time of diagnosis. Biopsy of abdominal fat or rectal or duodenal mucosa is indicated if there is suspicion for systemic amyloidosis. Affected tissues stained with Congo red should reveal characteristic apple-green birefringence under polarized microscopy.

Amyloidosis is classified according to the type of protein deposited. AL amyloidosis is the most common type of systemic amyloidosis in the United States. This condition is a primary disorder associated with deposition of immunoglobulin light chain or a fragment of a light chain. Detection of monoclonal immunoglobulin in serum, blood, or tissues differentiates AL amyloidosis from other forms of amyloidosis. AL amyloidosis can be treated with chemotherapeutic regimens such as high dose melphalan and autologous peripheral stem cell transplantation.

AA amyloidosis accounts for 45% of cases of systemic amyloidosis worldwide and is more common in developing countries. This condition is caused by deposition of the amyloid A protein that is a fragment of serum amyloid A, which is an acute phase reactant produced by the liver. AA amyloidosis develops secondary to chronic inflammatory states (chronic decubitus ulcers, rheumatoid arthritis, chronic osteomyelitis) and is associated with injection drug use (skin popping). The diagnosis of amyloidosis should be considered in patients with long-standing, chronic inflammatory disease who develop a pattern of multiorgan dysfunction, especially if the kidneys, liver, or bowel is involved. Control of the underlying infection is usually indicated for patients with AA amyloidosis. Colchicine may be effective for AA amyloidosis which may develop secondary to Familial Mediterranean Fever.

Familial (AF) amyloidosis is an autosomal dominant disorder that may be caused by abnormalities of transthyretin. Disorders of the fibrinogen A alpha chain also can cause hereditary amyloidosis. AF amyloidosis should be considered in patients with signs and symptoms of AL or AA amyloidosis with a clear cut inheritance pattern.

2. Diabetic Nephropathy

One of the most common secondary causes of the nephrotic syndrome is diabetic nephropathy. In the setting of long standing diabetes mellitus, the development of persistent albuminuria, increased blood pressure, and a declining glomerular filtration rate collectively constitute the clinical syndrome of diabetic nephropathy. Once established, the natural history of this lesion is characterized by a progressive decline in renal function eventuating in end-stage renal disease 5 to 10 years later. Diabetic nephropathy has become the single most common cause of renal failure in the United States today accounting for nearly one third of all patients enrolled in the medicare end stage renal disease program.

Renal failure is known to occur in both insulin-dependent diabetes mellitus (IDDM) and non-insulin--dependent diabetes mellitus (NIDDM). Approximately 45% of all patients with IDDM will develop nephropathy usually after 15 to 20 years duration of the disease. The frequency of nephropathy in NIDDM ranges from 8-20%. Despite this lower risk of renal involvement, patients with NIDDM constitute the majority of patients with diabetic end-stage renal disease since the total number of patients with NIDDM is much greater.

a. Natural history: Clinico-pathologic classification:

A useful framework for relating the clinical and histologic progression of diabetic renal disease views diabetic nephropathy as a continuum with several distinct stages.

Stage I: Renal hypertrophy and hyperfunction

In newly diagnosed patients with IDDM both kidney size and glomerular filtration rate (GFR) are typically increased. Microscopically, increased kidney volume results from enlargement of the glomeruli as well as renal tubules. In the glomeruli, capillary-surface area and mesangial volume are both increased.

Stage II: Clinically silent renal disease

Two to three years after diagnosis, patients enter a stage of disease characterized by the development of histologic abnormalities which are clinically silent. The GFR remains in the supernormal range and albuminuria is absent. On occasion, with marked hyperglycemia or ketosis, after severe exercise or intercurrent febrile illness, urinary protein excretion may increase transiently but becomes undetectable with improved metabolic control or resolution of the illness.

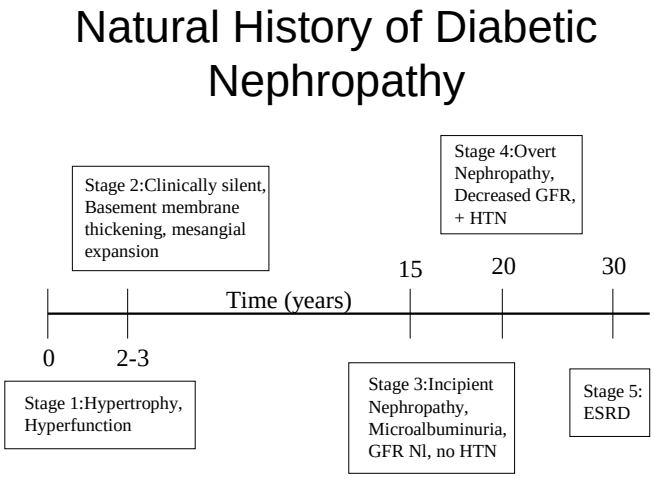
Stage III: Incipient nephropathy

Approximately 25% to 40% of patients with IDDM progress to a stage clinically characterized by the appearance of sustained microalbuminuria after 10 to 15 years of diabetes. Patients who advance to this stage are at high risk to develop overt diabetic nephropathy.

Microalbuminuria refers to increased urinary albumin excretion above the upper limit of normal but not yet detectable by standard clinical tests. Under normal circumstances, total urinary protein excretion ranges between 100 and 150 mg/24 hours. Of that total protein, the amount of albumin excreted in healthy subjects is less than 30 mg/24 h. The preferred way to screen for microalbuminuria is to obtain a spot urine and measure the albumin to creatinine ration (mg albumin/g creatinine) The normal ratio is <30. A ratio between 30-300 is microalbuminuria (the urine dipstick is negative in this range). A ratio >300 is overt or macroalbuminuria (urine dipstick is now positive).

Stage IV: Overt diabetic nephropathy

Clinical diabetic nephropathy develops in approximately 40% of patients with IDDM after 25 to 30 years of follow up. Microalbuminuria has progressed into clinically detectable proteinuria of more than 500 mg/day and often into the nephrotic range. Hypertension is well established and GFR has begun to decline. The decline in GFR is fairly predictable in individual patients and can range from 0.5 to 2.5 ml/min per month. Most patients will require some form of renal replacement therapy in the following 10 years.



b. Pathophysiologic mechanisms of diabetic nephropathy:

Evidence supporting a role for hemodynamic factors in the progression of diabetic nephropathy initially came from animal models in which renal mass was experimentally reduced. Surgical reduction in renal mass leads to a compensatory increase in GFR in the remaining nephrons. In this model, glomerular capillary plasma flow is increased owing to a decrease in the resistance of both the afferent and efferent arterioles. Glomerular capillary hydraulic pressure increases, however, because the decrease in afferent arteriolar resistance is proportionately greater than that in the efferent arteriole. The increase in glomerular capillary plasma flow and increase in capillary hydraulic pressure account for the increased single nephron GFR.

Initially, these hemodynamic changes serve to maintain kidney function but over time these alterations become maladaptive in that they contribute to a syndrome of proteinuria, glomerular sclerosis, and ultimately progressive azotemia. Evidence which supports a hemodynamic basis for the development of glomerular injury comes from studies in which these hemodynamic alterations are mitigated and the development of glomerular structural change is slowed. For example, dietary protein restriction has been shown to lower single nephron GFR by reducing both glomerular capillary plasma flow rate and glomerular capillary hydraulic pressure. Accompanying these changes is a reduction in glomerular structural lesions and proteinuria.

ACE inhibitors and angiotensin receptor blockers also lower glomerular capillary hydraulic pressure as these agents preferentially dilate the efferent arteriole. These agents have been shown in clinical trials to provide a renal protective effect beyond blood pressure control in patients with overt diabetic nephropathy as well as in patients with only microalbuminuria. In addition to blocking the renin-angiotensin system, the optimal treatment of diabetic patients with renal disease includes strict systemic blood pressure control, tight glycemic control, and aggressive treatment of lipids.

V. Summary: Approach to the Patient with Nephrotic Syndrome

The key to the approach to the patient with nephrotic syndrome is to distinguish between a primary or secondary cause of the glomerular disease. The history and physical exam is often helpful in making this distinction. In addition, the following laboratory tests are often utilized for this purpose.

Laboratory tests to evaluate the patient with nephrotic syndrome:

- Anti-nuclear antibody (ANA), rheumatoid factor (RF)
- Complement levels (C3 and C4)
- Hepatitis B surface antigen and hepatitis C serology, HIV
- Rapid plasma reagin (RPR, to detect secondary syphylis), anti-streptolysin O (ASO) titer
- Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP)
- Consider renal biopsy

Case presentation

History: 38 year old black man presents with a several week history of lower extremity edema. The patient denies use of OTC NSAID's and is taking no prescribed medications. There is no history of fever, joint pains, or rash. His past medical history is unremarkable and he denies use of intravenous drugs.

Physical examination: Well-developed, well-nourished black man, BP 156/94, pulse 76 bpm, respiratory rate 18 breaths per min, afebrile. The remainder of the examination is only remarkable for 2+ lower extremity edema.

Labs (mEq/l) Na 138, K 4.4, Cl 103, HCO3 24, (mg/dl) creatinine 1.8, BUN 24, albumin 1.7 g/dl, cholesterol 422
UA: SG 1.017, 4+ protein, 2-4 WBC/HPF, 3-5 RBC/HPF, oval fat bodies
24 hour urine: CrCl 48 ml/min, 8.5 gm protein, Nl sized kidneys by sonography
Serologic studies: (-) or normal to include ANA, RF, hepatitis B and C, HIV, RPR, ASO, SPEP, UPEP, C3 and C4. There is nothing in the history of physical examination to suggest a secondary cause of the nephrotic syndrome.

Differential Diagnosis of Idiopathic Nephrotic Syndrome:

- Minimal change disease
- Focal and segmental glomerulosclerosis
- Membranous glomerulopathy
- Membranoproliferative glomerulonephritis
- IgA nephropathy

A renal biopsy will help determine the etiology of the nephrotic syndrome in this case.