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RESEARCH ARTICLE

FIBRILLARY GLOMERULONEPHRITIS: THE IMPORTANCE OF DIAGNOSTIC APPROACH

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Abstract

Fibrillary Glomerulonephritis(FGN) is rare glomerular disease characterized by microscopic hematuria, proteinuria, hypertension and renal insufficiency.Crescentic pattern of FGN is uncommon and would be diagnosed as rapidly progressive renal failure unless Electron Microscopy and/ or special stains are done. We present a case report of a young male who presented as nephrotic syndrome who was diagnosed to have crescentic GN and was revised to crescentic FGN after electron microscopy and immunohistochemical staining with DNAJB9 stain. Patient treatment was changed to Rituximab. The case emphasizes the use of Electron microscopy and special stains in diagnosing rare diseases and importance of diagnostic approach to Fibrillary Glomerulonephritis.

Introduction:-

Fibrillary glomerulonephritis(FGN) is a rare glomerular disease characterized by non congophilic amyloid like fibrillary glomerular deposits, commonly presenting with hypertension, proteinuria, microscopic hematuria, and varying degree of renal insufficiency. FGN can present with different patterns of glomerular injury, more commonly mesangioproliferative, membranoproliferative, and membranous nephropathy and rarely crescentic glomerulonephritis. FGN has a poor prognosis, with a few effective treatment options, and often results in rapid deterioration of renal function leading to ESRD. There is also a risk of recurrence post transplantation. We discuss a case of an adult who presented with worsening hypertension, renal dysfunction, microscopic hematuria, massive proteinuria,who was diagnosed to have crescentic fibrillary GN on kidney biopsy with the help of EM, and on IHC – DNAJB9 positive marker.

A 40 year oldmarried male born of consanguineous marriage with prior mild intellectual disability, seizures, hypothyroidism (6 years duration), hypertension (4 years duration), diabetes mellitus type 2 (3 years duration), hypospadias (corrective surgery done at 20 years of age) and azoospermia presented on routine checkup with renal dysfunction with serum creatinine value of 2.06 mg/dl, proteinuria and microscopic hematuria. There was no preceding fever, cola colored urine, swelling of feet or decreased urine output.

On physical examination,there was no pallor or pedal edema. The blood pressure was 180/110 mmHg, with the rest of the physical examination being unremarkable.Fundus examinationshowed grade 3 hypertensive changes in both eyes. Urinalysis showed 4+ proteins, 10-15 RBCs/HPF, no dysmorphic RBCs. Initial laboratory investigations also revealed elevated serum creatinine of 2.15mg/dl (eGFR – 37.1ml/min), haemoglobin 10gm%, s. albumin/globulin-3.13/5.29, 24 hr urine protein – 8.8 gm/day. Serological tests including HbsAg, HCV antibody, ANA antibody, ANCA and anti GBM antibodies were all negative. Serum electrophoresis did not show any M band. The chest Xray

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was normal, EEG showed frontal and temporal epileptiform discharges. Renal sonogram revealed normal renal size, CMD and echogenicity of cortex. C3C value was 90.3mg/dl.

The patient underwent a renal biopsy, with results suggestive of Crescentic glomerulonephritis. Genetic study sent in view of various syndromic presentation showed:
1. Pathogenic CHD2 gene - heterozygous mutation which is associated with neurodevelopmental disorders and epileptic encephalopathy
2. Pathogenic FGA gene heterozygous mutation which is associated with systemic nonneurotic amyloidosis.

Light microscopy showed endocapillary proliferation with complete/partial cellular crescents with mild increase in mesangial matrix and cells. The tubules showed 1+ mild patchy atrophy. There was mild mononuclear infiltrates and mild patchy fibrosis in interstitium. Congo red stain was negative in glomeruli. Immunofluorescence microscopy showed 1+ coarse granular deposits of IgG along capillary wall, 2+ coarse granular deposits of C3 along the capillary wall with no glomerular staining for IgA , IgM, C1q with no Kappa-lambda restriction.

Electron Microscopy showed about 70% effacement of foot processes of visceral epithelial cells. There was accumulation of randomly oriented,non-branching fibrillary structures with mean fibril diameter of 18.4 nm in mesangial and subendothelial and subepithelial regions.

Special Immunohistochemistry for DNAJB9 showed intense 3+ positivity in glomerular mesangial areas and focally around capillary wall.

The kidney biopsy findings were consistent with Crescentric Fibrillary Glomerulonephritis.

The patient was started on intravenous pulse corticosteroids (methylprednisolone 1g) for 3 days followed by1mg/kg oral prednisolone and oral cyclophosphamide 1.5mg/kg therapy, after explaining all side effects including immunosuppression and sterility, while awaiting results of electron microscopy. Electron microscopy results later confirmed fibrillary glomerulonephritis. Patient was later initiated on Rituximab therapy 375 mg/m2 BSAbiweekly and on tapering doses of cyclophosphamide. The patient is currently clinically stable and has mild renal function recovery noted by reduction in proteinuria.

Discussion:-

FGN is a rare glomerular disease seen in 0.5-1% native kidney biopsy series(1,2). The mean age of presentation of FGN is 50-60 years. (1,2,3) Male: Female predisposition is1:1.2-1.8; white American: African American – 8.3-9.5:0.2-1. It is a rare proliferative form of glomerular disease characterized by deposition of randomly oriented fibrillar deposits with mean diameter of 20nm. Major component of fibrils is DNA J heat shock protein family member B9 (DNAJB9). Clinical presentation commonly included hypertension, proteinuria, hematuria, and varying degree of renal insufficiency. Serum creatinine values could also be in the normal range. Nephrotic range of proteinuria is seen in $1/3^{rd}$ of cases. (4) .

Previously thought to be an idiopathic condition, a study of 66 cases in a single institute found an association with malignancy(23% cases) (3), most common multiple myeloma (6 out of 15 cases of malignancy) and Hepatitis C viral infection. (5)

Diagnosis of FGN mandates the need for electron microscopy and DNAJB9 Immunohistochemistry typing.

FGN has a varying pattern of glomerular injury – mesangioproliferative being the most common with crescentric being rare. (1,2,3,4).

So if the patient has crescentric glomerulonephritis, with the most common causes being rule out with serology, one should emphasis the for early electron microscopy in the diagnostic workup.

This disease has poor prognosis with around half the patients progressing to ESRD within 2 years of diagnosis. (1,2,4) Optimal approach and therapy is not known. Very littleis known about the renal outcome to the use of only RAS blockers or immunosuppression with steroid, cyclophosphamide, or rituximab, the overall outcome being very poor. Outcomes are relatively better in the rituximab followed by steroid/cyclophosphamide group when compared

to no immunosuppression group. Crescentric form of FGN is rare and likely to have poor renal outcome and progression to ESRD despite all treatments currently available. Our presentation is a rare case where a patient has crescentric FGN associated with mental retardation, seizure disorder, hypospadias, hypothyroidism, hypertension, diabetes mellitus with mutation proven on genetic testing; and now with rituximab has relatively better stable renal function and decline in proteineuria. However, it is too early to opine on outcome, and proper follow-up is required.

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