Hello #medtwitter
This November's @ASPNeph Renal Pathology webinar was on ⚡Fibronectin glomerulopathy (FNG)⚡ Here are some interesting points I learned!

#medtweetorial #NephTwitter #ASPNeph #pedneph #Renalpath #Nephpath
Let's begin with a quick poll!

Fibronectin glomerulopathy is

Ans: D - All the above

Fibronectin glomerulopathy (FGN) is a rare genetic glomerular disease caused by deposition of fibronectin protein in the glomeruli

PMID: 26064516
Image @arkanalabs
4/ **Genetics**

- 40% of pts have fibronectin gene (FN1) mutations
- Most of the cases are familial inherited as autosomal-dominant (AD) glomerulopathy
- Sporadic cases have also been reported

PMID: 18268355
5/ FNG one entity: Many names!
- Familial glomerulonephritis with fibronectin deposits
- Familial lobular glomerulopathy
- Glomerular Nephritis with fibronectin deposits (GNFD)
- Glomerulopathy with fibronectin deposits
- Glomerulopathy with giant fibrillar deposits

6/ History of FNG
- Burgin first reported the disease in 1980
- Strom recognized it as autosomal dominant (AD) kidney disease with glomerular fibrillary deposits showing strong immune reactivity to fibronectin
- Sato (1998) reported the first Asian case in a 23Y old Japanese man
7A/ So, what is this fibronectin?
- Large, dimeric glycoprotein with two similar subunits
- Exists in 2 forms
- Soluble/plasma form is produced in liver & circulates in blood. Insoluble/cellular form is secreted by fibroblasts found in basement membranes & extracellular matrix

7B/ What does fibronectin do?
It is important for cell adhesion, growth, migration and differentiation thus playing a major role in wound healing & embryonic development
8/ Fibronectin Deposition

Usually found in normal glomerular mesangial matrix

Enhanced accumulation is seen in different glomerulopathies (Eg: diabetic nephropathy)

Increased expression is secondary to locally stimulated mesangial & epithelial cell production of cellular form
9/ Typical presents between the age of 20-40y
Slight male predominance in White and Asian individuals
Proteinuria (Mild to Nephrotic range)
Microscopic hematuria
Hypertension
Hemolytic anemia
Slow progression of CKD to ESKD
May recur after kidney transplant
PMID: 33551409

10/ Diagnosis is made only by kidney biopsy
It is suggested by the presence of large, finely granular, electron-dense deposits AND confirmed by the demonstration of fibronectin staining by immunohistochemistry or glomerular proteomics. No clinical/lab findings are characteristic
11/ Histopathologic Findings
11A/ Light Microscopy:
There is no consistent specific tubulointerstitial compartment abnormality. However, interstitial fibrosis and tubular atrophy become more prominent over time, a common finding in progressive kidney disease.

Light micrograph showing fibronectin glomerulopathy

Light micrograph (400x) of a glomerulus in a patient with fibronectin glomerulopathy. There is glomerular enlargement and minimal cellular proliferation, producing a lobular or clover-like appearance.
11B/ Immunofluorescence:
Immunoglobulin and complement component staining is absent or weak in GFND
Immunohistochemistry showing staining for fibronectin in the mesangium and along the capillary walls confirms the diagnosis.

11C/ Let's do another poll with numbers!
Fibronectin glomerulopathy fibrils are typically
11D/ Ans: C
Electron microscopy:
Large to massive, electron-dense sub-endothelial and mesangial deposits, finely granular or fibrillar in some cases
12/ Treatment
Optimal treatment for GNFD is uncertain
No high-quality data regarding the use of immunomodulating agents, plasmapheresis, or any other specific therapy
Nonspecific therapies like strict BP control & use of ACEI and ARBs for proteinuria may prolong kidney function
13/ Prognosis

- Factors associated with kidney function decline in FNG include - Nephrotic range proteinuria & Focal glomerular sclerosis.
- These can help clinicians to identify pts at risk of progressive kidney disease

PMID: 32923447

(A,B) Kaplan-Meier estimates of significant loss of renal function. Renal function was defined as impaired if serum creatinine (Scr) increased by 2-fold after biopsy, initiation of dialysis, transplantation or death.
14/ FNG & ESKD
Mgmt of ESKD in pts with FNG is similar to other types of Kidney diseases & these pts are candidates for all forms of kidney replacement therapy including transplantation
Disease recurrence is seen in some transplanted pts but the true risk isn't clearly understood

15A/ Recurrent Disease
- Seen in pts with kidney allografts transplanted for ESKD due to GFND
- The mechanism behind this is unclear
- Possible hypothesis renal accumulation of abnormal circulating plasma fibronectin

15B/ Fibronectin may be complexed with proteins like (matrix proteins fibulin-1 & fibulin-5) disrupting normal, fibronectin-dependent mesangial and/or podocyte motility, adhesion & spreading resulting in characteristic clinical features
🌟 unique finding to the deposits of GFND🌟
16A/ Genetic Counselling
Disease appearance in successive generations is consistent with an AD pattern of inheritance with age-related penetrance. However, there is a poor genotype to phenotype correlation

16B/ Genetic counseling should be proposed to all individuals having the disease-causing mutation informing them that the risk of passing the mutation to offspring is 50%

17/ FNG - Key Points
- Autosomal dominant disease
- Mutations in the FN1 locus at 2q32
- Massive glomerular deposits of glycoprotein fibronectin (soluble plasma FN) → ESKD
- Globulin-negative results in immunostaining
- No standard treatment has been established for FNG
18/ That's all folks
For a case-based clinical discussion with a pathology expert login to @ASPNeph website, November webinar #Membereducation #ASPNFOAM group

Special thanks to @drM_sudha @SwastiThinks and #ASPNFOAM group

Until next time...
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