Persistent Isolated Hematuria in a Japanese Woman

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Case Description
A 43-year-old Japanese woman, with a family history of hematuria, underwent a kidney biopsy because of persistent hematuria without proteinuria, with serum creatinine of 0.55 mg/dl. Light microscopy revealed minor glomerular abnormalities. Electron microscopy predominantly showed thinning of the glomerular basement membrane (GBM); thickening and lamination were observed in small portions of the GBM (Figure 1A). Atypical Alport syndrome (AS) was suspected. Type IV collagen staining revealed weak α5(IV) expression with enhanced expression of α2(IV) in segmental lesions, consistent with AS (Figure 1, B and C). This case was presumed to be autosomal dominant AS (ADAS), because of the family history and preserved α5(IV) expression in the Bowman’s capsule, which indicate the mutation of COL4A3 or COL4A4 (Figure 1C) (1). Diagnosis of typical AS, namely, X-linked AS in males and autosomal recessive AS, is straightforward, and often made in childhood. In contrast, ADAS is usually suspected in adults because of their mild clinical phenotype, and a pathologic diagnosis of ADAS is difficult because of its ultrastructural similarity to thin basement membrane nephropathy. Therefore, we should suspect ADAS in patients with predominant GBM thinning, but any clinical or pathologic sign of atypical AS. A defect in α5(IV) is seen in typical patients with AS, although α5(IV) staining is reported to be normal in patients with ADAS (2,3). However, we recently reported a case where α5(IV) staining was reduced in the GBM, with compensatory enhanced expression of α2(IV), laminin, and fibronectin (1). In addition, type IV collagen staining of both GBM and the Bowman’s capsule were key points to differentiate AS from thin basement membrane nephropathy and subtype their mode of inheritance. The scanning electron microscopy of kidney biopsy specimens usually analyzes a few glomeruli and observes limited areas of the GBM only. In contrast, type IV collagen staining shows more glomeruli with the Bowman’s capsule, which might be effective in diagnosing atypical AS. To identify the abnormality, we performed the staining using 2-μm thick frozen sections. Type IV collagen staining with a sufficiently thin frozen section is useful to diagnose atypical AS in adults.

Teaching Points
- Patients with classic or typical AS develop ESKD at a young age. However, family histories of moderate hematuria and proteinuria suggest atypical AS in adults.
- In our case, electron microscopy revealed predominant thinning of the GBM, although thickening, lamination, and wrinkling were observed in small portions of the GBM.
- Type IV collagen staining of the GBM and Bowman’s capsule were important for the diagnosis of AS and to subtype their mode of inheritance. A sufficiently thin frozen section is useful to visualize partially reduced α5(IV) staining, with compensatory enhanced expression of α2(IV) in GBM and mosaic reduced α5(IV) staining in the Bowman’s capsule.

Disclosures
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Informed consent was obtained from the patient.

Author Contributions
T. Mochizuki was responsible for the project administration; T. Mochizuki and K. Nitta provided supervision and reviewed and edited the manuscript; T. Mochizuki and M. Sato conceptualized the study and wrote the original draft; K.
Nitta was responsible for the funding acquisition; M. Sato was responsible for the data curation, investigation, resources, and visualization; and all authors approved the final version of the manuscript.

References


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Figure 1. | Microscopy images. (A) Electron microscopy image in this case. Electron microscopy showed predominant thinning of the glomerular basement membrane (GBM), although segmental thickening, lamination, and wrinkling (arrowhead) of the GBM were observed (×3000 magnification). (B) Dual immunofluorescence staining of α5(IV) and α2(IV) in control case without a GBM abnormality. α5(IV) staining (green) is positive for the GBM and α2(IV) staining (red) is limited to the mesangial region. (C) Dual immunofluorescence staining of α5(IV) and α2(IV) in this case. α5(IV) staining (green) was partially reduced with segmentally enhanced expression of α2(IV) (red) in the GBM (arrowhead), consistent with Alport syndrome. Preserved α5(IV) staining within the Bowman’s capsule was consistent with autosomal dominant Alport syndrome (×200 magnification).