Genes and GBM's: Inherited causes for glomerular basement membrane irregularities

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Abstract

Type IV collagen disorders due to pathogenic variants in COL4A5 (X-linked) or COL4A3/COL4A4 (autosomal) are associated with a heterogeneous clinicopathologic spectrum, ranging from asymptomatic microscopic hematuria to progressive chronic kidney disease with proteinuria, as well as extrarenal manifestations such as sensorineural hearing loss and visual disturbances. Because type IV collagen is a critical structural component of glomerular basement membranes (GBM), pathogenic mutations involving type IV collagen can result in GBM abnormalities appreciable by electron microscopy (EM) in the form of diffuse thinning, irregular thickening, and splitting (“basket-weave”) of the lamina densa. Two cases are presented. The first is a young man with classic clinicopathologic features of Alport syndrome. The second is an elderly patient with hematuria and proteinuria initially suspected to be IgA nephropathy, but EM instead showed diffusely thin GBMs, which was confirmed to be associated with a pathogenic variant of type IV collagen. These cases underscore the importance of EM in evaluating hematuria/proteinuria and highlight how recognition of GBM ultrastructural patterns can prompt targeted genetic testing and avoid misclassification as immune-complex glomerulonephritis.

References

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