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Hypertension and proteinuria - the needle in the haystack?:

Answers

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Keywords

Hypertension; obesity; proteinuria; children; fibronectin glomerulopathy

Answers | Fibronectin glomerulopathy: The fibril in the mesangium

The differential diagnosis for the presence of massive mesangial deposits seen on light microscopy and fibrillary ultrastructure on EM includes: amyloidosis, cryoglobulinemia, paraproteinemias, lymphoproliferative disorders, lupus, immunotactoid glomerulopathy, fibrillary glomerulonephritis and fibronectin glomerulopathy. The patient's age and negative Congo Red staining make amyloidosis unlikely, and the negative immunofluorescence for immunoglobulins and complement and negative immunohistochemistry (IHC) for kappa/lambda is inconsistent with the other aforementioned entities, except fibronectin glomerulopathy. Furthermore, the random orientation of the fibrils is not characteristic of immunotactoid glomerulopathy and cryoglobulinemia. IHC for fibronectin was performed and strongly stained the abnormal mesangial matrix (Figure 1), confirming the diagnosis of fibronectin glomerulopathy.

Fibronectin glomerulopathy is a rare glomerular disorder caused by extensive mesangial and subendothelial desposition of fibronectin. In a recent series, 10 cases were identified from among 35,088 kidney biopsies performed from 2003 to 2012 [1]. Fibronectin is an extracellular protein involved in cell-matrix interactions and exists in two forms: a cellular form produced by mesangial cells and a circulating form produced by the liver. Findings indicate that the glomerular deposits are derived primarily from the plasma form [2]. Inheritance is autosomal dominant with age-related penetrance. In 2008, heterozygous mutations in the fibronectin gene *FN1* were found in 40% of families studied (6/15 pedigrees) [3]. The case's family history of long-standing hypertension and proteinuria in his mother and ESKD in his maternal grandmother is consistent with this hereditary disorder. Given that his maternal grandmother never had a kidney biopsy, her ESKD may have been the result of fibronectin glomerulopathy rather than amyloidosis.

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Individuals can present at any age, with reported age of onset ranging from 3-64 years [4]. The predominant clinical presentation is proteinuria, often nephrotic-range, with or without hypertension, reduced kidney function, or microscopic hematuria. The characteristic biopsy findings, illustrated by this case, include: marked eosinophilic and PAS positive mesangial and subendothelial deposits with glomerulomegaly and lobulation of tufts, negative Jones and Congo Red stains, and granular electron-dense mesangial and subendothelial deposits on EM, which may appear fibrillary. Progression to end-stage kidney disease within 15-20 years is frequent [1,2,5,6]. Recurrence after renal transplantation has been reported [6,7]. Due to the limited data available on fibronectin glomerulopathy, therapeutic management is not well-defined. The current approach is aimed at renoprotection with anti-proteinuric and anti-hypertensive agents.

Fibronectin glomerulopathy should be considered in the differential diagnosis of significant proteinuria, particularly when features of marked glomerulomegaly and mesangial deposits are seen on biopsy. This case highlights the importance of recognizing this clinical entity in the pediatric population in whom other conditions associated with fibrillary electron dense deposits are very rare.

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Figure 1. Immunohistochemistry for fibronectin shows diffuse positivity within the glomerular mesangium (200 $\times$).