Hashemite University
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Scientific Team
الفريق العلمي

PATHOLOGY

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-يعطيكم العافية التلخيص بيشمل من موضوع membranous Gn ولغاية ال hereditary nephritis
-الشرح باللون النهدي وحيكون من كتاب باثوما ومن اسموسيز

-بالبداية ال nephrotic syndrome بتشمل :
MCD-1
FSGS-2
MGN-3
Membranous proliferative GN-4
diabetes mellitus-5
systemic amylodosis-6

-Membranous GN (MGN) =Membranous Nephropathy MN)

-most common nephrotic synd in Caucasian adults.
-A slowly progressive disease, most common in the 30-50 years age group, characterized by the presence of:
(I) diffuse thickening of the capillary wall.
(II) sub epithelial immunoglobulin-containing deposits.

-Pathogenesis

-MGN is a form of chronic immune complex nephritis.
-Although circulating complexes of known exogenous (e.g., hepatitis B virus) or endogenous (DNA in SLE) Ag can cause MGN, it is now thought that most idiopathic MGN are induced by Abs reacting in situ to endogenous, or, planted G Ags.

-Types of Membranous glomerulonephritis:

عادة بكون idiopathic ولكن ممكن يكون مصاحب ل HBV or HCV او solid tumor او SLE او Drug زي pencillamine, NSAIDS حتى

1-Idiopathic (85% of cases): antibodies against podocyte antigen phospholipase A2 receptor (PLA2R) antigen
2-Secondary membranous nephropathy

(1) Infections (HBV, syphilis, schistosomiasis, malaria).

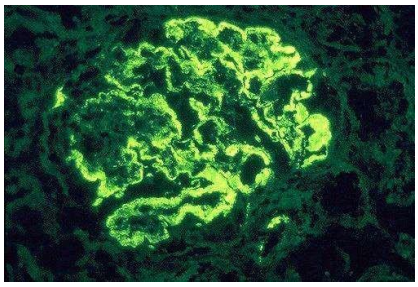
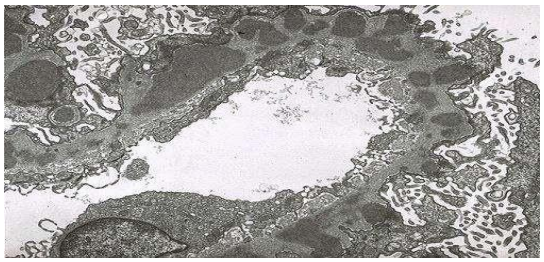
(2) Malignant tumors (lung, colon and melanoma).

(3) Autoimmune diseases as SLE.

(4) Inorganic salts exposure (gold, mercury).

(5) drugs (penicillamine, captopril,NSAID).

-Morphology:

-LM	IF	EM
-diffuse thickening of the GBM. -بنستخدم ال E-h stain	-deposits of immunoglobulins and complement along the GBM (IgG) 	(1) the podocytes show effacement of foot processes, & (2) the diffuse thickening of the GBM is caused in part by subepithelial dome deposits that nestle against the GBM & are separated from each other by small, spike like protrusions of GBM matrix that form in Reaction to the dome deposits, resulting in a (spike & dome pattern). 

-As the disease progresses, these spikes close over the deposits, incorporating them into the GBM.

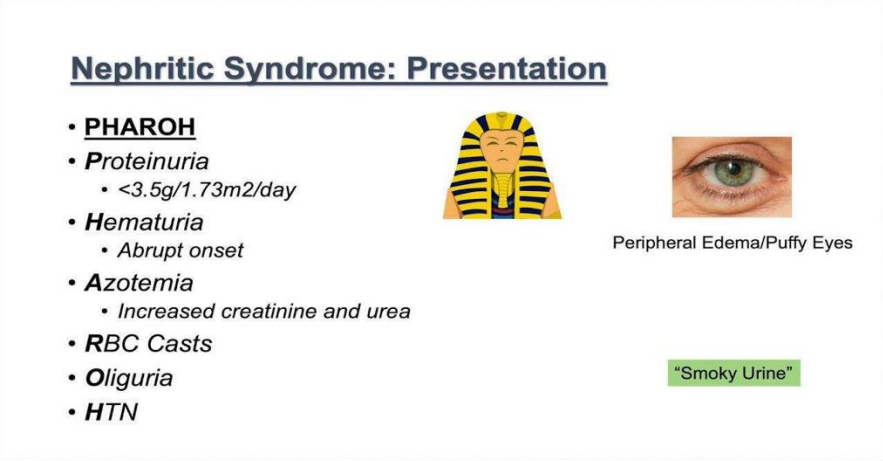
-Clinical Course

-Clinically, idiopathic MGN characterized by insidious development of the nephrotic syndrome, usually without antecedent illness.
-In contrast to MCD,
(I) the proteinuria is nonselective,
(II) does not usually respond to corticosteroid therapy.
-poor response to corticosteroid therapy.

-وكمان progress to chronic renal failure

-Secondary causes of MGN should be ruled out.
-Prognosis:
-60% of cases →proteinuria persists
-About 40%→progressive disease and renal failure 2 to 20 yr.
-30% →partial / complete remission of proteinuria.

-The Nephritic Syndrome:
-characterized by inflammation and bleeding
-Pathogenesis: inflammation
-Proliferation of the cells in glomeruli& leukocytic infiltrate →Injured capillary walls
-escape of RBCs into urine →↓GFR →oliguria, fluid retention, and azotemia.
-Hypertension (a result of both the fluid retention and some augmented renin release from kidneys).
-Glomerular diseases mostly presenting with nephritic syndrome.



-Membranoproliferative GN(MPGN):

-Is manifested H, by alterations in the GBM & mesangium & by proliferation of G cells.
-MPGN accounts for 10% of cases of idiopathic nephrotic syndrome in children & adults.
-Some individuals present only with hematuria or proteinuria in the nonnephrotic range; others have nephritic syndrome or a combined nephrotic-nephritic picture.

-types of MPGN:

-هسا عنا نوعين
-الاولsubendothelial بكون مصاحب للHBV and HCV
-الثاني dense deposit disease بكون:
intramembranous-1
associated with c3 factor -2

1-type I (80% of cases)-immune complex disease (The inciting antigen is not known)
2-type II- excessive complement activation

-Pathogenesis of MPGN
-Different pathogenic mechanisms are involved in the development of type I & type II MPGN.
-Most cases of type I MPGN are caused by circulating immune complexes, but the inciting Ag is not known.
-Like many other GNs, type I MPGN may also occur in association with other known disorders (secondary MPGN),such as SLE, hepatitis B & C, chronic liver disease or infected A-V shunt .

-Type II MPGN (dense-deposit disease)

-Cause: excessive complement activation

-autoantibody against C3 convertase called C3 nephritic factor (it stabilizes the enzyme and lead to uncontrolled cleavage of C3 and activation of the alternative complement pathway).
-Result: Hypocomplementemia

-Morphology

-LM
-Both types of MPGN are similar by LM.
-Glomeruli are large with accentuated lobular appearance and show proliferation of mesangial and endothelial cells as well as infiltrating leukocytes.
-GBM is thickened (double contour or "tram track")
-The tram track appearance is caused by "splitting" of the GBM due to the inclusion within it of processes of mesangial & inflammatory cells extending into the peripheral capillary loops.

-Types I & II have different ultrastructural & immunofluorescence microscopic features.

-Type I MPGN is characterized by discrete sub endothelial electron dense deposits.
-By immunofluorescence M, C3 is deposited in an irregular granular pattern, & IgG & early complement components (C1q & C4) are often also present, indicative of an immune complex pathogenesis.
-Type II MPGN-C3 alone in GBM
-In type II lesions the lamina densa & the subendothelial space of the GBM are transformed into an irregular, ribbon-like, extremely electron-dense structure, resulting from the deposition of material of unknown composition, giving rise to the term dense-deposit disease.

-C3 is present in irregular chunky & segmental linear foci in the BMs & in the mesangium but the IgG & the early components of the classical complement pathway (C1q & C4) are usually absent.

Clinical Course

-Clinically, 50% of MPGN cases presented with nephrotic syndrome, although it may begin as acute nephritis or mild proteinuria.

-prognosis poor.
-No remission.
-40% progress to end-stage renal failure.
-30% had variable degrees of renal insufficiency.
-the remaining 30% had persistent nephrotic syndrome without RF.
-Dense-deposit disease (type II) has a worse prognosis.
-It tends to recur in renal transplant recipients

2-Acute Post infectious (Post streptococcal) Glomerulonephritis (PSGN)

-A frequent GN,typically caused by deposition of immune complexes in the Resulting in diffuse proliferation & swelling of resident G cells & frequent infiltration by neutrophils.

-The inciting Ag may be exogenous or endogenous.
-No direct infection of the kidney.
-The prototypic exogenous pattern is seen in post streptococcal GN, & a similar proliferative GN may occur in association with infections by other organisms, including certain pneumococcal & staphylococcal infections, several common viral diseases such as mumps, measles, chickenpox, & hepatitis B & C.
-Endogenous antigens, as occur in SLE.
-Classically, post streptococcal GN develops in children 1 to 4 weeks after they recover from a group A, "nephritogenic" strains of β-hemolytic streptococcal infection.
-In most cases the initial infection is in the pharynx or skin.

-Pathogenesis of Acute Post streptococcal GN

-Is immune complex deposition, because the typical features of immune complex disease are seen, including,

(1) Granular deposits of IgG & complement on the GBM

(2) Hypo complementemia.

LM	-proliferation of endothelial and mesangial cells and neutrophilic infiltrate. -In post infectious GN, the most characteristic change by light microscopy is a Diffuse (affecting nearly all glomeruli), uniform increased cellularity of the G tufts(caused both by swelling & proliferation of EC & mesangial cells & by a neutrophilic & monocytic infiltrate) Sometimes there is necrosis of the capillary walls & In a few cases, there may also be "crescents "within the urinary space in response to the severe inflammatory injury. -In general, both of these findings are ominous.
IF	-Immunofluorescence M reveals scattered granular deposits of IgG & complement corresponding to the deposits visualized by EM. -Deposits usually cleared in a period of about 2 months.
EM	-immune complexes “subepithelial"humps"in GBM.

-PSGN-Clinical Course

-Acute onset .
-Fever, nausea, and nephritic syndrome.
-Gross hematuria with smoky brown rather than bright red urine .
-Mild proteinuria.
-Serum complement levels are low during the active phase of the disease.
-↑serum anti-streptolysin O antibody titers.
-Recovery occurs in most children.

-IgA Nephropathy (Berger Disease)

-IgA nephropathy is one of the most common causes of recurrent microscopic or gross hematuria &is the most common G disease revealed by renal biopsies worldwide.
-The pathogenic hallmark is the deposition of IgA in the mesangium.

-Clinically, IgA nephropathy usually & most often affects children & young adults.
-More than 50%of patients present with gross hematuria (that occurs within 1 or 2 days of a nonspecific upper RTI, or, less commonly, GIT or UT infection); the

hematuria typically lasts for several days & then subsides, only to return every few months & is often associated with loin pain.
-40%have only microscopic hematuria, with or without proteinuria;
-up to 10%develop acute nephritic syndrome.

Pathogenesis of IgA nephropathy.

-Normally, IgA, the main immunoglobulin in mucosal secretions, is at low levels in normal serum. IgA is in 50% of patients with IgA nephropathy due to production in the bone marrow.
-A genetic influence is suggested by it's occurrence in families & in HLA-identical siblings.
-Studies suggest that IgA synthesis in response to respiratory or GIT exposure to environmental agents (e.g., viruses, bacteria, & food proteins) may lead to deposition of IgA & IgA-containing immune complexes in the mesangium, where they activate the alternative complement pathway & initiate G injury.
-So pathogenesis : abnormality in IgA production and clearance.

Morphology

-LM	- Variable. -The lesions in IgA nephropathy vary considerably. -The G may be normal, or may show mesangial widening & segmental inflammation confined to some G (focal proliferative GN); diffuse mesangial proliferation (mesangioproliferative); or (rarely) overt crescentic GN.
-IF	mesangial deposition of IgA with C3
-EM	deposits in the mesangium

-Rapidly Progressive (Crescentic) Glomerulonephritis

-RPGN is not a specific etiologic form of GN. But a clinical syndrome characterized by rapid & progressive loss of renal function with features of the nephritic syndrome, often with severe oliguria & (if untreated) death from RF within weeks to months.

-Regardless of the cause, the histologic picture is characterized by the presence of crescents (named after their shape as they fill Bowman's space)

-Proliferation of the parietal epithelial cells of Bowman's capsule in response to injury and infiltration of monocytes and macrophages
-Nephritic syndrome rapidly progresses to oliguria and azotemia.

-Pathogenesis

-The G injury is immunologically mediated.
-Cr GN is caused by different diseases, some restricted to the kidney & others systemic; therefore, a practical classification divides CrGN into 3 groups on the basis of immunologic findings ; all have severe G injury, In each group, the disease may be:
(I) idiopathic, or it may be
(II) associated with a known, well-defined renal or extrarenal disease.

-Crescentic GN

1-Group A (Anti-Glomerular BM Antibody): 12% of cases	-Idiopathic (in which there is renal involvement in the absence of pulmonary disease) -Goodpasture syndrome(with renal & pulmonary involvement)
2-Group B (Immune Complex): 44% of cases	-Idiopathic -Postinfectious/infection related -SLE -Henoch-Schönlein Purpura /IgA nephropathy

3-Group C (Pauci-Immune): Antineutrophil cytoplasmic antibody (ANCA) Associated: 44% of cases	-Idiopathic -Wegener granulomatosis -Microscopic polyangiitis

Morphology of Crescentic GN

-Common features for all 3 groups A, B, & C Cr GN are:
Grossly enlarged & pale kidneys, often with cortical petechial hemorrhages
-H, G show:
(1) segmental necrosis, (2)GBM breaks, with resulting (3) crescents.

-Crescents are produced by:

(I) proliferation of the parietal epithelial cells of Bowman's capsule in response to injury & exudation of plasma proteins, including fibrin, into Bowman's space
(II) migration & infiltration of monocytes /macrophages into Bowman's space

-Group A :(12%) Anti-GBM Antibody Crescentic GN

-Characterized by linear deposits of IgG & C3 along the GBM (which can be seen by immunofluorescence M
-Anti-GBM Abs are present in the serum of all patients& are helpful in their diagnosis & patients benefit from plasmapheresis or immunoadsorption,which removes pathogenic Abs from their circulation
-The disease is either:
(I) Idiopathic Anti-GBM Ab GN cases, in which the anti-GBM Abs bind to renal GBM only, without pulmonary lesions, or
(II) Goodpasture syndrome cases of Anti-GBM Ab GN,in which the anti-GBM Abs bind to GBM as well as to pulmonary alveolar capillary BM, causing pulmonary hemorrhages.

Group B:(44%) Immune Complex-Mediated Crescentic GN

-Are immune complex-mediated disorders. This can be a complication of any of the immune complex nephritides, including post streptococcal GN, SLE, IgA

nephropathy, & Henoch-Schönlein purpura.
-In some cases, immune complexes can be demonstrated but the underlying cause is undetermined (Idiopathic).

-In all these cases, immunofluorescence studies reveal the characteristic granular ("lumpy bumpy") pattern of staining of the GBM &/or mesangium for immunoglobulin &/or complement.
-These individuals cannot usually be helped by plasmapheresis

Group C:(44%) Pauci-Immune Crescentic GN

-Defined by the lack of anti-GBM Abs or significant immune complex deposition detectable by immunofluorescence & EM.
-Most of these individuals have anti-neutrophil cytoplasmic Abs in the serum, which have a role in some vasculitis.
-therefore, (I) in some cases group C CrGN is a component of a systemic vasculitis such as microscopic polyangiitis or Wegener granulomatosis,
(II) While in many cases, however, pauci-immune CrGN is limited to the kidney & is thus called idiopathic.

-immunofluorescence M shows NO immunoglobulin or complement, & NO EM detectable deposits.

-Clinical Course of all RPGN (CrGN)

-RPGN present as nephritic syndrome with severe oliguria & azotemia, & proteinuria sometimes approaching nephrotic range.
-Some patients become anuric & require long-term dialysis or transplantation.

-Hereditary Nephritis

-Are a group of hereditary G diseases caused by mutations in GBM proteins, the best-studied one is, Alport syndrome in which nephritis is accompanied by nerve deafness & eye disorders, including lens dislocation & cataracts.

-Pathogenesis.

-Normally, the GBM is largely composed of type IV collagen, also crucial for normal function of the lens & cochlea.
-The disease is NOT immunologically mediated disease.

-Morphology

-the G in hereditary nephritis appear unremarkable until late in the course, when secondary sclerosis may occur. In some kidneys, interstitial cells take on a foamy appearance as a result of accumulation of neutral fats (foam cells)as a reaction to marked proteinuria.
-With progression, there is glomerulosclerosis, vascular sclerosis, tubular atrophy, & interstitial fibrosis.

-Pathogenesis:

-Mutation of any one of the α chains of type IV collagen

-renal failure occurs between 20-50 yrs of age

-EM GBM thin and attenuated.

-GBM later develops splitting and lamination "basket-weave" appearance .

-Clinically: The inheritance is heterogeneous, being most commonly X-linked as a result of mutation of the gene encoding α5 type IV collagen.
-Males therefore tend to be affected more frequently & more severely & are more likely to develop RF than females
-Patients present at the age 5 to 20 years with gross or microscopic hematuria & proteinuria, & overt RF occurs between 20 & 50 years of age.

Disease	Presentation	Age	LM	IF	EM	Prognosis
MCD	nephrotic	Children	none	negative	Effaced foot processes	good
FSGS	nephrotic	adults	Segmental sclerosis	negative	Effaced foot processes	Poor?
MNP	nephrotic	adults	Thickened GBM	IgG+ C3+	Sub-epithelial spikes and domes	Poor?
MPGN-type1	Nephritic/ nephrotic	adults	Tram track	Ig s	Subendothelial deposits	poor
MPGN-type2	Nephritic/ nephrotic	adults	Tram track	C3+	Dense deposits	poor
IgA nephropth	nephritic	Children, young adults	variable	IgA+	Mesangial deposits	variable
PSGN	nephritic	children	hypercellularity	IgG+ C3+	Subepithelial deposits (humps)	good
Alport syndrome	hematuria, hearing loss	children	variable	negative	Basket weave GBM	poor