Kidney International, Vol. 49 (1996), pp. 168–173

Loin pain-hematuria syndrome associated with thin glomerular basement membrane disease and hemorrhage into renal tubules

LEE A. HEBERT, JUDITH A. BETTS, DANIEL D. SEDMAK, FERNANDO G. COSIO, WILLIAM H. BAY, and SHARON CARLTON

Departments of Internal Medicine and Pathology, The Ohio State University, Columbus, Ohio, USA

Loin pain-hematuria syndrome associated with thin glomerular basement membrane disease and hemorrhage into renal tubules. Loin pain-hematuria (LPH) syndrome is a poorly understood disorder in which the patients, mainly young women, experience unexplained severe chronic unilateral or bilateral flank pain associated with gross and/or microscopic hematuria. By contrast, thin glomerular basement membrane (GBM) disease is generally thought to be a benign disorder, affecting males and females equally, in which the major manifestation is asymptomatic microscopic hematuria. Herein we describe seven patients (6 females, 1 male) in whom thin GBM appeared to be the cause of the LPH syndrome. The gross hematuria in these patients could be attributed to thin GBM disease because the renal biopsy demonstrated red cells in renal tubules (indicating glomerular hematuria) and the only glomerular abnormality present was thin GBM. In addition, the other causes of gross hematuria were excluded by appropriate testing. The flank pain in these patients might also have been the result of their thin GBM disease. This is suggested by renal biopsy findings of multiple renal tubules filled with red cells, apparently occluding the tubules. We suggest that occlusion of a relatively small fraction of renal tubules could cause renal pain if back-leak of glomerular filtrate occurred that was of sufficient magnitude to expand renal parenchymal volume and stretch the renal capsule. Preliminary observations suggest that treatment with the angiotensin converting enzyme (ACE) inhibitor enalapril importantly reduces the frequency and severity of the episodes of gross hematuria and flank pain in most patients. ACE inhibition might decrease glomerular hemorrhage in patients with thin GBM by decreasing glomerular hydrostatic pressure. We conclude that (1) Thin GBM disease can be the cause of gross hematuria, apparently as a result of rupture of thin GBM. (2) Rupture of thin GBM resulting in hemorrhage into renal tubules may be the cause of the flank pain and gross hematuria in some patients with the LPH syndrome.

LPH syndrome is a poorly understood disorder in which the patients, mainly young women, experience severe chronic, unilateral or bilateral flank pain and microscopic or gross hematuria [1–11]. The usual causes of flank pain and hematuria (urolithiasis, obstructive uropathy, pyelonephritis, polycystic kidney disease, acute glomerulonephritis, renal embolism, papillary necrosis, renal vein thrombosis, renal vein entrapment, trauma, or renal tumor) are not present. The cause or causes of the LPH syndrome are unknown. However, nephrectomy specimens from some patients with this disorder have shown severe atherosclerosis in the arcuate, lobular, and interlobar arteries [7, 8]. The presence of this arterial disease is unexpected because of the youth of most of these patients. Renal biopsy specimens sometimes also show C3 deposits in arterioles [2, 6, 9, 10]. Various coagulation abnormalities have also been reported in association with the LPH syndrome. These include increased platelet factor III, plasma serotonin, platelet aggregates, and fibrinopeptide A levels [11]. In addition, the plasma of these patients may not normally support prostacyclin production by endothelial cells in culture [8].

It has been suggested that in some LPH syndrome patients, microinfarcts of the kidney may be the cause of the renal pain and hematuria [12]. The infarcts could be the result of arterial thrombotic episodes induced by coagulation abnormalities or vasospasm [12]. Despite these pathologic findings, patients with the LPH syndrome are not thought to develop progressive loss of kidney function [12].

In contrast to LPH syndrome, thin GBM disease involves males and females equally, and is generally thought to be a benign disorder manifested mainly by microscopic hematuria [13]. Herein we provide evidence that thin GBM may also be a cause of the LPH syndrome.

Methods

Patient population

Since 1979, 15 patients have undergone renal biopsy in our program for evaluation of possible LPH syndrome. Of these, 7 were found to have thin GBM. These patients are the basis for the present report.

LPH syndrome was considered when patients had: (1) six months or more of unilateral or bilateral episodes of flank pain which lasted for days at a time or was chronic. On physical examination there was little or no tenderness to gentle palpation of the region of the costovertebral angle. However, a gentle punch to that area elicited deep pain. (2) Hematuria was virtually always present either as microscopic or recurring episodes of gross hematuria. (3) The episodes of flank pain were almost always worse when gross hematuria was present but flank pain could be present without gross hematuria. (4) Clots were not observed in the grossly bloody urine. (5) Detailed evaluation for known causes of gross hematuria was negative or normal. Specifically all patients

Received for publication January 4, 1995
and in revised form July 20, 1995
Accepted for publication August 3, 1995

Table 1. Clinical characteristics of patients with loin-pain hematuria syndrome and thin glomerular basement membranes

	Age, *years*		Duration,				Location	Exercise-	Serum creat.	24-hr proteinuria,
	Onset[a]	Current	*years*[b]	Gender[c]	Race[d]	Hypertension[e]	of pain[f]	related[g]	*mg/dl*[h]	*mg*[i]
Case 1	21	40	19	F	W	N	R	Y	0.9	178
Case 2	52	56	4	F	W	Y	R	N	1.0	110
Case 3	43	45	2	F	W	N	L	N	0.8	1053
Case 4	35	46	11	F	W	Y	B	Y	1.0	474
Case 5	34	37	3	F	W	N	R	N	1.0	0
Case 6	18	21	3	M	W	N	B	Y	1.2	83
Case 7	27	30	3	F	W	N	B	Y	0.9	96

[a] At onset of LPH syndrome
[b] Duration of active LPH
[c] F, female; M, male
[d] W, Caucasian
[e] N, no; Y, yes; hypertension defined as systolic > 140 or diastolic > 90 mm Hg
[f] R, right flank; L, left flank; B, both flanks
[g] Episodes of gross hematuria and flank pain often preceded by increased physical activity
[h] At time of renal biopsy
[i] Obtained when patient did not have gross hematuria

underwent intravenous pyelography (usually on multiple occasions, including during episodes of gross hematuria), contrast enhanced scan of the kidney and surrounding structures by computed axial tomography (CAT), and tests for blood coagulation abnormalities. Some patients also had undergone renal arteriography. All but one patient had undergone cystoscopy with ureteroscopy on at least one occasion. Urinary tract infection was excluded by absence of pyuria and bacteruria by urinalysis, and by negative routine urine culture for bacteria.

Determination of glomerular hematuria from analysis of the renal biopsy

The presence of red cells in renal tubules is generally regarded as evidence of glomerular hematuria. However, it is possible that in some instances the trauma caused by the renal biopsy could account for intratubular red cells. To assess the extent to which this might occur, we examined renal biopsy specimens from normal cynomolgus or rhesus monkeys ($N = 9$) involved in a study of experimental glomerulonephritis that had undergone closed needle biopsy at baseline using standard techniques [14] comparable to that used in our patients.

The protocol to assess for red cells in tubules in renal biopsy specimens was as follows: The number of tubular lumens in the cross section of each periodic acid-Schiff (PAS) stained renal biopsy specimen was estimated by counting the number of 20 times magnification (20×) microscopic fields contained within the renal biopsy cross section. That number was multiplied by 100, which is the average number of tubular cross sections in a 20× microscopic field. Each tubular lumen in the renal biopsy specimen was examined for the presence of red cells. If red cells were present, they were counted. This protocol was also used to assess for intratubular red cells in the renal biopsy specimens of the patients of this study.

Histology methods

The renal biopsy specimens were prepared and analyzed by routine light, immunofluorescence and electron microscopy techniques, as previously described [13]. The diagnosis of thin GBM disease was based on electron microscopy findings of GBM thickness of less than 200 nm involving 50% or more of capillary wall length, as previously described [13].

Data analysis

The statistical tests used are discussed in relationship to the data.

Results

Clinical characteristics of the patients with LPH syndrome and thin GBM

Table 1 shows that one of the seven patients is a male. In four of the seven patients, exercise provoked episodes of gross hematuria and flank pain. The male patient had to quit varsity athletics (gymnastics) because severe exertion caused gross hematuria and flank pain. None of the patients had elevated serum creatinine levels. However, low level proteinuria was seen in three of the seven patients.

Evidence for glomerular hematuria in the patients with LPH syndrome and thin GBM

Table 2 shows the quantitation of blood in renal tubules in the renal biopsy of each patient. As can be seen, in each patient red cells were found in multiple tubular lumens. In most of the tubules that contained red cells, the number of red cells was small (< 5). In four patients, multiple proximal tubules were filled with red cells. The renal biopsy findings in Case 1 are shown in Figure 1.

To assess whether the intratubular red cells could be the result of the renal biopsy procedure itself, we examined renal biopsy specimens from nine normal nonhuman primates (rhesus or cynomolgus monkeys) that had undergone closed needle biopsy of the kidney [14] using the same techniques that were used in the human renal biopsies. We found that red cells were present in renal tubular lumens in six of the nine renal biopsies. However, in each instance, only one tubular lumen per biopsy contained red cells and the red cells were few in number (range 1 to 10) and loosely arranged in the tubule. The range of tubular lumens per biopsy specimen was 300 to 3,000, median 1,000. Thus, the percent of tubular lumens containing red cells was about 0.1% per biopsy,

Table 2. Renal biopsy findings in patients with LPH syndrome and thin GBM

	Tubules with red cells[a]	Tubules filled with red cells[b]	Sclerotic glomeruli[c]	Interstitial fibrosis[d]	C3 in arterioles	Minimum GBM, *nm*
Case 1	50	40	0	0	+++	175
Case 2	5	0	18	+	++++	163
Case 3	30	5	0	0	0	147
Case 4	25	10	25	++	0	110
Case 5	25	10	0	0	++++	142
Case 6	7	0	0	+	+	100
Case 7	10	0	0	+	+	120

[a] Percentage of tubular lumens containing red blood cells
[b] Percentage of tubules completely filled with red blood cells
[c] Percentage of glomeruli with any degree of sclerosis
[d] Percentage of interstitial volume occupied by fibrosis; 0, no fibrosis; +, 1–10%; ++, 11–25%; +++, 26–50%; ++++, >50%

a value much lower than that of the patients (Table 2). Also, in no instance did we find red cells in amounts sufficient to completely fill tubular lumens. Thus, the presence of multiple renal tubules containing red cells, and red cells filling tubular lumens, as shown in Figure 1, can be regarded as the result of glomerular hematuria, not the renal biopsy procedure.

Other renal biopsy findings in patients with LPH syndrome and thin GBM

Interstitial edema, similar to that shown in Figure 1, was found in the renal biopsies of some of the other patients with LPH syndrome and thin GBM disease. However, interstitial edema was not a consistent feature, perhaps because most of the patients underwent renal biopsy when they were not having pain.

Table 2 also shows that two of seven patients had sclerotic glomeruli. Four of the patients had some degree of interstitial fibrosis. In five of seven patients C3 was identified in arterioles, a finding that is thought to be characteristic of LPH syndrome [12]. All patients had moderate to severe thinning of GBM.

Effect of enalapril therapy on episodes of LPH syndrome in patients with thin GBM

Table 3 summarizes the results of enalapril therapy in our patients who received this drug for treatment of the symptoms of gross hematuria and/or flank pain. As can be seen, four patients experienced important improvement in symptoms. Enalapril was begun at 2.5 or 5.0 mg daily. The dose was titrated upwards, if needed and as tolerated. Only one patient (Case 2) experienced symptomatic hypotension. This was corrected by changing the enalapril from 5 mg daily to 2.5 mg morning and evening. In this patient, dividing the dose of enalapril was also associated with better control of flank pain and episodes of gross hematuria.

Discussion

The present study shows that some patients who present with the LPH syndrome have thin GBM disease and evidence of hemorrhage into tubules. A detailed clinical evaluation of these patients failed to demonstrate any nonglomerular cause for hematuria. We have concluded, therefore, that the patient's gross hematuria is glomerular in origin. To our knowledge, this is the first clear demonstration that thin GBM disease can cause gross hematuria. Generally, thin GBM disease is regarded only as a cause of microscopic hematuria [13, 15]. Previous reports of an association of thin GBM disease with episodes of gross hematuria are difficult to interpret because the reports either did not perform immunofluorescence microscopy on the renal biopsy specimens to exclude disorders such as IgA nephritis, and/or did not perform electron microscopy to document abnormal GBM thickness, or exclude the possible role of other known causes of gross hematuria [reviewed in 15].

The present study also suggests that the flank pain observed in our patients was in some way the result of the gross hematuria. The causal relationship between the gross hematuria and the flank pain is suggested by the frequent temporal relationship between the onset of gross hematuria and the onset of flank pain. The mechanism by which gross hematuria could cause flank pain in our patients is not clear. However, obstruction of the kidney due to urinary clot formation is unlikely because none of our patients reported passing obvious clots in the urine. Furthermore, in six of the seven patients (Cases #1 through 6) an intravenous pyelogram was done during painful episodes of gross hematuria and no obstruction was documented. We suggest that the flank pain associated with gross hematuria might be the result of obstruction of multiple renal tubules sufficient to cause substantial backflux of glomerular filtrate, renal parenchymal volume expansion, and flank pain. In support of this hypothesis is the finding that in our patients, up to 40% of renal tubules were found to be completely filled with red cells at the time of renal biopsy. It is well known that bilateral renal pain is associated with severe episodes of glomerulonephritis, which are accompanied by renal swelling and in some instances by occlusion of multiple renal tubules with red blood cells [16–18]. Thus, it is possible that the pain experienced in our patients is a variation of this well documented phenomenon of renal pain in severe glomerulonephritis.

Rupture of renal interstitial blood vessels could also explain gross hematuria, flank pain, and red cells filling renal tubules, if the interstitial hemorrhage resulted in dissection of the blood into renal tubules. However, none of our renal biopsy specimens showed interstitial hemorrhage.

Renal imaging studies in our patients did not show abnormally enlarged kidneys at the time of the flank pain. However, the amount of renal swelling needed to markedly increase the pressure transmitted to the renal capsule is relatively small. For example, we have shown that in the dog undergoing ureteral obstruction during saline loading, only a 10% increase in renal volume (approximately a 3% increase in the diameters in the kidney) causes an increase of 40 to 60 mm Hg in hydrostatic pressure transmitted to the renal capsule [19]. Thus, if renal swelling is the mechanism of pain in our patients with thin GBM disease and hemorrhage into tubules, it is not surprising that nephromegaly was not observed. Some of the renal biopsy specimens showed interstitial edema, as in Figure 1. However, this was not a constant feature of the renal biopsies, perhaps because many of the patients were biopsied when they were not having pain.

Unresolved is the question of how multiple glomeruli come to be hemorrhaging at the same time so that gross hematuria

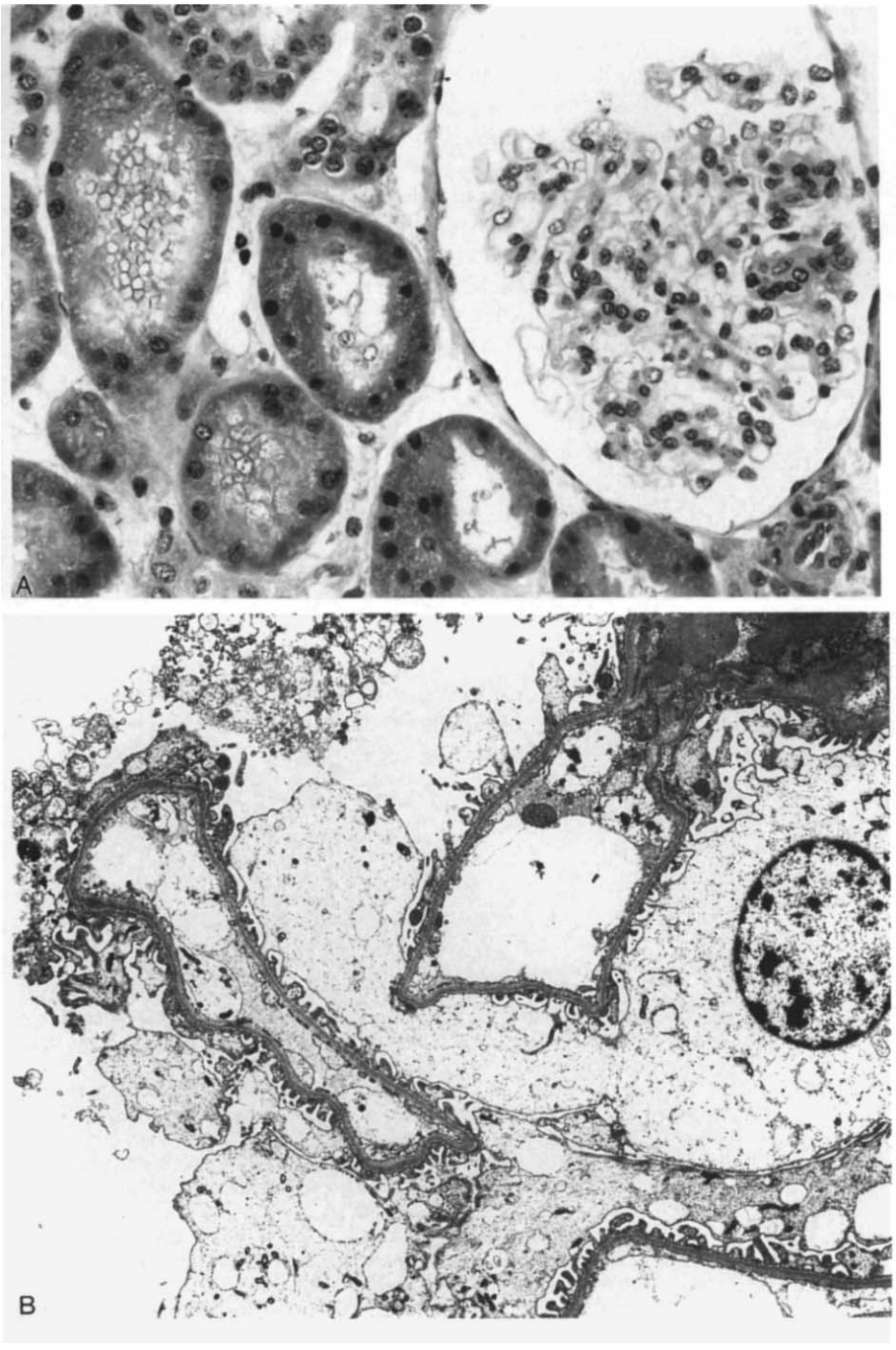

Fig. 1. *Panel A.* Representative light microscopy field of the renal biopsy of Case 1. The proximal tubule at nine o'clock is filled with red cells. Smaller numbers of red cells are in the proximal tubule at eight o'clock. There is separation of tubules indicating interstitial edema. The glomerulus is normal by light microscopy and negative by routine immunofluorescent microscopy (100 × magnification, periodic acid-Schiff (PAS) stain). *Panel B.* Representative electron photomicrographs of the renal biopsy of Case 1 showing GBM thinning. Minimum GBM thickness is 175 nm (2682 × magnification).

develops. We suggest that the process could be a "domino" effect which starts with hemorrhage from just a few glomeruli which become obstructed, resulting in localized expansion and compression of adjacent tubules. This would lead to partial obstruction of the adjacent tubules and an increase in the hydrostatic pressure of the glomerulus serving those tubules [20]. The increase in glomerular hydrostatic pressure would result in rupture of the focally thinned glomerular capillary resulting in hemorrhage into that tubule, causing further tubular obstruction. This process could then be repeated in adjacent nephrons, resulting in the domino effect suggested above.

Factors that increase glomerular hydrostatic pressure, such as exercise [21], might promote glomerular hemorrhage in patients with thin GBM disease. Indeed, this could explain the strong association that we observed between exercise and gross hematuria with flank pain, in some of our patients.

Our favorable, but uncontrolled, experience with the use of ACE inhibitor therapy in some patients with thin GBM and LPH syndrome is consistent with the hypothesis that increased glomerular hydrostatic pressure is an important determinant of glomerular hemorrhage in patients with thin GBM. ACE inhibitor therapy lowers glomerular hydrostatic pressure [22]. In our patients, this

Table 3. Effect of enalapril therapy on loin pain-hematuria syndrome

	Duration of enalapril therapy, *months*	Favorable response to enalapril[a]
Case 1	27	Y
Case 2	17	Y
Case 3	15	N
Case 4	48	N
Case 5	14	Y
Case 6	18	Y
Case 7	7	N

[a] The patient reports fewer or less severe episodes of flank pain or gross hematuria; Y, yes; N, no

effect of ACE inhibition could reduce the potential for rupture of glomerular capillaries with thin basement membranes.

The natural history of patients with LPH syndrome and thin GBM is unclear. However, in our entire experience with patients who progress to end-stage kidney failure, we have never observed clinical scenarios that resemble those of the present patients. In many respects our patients closely resemble those in a 1979 report by the Mayo Clinic in which patients with unexplained recurrent bouts of gross hematuria and flank pain had long-term favorable outcomes [23]. Although the Mayo Clinic patients did not undergo renal biopsy, it seems likely that they are examples of the syndrome described herein.

The renal biopsies of some of our patients show a surprisingly large amount of glomerular sclerosis and interstitial fibrosis. Perhaps this is the result of damage from episodes of tubular obstruction from glomerular hemorrhage. Nevertheless, if only a relatively small percent of glomeruli have thin GBM susceptible to rupture, it can be readily understood why this disorder is unlikely to be a cause of progressive renal failure.

The present observations do not provide an estimate of the fraction of patients with LPH syndrome who have thin GBM. However, we have obtained renal biopsies in eight patients with LPH syndrome who did not have thin GBM, some of whom we have reported previously [12]. Thus, our experience suggests that a large fraction of the patients with LPH syndrome have thin GBM.

Of note is the presence of heavy C3 deposits in renal arterioles of three of our seven patients. This finding is commonly cited as an abnormality characteristic of LPH syndrome [12]. The present findings cast doubt on this interpretation because the C3 deposits do not correlate with the symptomatology in our patients and there is no obvious connection between arterial C3 deposits and thin GBM disease. We suggest that arterial C3 deposits are a common finding resulting from mild arterial hyalinosis, and are mentioned in connection with LPH syndrome simply because in some patients it was the only remarkable finding on the renal biopsy.

Analysis of the renal biopsies in the normal nonhuman primates indicates that the renal biopsy procedure itself can result in intratubular red cells. However, the biopsy procedure itself causes red cells in tubules in only about 1 per 1,000 tubules. By contrast, glomerular hematuria is associated with much higher rates of red cells in tubules. Furthermore, the finding of red blood cells completely filling tubular lumens was seen only in the patients of this study. Thus, we suggest that the finding on renal biopsy of multiple tubules containing red blood cells and/or the finding of red cells filling tubules is diagnostic of glomerular hematuria.

In summary, the present study provides evidence that there is a subset of patients with the LPH syndrome in whom the gross hematuria and flank pain are caused by rupture of thin GBM. Measures that increase glomerular hydrostatic pressure (exercise and, perhaps, hypertension) may adversely affect this condition. By contrast, measures that reduce glomerular hydrostatic pressure (such as ACE inhibitor therapy, and avoiding exertion) may benefit these patients. These hypotheses, however, remain to be proved. Long-term follow-up in patients with LPH syndrome and thin GBM is lacking. Nevertheless, there is no evidence that this disorder leads to progressive renal failure.

Acknowledgment

This study was supported in part by NIH grants HL 25404 and DK 43886. This work was presented in part at the 1993 American Society of Nephrology Annual Meeting, Boston, MA.

Reprint requests to Lee A. Hebert, M.D., Department of Nephrology, Ohio State University, 1654 Upham Dr., Room N210 Means Hall, Columbus, Ohio 43210, USA.

References

1. Little PJ, Sloper JS, Dewardener HE: A syndrome of loin pain and haematuria associated with disease of peripheral renal arteries. *Q J Med* 36:253–259, 1967
2. Burden RP, Dathan JR, Etherington MD, Guyer PB, MacIver AG: The loin-pain/haematuria syndrome. *Lancet* 1:897–900, 1979
3. Habte B, Dobbie JW, Boulton-Jones M: The loin pain-haematuria syndrome in males. *Scott Med J* 26:118, 1981
4. Sheil AGR, Ibels LS, Thomas MAB,Graham JC: Renal autotransplantation for severe loin-pain/haematuria syndrome. *Lancet* 2:1216–1217, 1985
5. Bloom PB, Viner ED, Mazala M, Jannetta PJ, Steiber AC, Simmons RL: Treatment of loin pain hematuria syndrome by renal autotransplantation CITATION?
6. Fletcher P, Al-Khader AA, Parsons V, Aber GM: The pathology of intrarenal vascular lesions associated with the loin-pain-haematuria syndrome. *Nephron* 24:150–154, 1979
7. Siegler RL, Brewer ED, Hammond E: Platelet activation and prostacyclin supporting capacity in the loin pain hematuria syndrome. *Am J Kidney Dis* 12:156–160, 1988
8. Naish PF, Abert GM, Boyd WN: C3 deposition in renal arterioles in the loin-pain and haematuria syndrome. *Br Med J* 3:746, 1975
9. Pollock CA, Ibels LS, Eckstein RP, Thomas AB, Laver C, Moir D: Afferent arteriolar C3 disease–A distinct pathological entity. *Am J Kidney Dis* 14:31–38, 1989
10. Leaker BR, Gordge MP, Patel A, Neild GH: Haemostatic changes in the loin pain and haematuria syndrome: secondary to renal vasospasm? *Q J Med* 76:969–979, 1990
11. Bergroth V, Konttinen YT, Nordstrom D, Laasonen L: Loin pain and haematuria syndrome: Possible association with intrarenal arterial spasms. *Br J Med* 294:1657, 1987
12. Dimski DS, Hebert LA, Sedmak D, et al: Renal autotransplantation in the loin pain-hematuria syndrome: A cautionary note. *Am J Kidney Dis* 20(2):180–184, 1992
13. Cosio FG, Falkenhain ME, Sedmak DD: Association of thin

glomerular basement membrane with other glomerulopathies. *Kidney Int* 46:471–474, 1994
14. HEBERT LA, BIRMINGHAM DJ, MAHAN JD, SHEN X-P, MCALLISTER C, COSIO FG, DILLON JJ: Effect of chronically increased erythrocyte complement receptors on immune complex nephritis. *Kidney Int* 45:493–499, 1994
15. BODZIAK KA, HAMMOND WS, MOLITORIS BA: Inherited diseases of the glomerular basement membrane. *Am J Kidney Dis* 23(4):605–618, 1994
16. KINCAID-SMITH P, BENNETT WM, DOWLING JP, RYAN GB: Acute renal failure and tubular necrosis associated with hematuria due to glomerulonephritis. *Clinical Nephrology* 19(4):206–210, 1983
17. LEE HS, PYO H-J, KOH H: Acute renal failure associated with hematuria in IgA nephropathy. *Am J Kidney Dis* 12(3):236–239, 1988
18. FOGAZZI GB, BANFI G, PONTICELLI C: Acute tubular necrosis caused by gross hematuria in a patient with focal and segmental necrotizing glomerulonephritis. *Nephron* 61:102–105, 1992
19. HEBERT LA, STUART KA, STEMPER JA: Whole kidney volume/pressure relationships. *Kidney Int* 7:45–54, 1975
20. PIMENTEL JL, MARTINEZ-MALDONADO M, WILCOX JN, WANG S, LUO C: Regulation of renin-angiotensin system in unilateral ureteral obstruction. *Kidney Int* 44:390–400, 1993
21. STEFANIAK JE, HEBERT LA, GARANCIS JC, SADOWSKI ME, SHAPIRO DS, FITTS RH, COURTRIGHT JB, CORNACOFF JB: Effect of moderate daily exercise on acute glomerulonephritis. *Nephron* 29:49–54, 1981
22. ANDERSON S, MEYER TW, RENNKE HG, ET AL: Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 76:612–619, 1985
23. LANO MD, WAGONER RD, LEAERY FJ: Unilateral essential hematuria. *Mayo Clin Proc* 54:88–90, 1979