Non-Familial Thin Basement Membrane Disease with an Unique Ultrastructural Feature: Report of a Case

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Abstract = We described a case of non-familial thin basement membrane disease from an 8 year old girl who presented with recurrent gross hematuria without familial background of renal disease. Ultrastructurally, the glomerular changes were identical with those of benign familial hematuria, being characterized by uniform and marked thinning/attenuation of lamina densa with focal gap formation. The relative diagnostic specificity of the findings and the possibility of sporadic and non-familial occurrence were discussed.

Key words: Non-familial thin basement membrane disease, Benign familial hematuria

INTRODUCTION

Differed from a relatively common Alport’s syndrome, among a variety of hereditary glomerulopathy, is a benign familial hematuria which is characterized by recurrent hematuria and its marked thinning/attenuation of glomerular basement membrane (Marks and Drummond 1969; McConville et al. 1966; Rogers et al. 1973). Similar ultrastructural findings, however, are often associated with other glomerular diseases and claimed totally unhelpful or at least not pathognomonic for diagnostic implication (Hill et al. 1974; Yum and Bergstein 1983). Non-familial or spontaneous development is also an unusual presentation in the context of this morphological features.

The purposes of this presentation are to describe the unique ultrastructural characteristics of thin basement membrane disease from a case of 8 year old girl with recurrent gross hematuria and no familial background of renal disease, and to compare them with those of benign familial hematuria, Alport’s syndrome, Henoch-Schoenlein nephritis, and IgA nephropathy. The possible pathogenesis and diagnostic as with prognostic implications of this lesion are also discussed.

CASE

A seven year and 10 month old, otherwise healthy girl was admitted to the Seoul National University Hospital (SNUH) because of recurrent gross hematuria. She had been relatively well until 2 year and 8 month of her age, when she first developed dark reddish urine 2 to 3 days after the symptoms of the upper respiratory tract infection. At that time, she was admitted to a local hospital where intravenous pyelography was performed but showed no abnormality. She received no specific management during the admission. After discharge, intermittent gross hematuria had frequently recurred with usual preceding symptoms of the upper respiratory tract infection or exercises. Gross hematuria, once started, persisted for several days and was occasionally accompanied by abdominal discomfort, headache and nausea. But hypertension or edema was absent. Three weeks prior to the second admission, she developed vomiting and was admitted to another hospital, where she was suspected for aseptic meningitis with some improvement. On the 9th hospital day, abdominal discomfort, headache and nausea developed, and then gross hematuria reappeared. Other symptoms immediately subsided, but gross hematuria persisted till the 17th hospital day, when she was transferred to SNUH for further evaluation and management.

On family history, her father received transurethral removal of renal stone 3 years ago. Her mother suffered from acute viral hepatitis and was admitted to a local hospital, one year ago. Her ur-
nalysis during the hospitalization was within normal limits. Her siblings had neither history of hematuria, proteinuria, nor hearing loss.

On admission, the patient was alert, slightly pale, but not puff faced. Blood pressure was 105/70 mmHg, and body temperature 36.5°C. Respiration rate was 18/min., pulse 90/min., body weight 24.5 kg (90–97 percentile), and height 122.3 cm (75–90 percentile). Head was normocephalic without scar. Pupils were isocoric with prompt light reflexes. Conjunctivae were slightly anemic, and sclerae not icteric. There was neither neck stiffness nor venous engorgement in the neck. Breathing sounds were clear and no rales were heard. Heart beats were regular without murmurs. Abdomen was soft, flat, and neither hepatomegaly nor other organomegaly was felt. Both lower extremities revealed no pitting edema. There were café-au-lait spots on the anterior chest and a match-head sized hemangioma on the upper lip.

The admission laboratory tests showed hemoglobin 9.2 gm%, hematocrit 27.5%, white blood cells 6,300/mm³ with normal differential counts and platelet 229,000/mm³. Total serum protein/albumin level was 6.5/3.8 gm%, cholesterol 180 mg%, and BUN/creatinine 12/0.6 mg%. Urinalysis revealed specific gravity of 1.009, 3(+) blood, trace albuminuria, numerous RBC and 1-2 WBC/HPF. No organism grew in the urine culture. Serum immunoglobulin quantitation showed IgG 1,310 mg%, IgA 200 mg%, IgM 329 mg%, IgD 2.0 mg%, and IgE 115 IU/l. Complement profile were C₃ 116, C₄ 28.6, and CH₅₀ 37.1 mg%. Serum iron was 84 g/100ml, Hepatitis B marker study exhibited positive reactions to HBsAg and HbcAb. Radiological studies including intravenous pyelography were all negative. Audiometric finding was within normal limits with no evidence of sensory neural hearing loss, but ophthalmologic examination revealed entropion, otherwise unremarkable.

On the first admission day a percutaneous kidney needle biopsy was performed without complication. From the second hospital day, iron supplementation was started for iron deficiency anemia. The patient was discharged on the 6th hospital day, and was regularly followed up through the outpatient clinic. Three weeks after discharge, dipyriramole was given, but gross hematuria had been noted continuously without any clinical evidence of renal failure for last 2 years after biopsy.

**PATHOLOGIC STUDIES**

Light microscopy (S84–7768): Two pieces of renal cortical tissue were submitted for light microscopic investigation and contained a total of 21 glomeruli. One of them was globally obsolescent and the remainders were regularly approximated and normal in size, shape and cellularity. Capillary lumens appeared widely opened, and mesangial spaces were neither expanded nor sclerotic. Capillary walls seemed evenly thin and delicate without discernable splitting or gap of the glomerular basement membrane. Urinary spaces were well patent and occasionally contained a few fresh red blood cells which were freely floating between the glomerular tuft and the Bowman’s capsule (Fig. 1). Tubules were relatively well maintained except for mild luminal dilatation and inspissation of many red blood cells. Interstitium and blood vessels were all unremarkable. There was no foam cell collection throughout.

Immunofluorescence study (IF84–177): Three glomeruli were examined to demonstrate scanty amount of mesangial C₃ and IgM deposits. Tubules, interstitium and blood vessels were free of deposits.

Electron microscopy (E84–319): One glomerulus was under the investigation, showing normocellular tuft. Almost all capillary loops exhibited uniformly thin and attenuated basal lamina with no evidence of electron dense deposit. Both lamina rara interna and externa were in regular contour, and the overlying foot processes were well retained. Mesangial spaces were mildly expanded, but also free of deposit (Fig. 2). Silver impregnation technique on whole glomerular structures illustrated a diffuse and marked thinning of the lamina densa up to 1,000 Å in average (Fig. 3), together with focal gap, through which herniation of the covering podocyte occurred (Fig. 4). Attenuation of the lamina densa was rather smooth, even with only focal splitting and uneven rarefaction of short length, but neither lamellation nor granulation was suggestive.

**DISCUSSION**

Benign familial hematuria is a recently described entity which is distinguished from Alport’s syndrome (Ayoub and Vernier 1965). This condition, as its name implies, is a clinical term and may present at any age, most usually in childhood, as asymptomatic recurrent hematuria. As in Alport’s syndrome, there is claimed its hereditary pattern of
Fig. 1. Two-micra thick section of a normocellular glomerulus showing evenly thin and delicate capillary walls and widely patent capillary lumina. A few red blood cells are freely floating in the urinary space between capillary tuft and Bowman’s capsule (arrow). PAM, X400.

Fig. 2. Electron micrograph of a glomerulus. Capillary loops exhibit diffuse and uniform thinning/ attenuation of basal lamina. Overlying foot processes are well retained. Mesangial spaces are mildly expanded, being devoid of deposit. Uranyl acetate-lead citrate. X8,400.
Fig. 3. Comparison of the thickness of GBM between this case (above) and minimal change lesion (below) under the same magnification. Lamina densa of this case reveals marked thinning up to 1,000 Å in average, and maintains characteristic smooth contouring without evidence of lamellation or granulation. Uranyl acetate–lead citrate, X16,800.

Fig. 4. There is a focal gap (arrows) of lamina densa, through which herniation of covering podocyte occurred. PAM. x6,300.
transmission (McConville et al. 1966; Rogers et al. 1973). However, 10 out of 29 cases in a series (Hamberger et al. 1968) developed spontaneously without familial background as in this case, to suggest a random development of this disorder but without support by ultrastructural proof. Also unlike Alport's syndrome, there is no evidence of progression and without evidence of any deterioration of renal function (McConville et al. 1966).

Light microscopic examination is not contributory and reveals no significant lesions, with which an erroneous interpretation may lead to the diagnosis of minor change category. The most distinctive and reliable feature, however, is the observation on electron microscopic study that the majority of the peripheral glomerular capillary basement membranes are remarkably thin and attenuated with occasional ones showing actual rupture, presumably the source of the patient's hematuria (Rogers et al. 1973).

The major point of debate in this disease lies in regard with its specificity of the lesion and differential diagnosis from Alport's syndrome which may present similarly extreme attenuation or thinning of the glomerular basement membrane as a part of its distinct glomerulopathy. This raises the question of the degree of overlap between Alport's syndrome and the benign familial hematuria, unless it is determined the relative frequency of this ultrastructural alteration, not only in Alport's syndrome, but also in other conditions as well. However, it is widely accepted that such alteration in Alport's syndrome is usually segmental or of short length involvement, and mostly manifested by thickening of the basal lamina with characteristic lamellation, rarefaction and intramembranous granular particulation (Churg and Sherman 1973; Gubler et al. 1981; Hinglais et al. 1972; Kaufman et al. 1970; Krickstein et al. 1966; Sherman et al. 1974; Spear and Slusser 1972; Spear 1983). Of analysis of 10 cases of the proven Alport's syndrome at our laboratory (Kim et al. 1986), none of the patients showed an unique feature of extreme attenuation of whole loop at any glomerular capillaries, although an alternate thinning and thickening of basement membrane is a frequent association, aside from lacy network appearance by lamellation.

Also are described other diseases accompanying similar nature of glomerular changes to benign familial hematuria. Hill et al. (1974) listed 3 conditions; resolving phase of poststreptococcal glomerulonephritis, focal segmental glomerulosclerosis and IgA nephropathy, all of which showed varying amount of the basement membrane attenuation. Similar features were also partly confirmed by the present authors (Park et al. 1985) who reviewed the glomerular ultrastructures of 46 cases of Henoch-Schönlein nephritis and 49 cases of IgA nephropathy. We demonstrated thinning/attenuation of glomerular basement membrane of 56.6% of Henoch-Schönlein nephritis and 18.2% of IgA nephropathy, but these were only segmental or of very short loop involvement, being correlated with the histopathologic grading of glomerular changes. Thus, glomerular basement membrane changes in the above diseases reflected only a part of easily recognizable morphological lesions, and none of the cases shared diffuse involvement as shown in benign familial hematuria.

Not only uniform attenuation of the basal lamina, but also smooth contouring with neither lamellation, splitting, nor granulation in this case may give clinically better prognosis than Alport's syndrome. Maintenance of function despite of recurrent gross hematuria for 6 years after the first onset would be the tentative parameter for this benign prognosis. This form of glomerulopathy regardless its familial clustering has not been documented in Korean literature and it is the first proven case of near 2,000 primary renal diseases with needle biopsies in our institution. But benign familial hematuria itself may not be a rare form of recurrent hematuria syndromes; unless it is progressive, a morphologic study is often escaped from confirmatory diagnostic procedure, and this ultrastructural feature of thinning is also not usually examined with attention.

REFERENCES
Hill GS, Jenis EH, Goodloe S Jr. The nonspecificity of the ultrastructural alterations in hereditary nephritis with additional observations on benign familial hematuria. Lab Invest. 1974, 31:516-532
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非家族性 絲緞體 薄基底膜症
－1종례보고 및 산발적 발생 가능성 검토－

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저자들은 반복성 육안적 혈뇨를 주소로 한 8세 여아의 신생경 조직에서 특징적인 진전력성 소견을 보이는 비가족성 사구체 박기저막증(non-familial thin basement membrane disease)을 경험하고, 산발적 비가족성 발생의 가능성을 제시하고자 한다.

환자는 신결핵의 가족력이 없었으며, 6년간 간헐적으로 반복된 혈뇨외에는 진행성 신기능 약화 및 검사 소견의 이상을 동반하지 않아 Alport 증후군 및 IgA 신염증 등 다른 신결핵이 가능성을 배제할 수 있었다.

진전력형으로 분류되는 본질적 혈뇨(benign familial hematuria)와 동일한 소견을 보였으며, 사구체 가격막이 미만성으로 보임이 있었다. Lamina densa는 모세혈관 생성에 걸쳐 형질환을 보이며 약간의 원형으로 형만화된 형성이나 파편 형성 등의 수반되지 않고 곤다성 빛을 나타내므로서 Alport 증후군 및 IgA 신염증, Henoch-Schoenlein 신염 등과 혈미학적으로 감별할 수 있으며, 임상적으로 본질환의 좋은 예후와 관련 있다고 사료하였다.

또한 lamina densa가 소견상으로 파악되어 ‘focal gap’을 형성한 곳이 여러군에 관찰됨으로서 상피세포의 탈출과 함께 본질환에서의 혈뇨의 발생기전을 추정해 보았다.

가족력성 유사한 발생이 없는 점으로 보아 이 병변의 비가족성 산발적 발생 가능성을 시사하였다.

*본례는 1984년 10월 대한병리학회 추계학술대회에서 보고된 바 있어.