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Ureteropelvic junction obstruction: morphological and clinical studies

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Abstract This study included 27 patients with ureteropelvic (UPJ) obstruction. Both renal parenchyma and the junctional abnormality were examined and correlated with clinical findings. Renal biopsies were categorized into grades 1–4. Those with normal or minimal findings (grade 1 and 2, respectively) had excellent renal function as assessed by radionuclide studies. Those with grade 4 had severe histological abnormalities associated with poor renal function. Grade 3 renal changes were seen in patients whose renal function varied greatly and did not correlate with the extent of the limited histological abnormalities. Although there was great variation in the renal biopsies, glomerulosclerosis was a consistent finding, associated with extracapillary proliferation and periodic acid-Schiff-positive material (? Tamm-Horsfall protein) in the urinary space of glomeruli in 91% (10/11) of grade 3 or 4 renal biopsies. No extracapillary proliferation was seen in grade 1 renal biopsies. The UPJ obstruction area was consistently inflamed and markedly thickened due to varying degrees of perifascicular fibrosis and muscular hypertrophy. Extensive fibrosis with associated muscular atrophy was the most-severe change in this spectrum.

Key words Renal biopsy · Glomerulosclerosis · Muscular hypertrophy · Muscular atrophy · Perifascicular fibrosis

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Introduction

Ureteropelvic junction (UPJ) obstruction, either due to "intrinsic" factors (idiopathic) or by compression of aberrant vessels [1–8], is a common cause of ureteral obstruction in childhood. The histological appearance of UPJ obstruction has received varying descriptions ranging from segmental smooth muscle attenuation with predominance of longitudinal fibers to diffuse loss of muscle or muscle disorganization [1–8]. The valves that have been noted at the UPJ are thought to result from herniated tissue at the site of the muscular abnormality [3]. A "deficiency or abnormality" of innervation has been observed [9, 10]. Recent studies have examined the correlation between renal function and findings in renal biopsies before pyeloplasty, attempting to use renal biopsy results as a predictor of post-operative improvement of renal function [11–14]. These studies showed that less than 35% of renal function correlated with severe parenchymal injury and was associated with little post-operative improvement in renal function [11]. The current study confirms and extends these observations, examines the histology of the UPJ in detail, and documents an extracapillary proliferative component to the glomerular sclerosis characteristic of this entity.

Materials and methods

Clinical

This prospective study included all patients with UPJ obstruction who underwent reconstruction in Children's Hospital, Boston between April 1997 and April 1999. Of a total of 27 patients, most had pre-operative studies of hydronephrosis (n=24) and renal function by kidney scan (n=22). A few referral patients (n=5) had these studies performed in other institutions; data on hydronephrosis grade and renal function from these patients were not used to assure consistency of interpretation.

Hydronephrosis grade (grade 1–5) was assessed by various imaging studies, including ultrasonography, intravenous pyelography or computed tomographic (CT) scan. A grading system involving both renal pelvic dilation as well as caliceal dilation was used.

Grade five hydronephrosis included marked pelvic distention with diffuse caliceal dilation, usually associated with the appearance of a thin renal parenchymal cortex. Lesser degrees of hydronephrosis (grade 1–4) reflected decreased severity of caliceal dilation. Renal function was assessed by radionuclide renal scanning, using either dimercaptosuccinic acid or MAG-3. The split renal function reflects the relative uptake of tracer at 2 min post injection by the affected kidney. The contralateral kidney always functions so that the combination of the two split renal functions equals 100%. Therefore, a normal kidney has approximately 50% renal function.

Indications for surgery reflected individual physician preferences and parental choice. In general, surgery would be recommended for patients with split renal function of <35%. Surgery was similarly recommended for those with symptomatic presentation. Surgical indications are controversial and remain in a state of evolution, for those with asymptomatic presentation, predominantly those with a prenatal diagnosis. Some of the patients are enrolled in an ongoing prospective trial of the management of prenatally detected severe unilateral UPJ obstruction.

During surgery aberrant renal vessels crossing the UPJ were identified in 5 patients, whereas there was no evidence of any extrinsic compression at the UPJ area in the remaining 22 patients. Each patient underwent reconstruction of UPJ (pyeloplasty) and renal wedge biopsies were obtained from 21 patients.

Pathological evaluation

The UPJ specimens were fixed in formalin, processed routinely, and stained with hematoxylin and eosin (H&E) and Masson trichrome. Renal wedge biopsies were fixed in Bouin's solution and stained with H&E and periodic acid-Schiff (PAS); some were also stained with Masson trichrome and the Jones silver stain. In 3 cases, material was processed for immunofluorescence and in 8 cases for electron microscopy. Histological sections of both the UPJ and renal wedge biopsies were evaluated by two pathologists (P.L.Z. and S.R.). Renal wedge biopsies were histologically graded according to the glomerular and tubulointerstitial alterations defined in Table 1. Grade 1 indicated no abnormality and grade 2 was characterized by occasional glomerulosclerotic change. Grade 3 cases included more-prominent glomerular sclerosis, as well as mild interstitial fibrosis and tubular atrophy. Grade 4 cases had severe alterations: cystic changes with parenchymal loss, many sclerotic glomeruli, and extensive loss or maldevelopment of tubules. In addition, a variety of glomerular patterns was seen, ranging from limited to extensive extracapillary proliferation with or without weakly PAS-positive material in the urinary space of glomeruli (? Tamm-Horsfall protein). The percentage of cases with extracapillary proliferation was calculated from all renal biopsies. Perifascicular fibrosis of the UPJ was assessed by the Masson trichrome stain. Mural thickness was measured from umbrella cells of urothelium to the external surface of the UPJ adventitia. Muscularis propria thickness was measured separately as an index for muscular hypertrophy. Inflammatory cells in the lamina propria were counted based on numbers of inflammatory cells per high-power field (at three different foci). Criteria for grading perifascicular fibrosis, muscular hypertrophy, and lamina propria inflammation are listed in Table 1.

To establish a concept of "normal UPJ," we searched for all autopsies performed in infants and young children who died during the same period as our study. Twelve autopsy cases without obvious ureteral and renal abnormalities were selected to define the baseline of normal kidney and UPJ. The UPJ and kidney sections of these autopsy cases were subsequently assessed based on the pathological criteria described above for the UPJ obstruction cases.

Statistical analysis

Statistical evaluations for significant differences between the two groups were performed for continuous variables using a two-tailed paired Student's *t*-test. Results were expressed as mean ±SE. Pearson's chi-squared test was used to analyze discontinuous variables in specimens, e.g., the percentage of extracapillary proliferation in patients with UPJ obstruction and controls.

Results

The age of patients with UPJ obstruction ranged from 1 month to 8 years. The male to female ratio was approximately 2:1 in the group with UPJ obstruction. UPJ obstruction was on the left in 66% and on the right in 22% of patients; 11% had bilateral involvement. Severe hydronephrosis (grade 5) before surgery was seen in 70%

Table 1 Definition of grading systems – renal biopsies and ureteropelvic junction (UPJ)

Grade of renal wedge biopsies
1 No abnormality
2 Occasional glomerulosclerosis; otherwise unremarkable; minimal tubular atrophy
3 Great variation but with generally limited glomerulosclerosis; mild interstitial fibrosis and tubular atrophy
4 Severe alterations including "dysplastic changes," over 20% glomerulosclerosis, extensive interstitial fibrosis and tubular atrophy, as well as extravasation of Tamm-Horsfall protein-like material
UPJ indices
Grade of UPJ fibrosis
1 No abnormality
2 Mild perifascicular fibrosis with muscle hypertrophy
3 Moderate perifascicular fibrosis with muscle hypertrophy
4 Severe perifascicular fibrosis with muscle atrophy
Grade of muscular hypertrophy/muscularis propria thickness at UPJ
1 <0.2 mm
2 0.4–0.8 mm
3 >0.8 mm
Grade of inflammation in UPJ lamina propria
1 No or rare inflammatory cells
2 Mild inflammation (>15 but <30 inflammatory cells per high-power field)
3 More than mild inflammation (>30 inflammatory cells per high-power field)

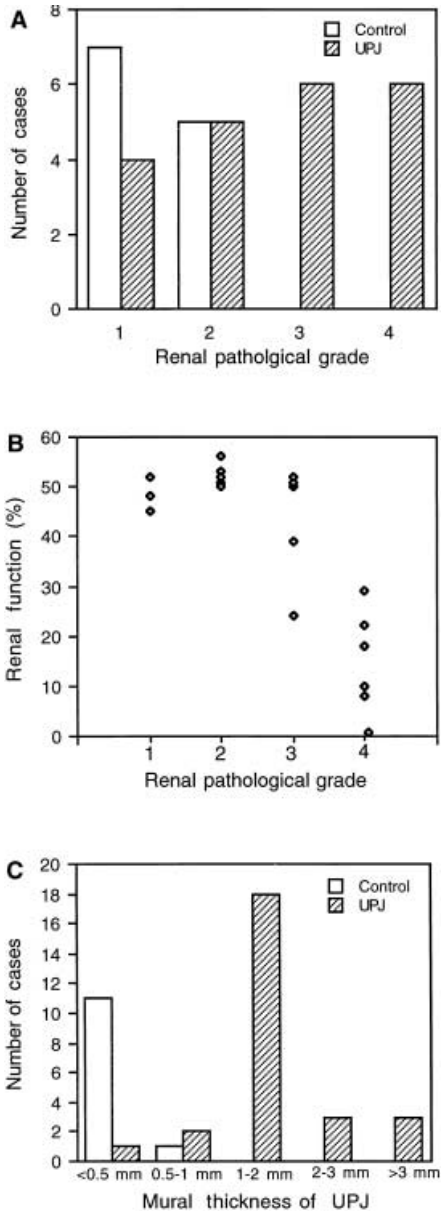

Fig. 1 **A** Distribution of different renal pathological grades in patients with ureteropelvic junction (*UPJ*) obstruction and controls. **B** Correlation of renal pathological grades in renal wedge biopsies with percentage renal function in patients with UPJ obstruction. **C** Mural thickness of the UPJ in patients with UPJ obstruction and controls

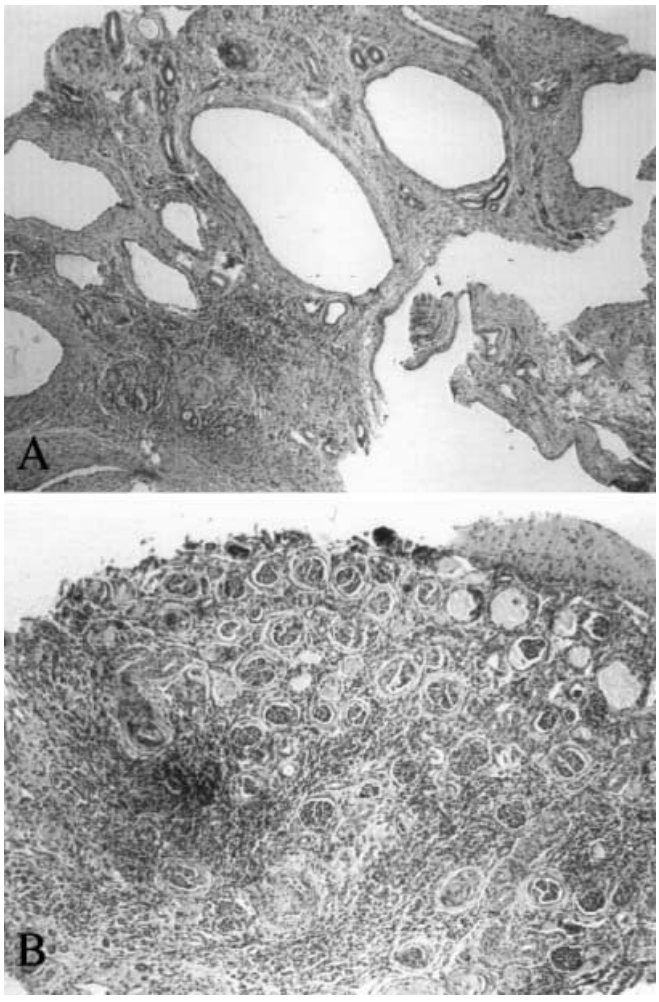

Fig. 2 Severe alterations in grade 4 renal biopsies include dysplastic changes (**A**) or extensive interstitial fibrosis and tubular atrophy (**B**) (hematoxylin and eosin, ×125)

(17/24) of patients. Grades 1, 3, and 4 hydronephrosis were identified in 4% (1/24), 12% (3/24), and 17% (4/24) of patients. Several patients had variable degrees of hydronephrosis. One patient presented with acute flank pain and a perinephric urinoma due to acute UPJ obstruction, which on subsequent imaging was only a grade 3 hydronephrosis with mild caliceal dilation. Another patient presented with a massively dilated kidney on CT scan following trauma; subsequent evaluation showed minimal hydronephrosis and yet the patient had a severe kink of the proximal ureter and markedly decreased function (scanning renal function 24%). Fifty-seven percent of patients showed grade 3 or 4 changes in renal biopsies, which were not seen in controls (Fig. 1A). There was a large spectrum of renal functional alterations in patients, ranging from no change to severe impairment, with approximately one-third of patients having renal function less than 30%.

There was a good correlation between the percentage function by renal scan and renal pathological grades. No or minimal changes (grade 1) were associated with normal renal function (Fig. 1B). Mild-to-moderate changes (grade 3) were associated with variable function, ranging from normal (50%) to severely impaired function (less than 30%). Six cases with severe alterations (grade 4) (Fig. 2) in renal biopsies were all correlated with poor renal function ranging from 0% to 29% (Fig. 1B). Among patients with UPJ obstruction, the mean renal function of those with grade 1 and 2 renal biopsies (50.1±0.9, n=8) was not significantly different from those with grade 3 renal biopsies (44.2±5.7, n=5), but was significantly higher than in patients with grade 4 re-

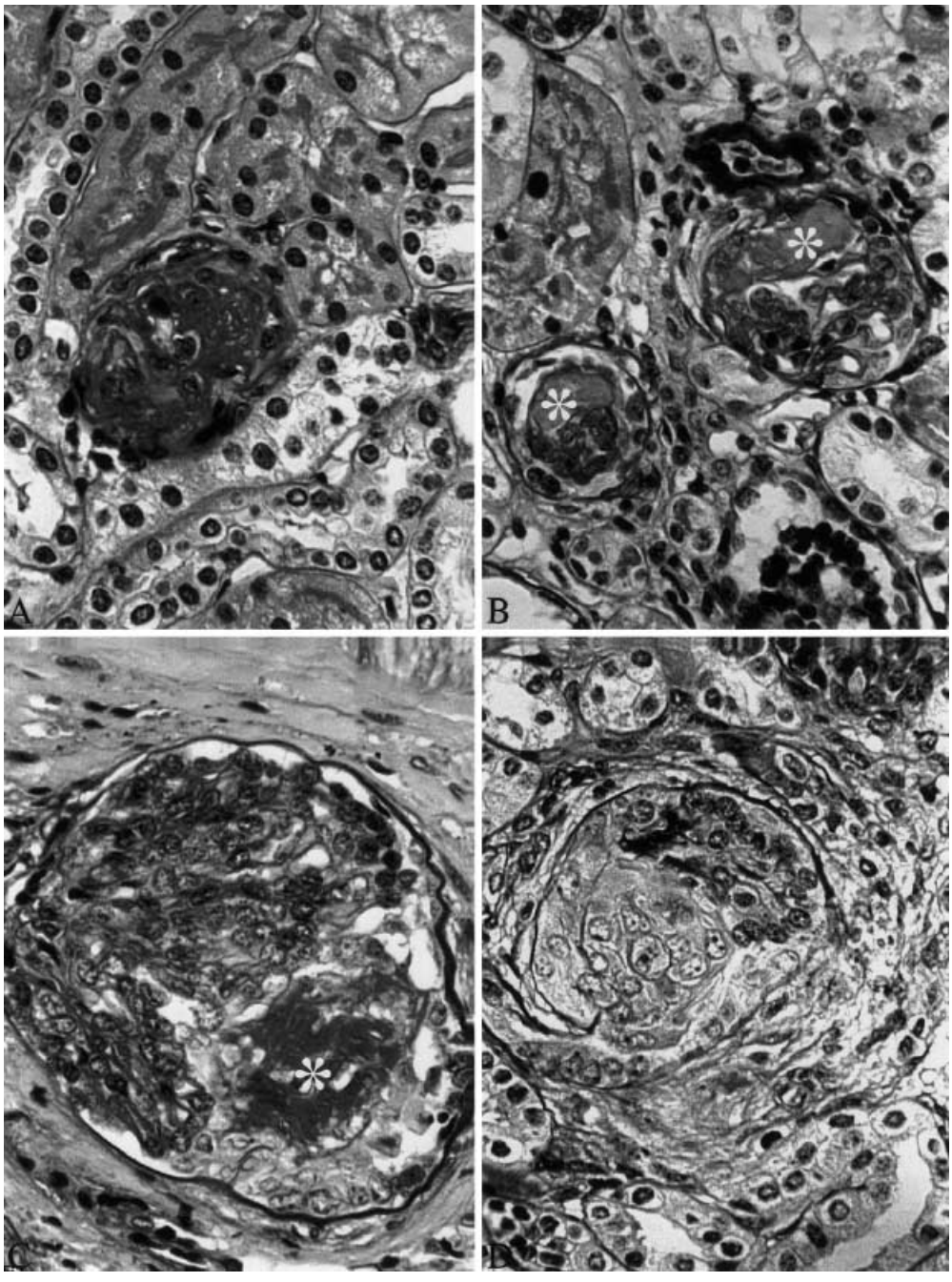

Fig. 3 The glomerulosclerosis in the renal biopsies from patients with UPJ obstruction may be simply complete sclerosis (**A**) or collapse/sclerosis with associated Tamm-Horsfall protein-like material (*asterisk*). The latter may be associated with either minimal (**B**) or obvious (**C**) extracapillary proliferation. In **D**, the proliferative process was related to the destruction of Bowman's capsule (periodic acid-Schiff, ×480)

nal biopsies (14.5±4.3, $P<0.05$, $n=6$). The mean renal biopsy grade was significantly higher in the group with UPJ obstruction (grade 2.7±0.2, $P<0.01$) than in the control group (grade 1.4±0.1). The glomerulosclerotic changes varied from global sclerosis (often very small glomeruli) to sclerosis in which the urinary space was seen to contain homogeneous weakly PAS-positive material (Fig. 3). Extracapillary proliferation was frequently associated with the latter and frank crescents with destruction of Bowman's capsule were occasionally seen (Fig. 3). The proliferative changes were associated with collapsed or globally sclerotic glomeruli. The consistent findings were that the extracapillary proliferation with associated material was seen in 91% of grade 3 or 4 renal biopsies (10/11). Extracapillary proliferation was seen significantly more often in the UPJ obstruction group (37%, $P<0.05$) than the control group (0%). In some of these renal biopsies in which proliferative changes were seen, immunofluorescence and electron microscopy were negative for immune complex and fibrin deposition. Neither hydronephrosis grade nor patient age was correlated with renal pathological grade. Mural thickness did not correlate with age, renal pathological, grade, or any clinical findings.

The average thickness of the UPJ was 0.34 mm in control cases. In most patients with UPJ obstruction,

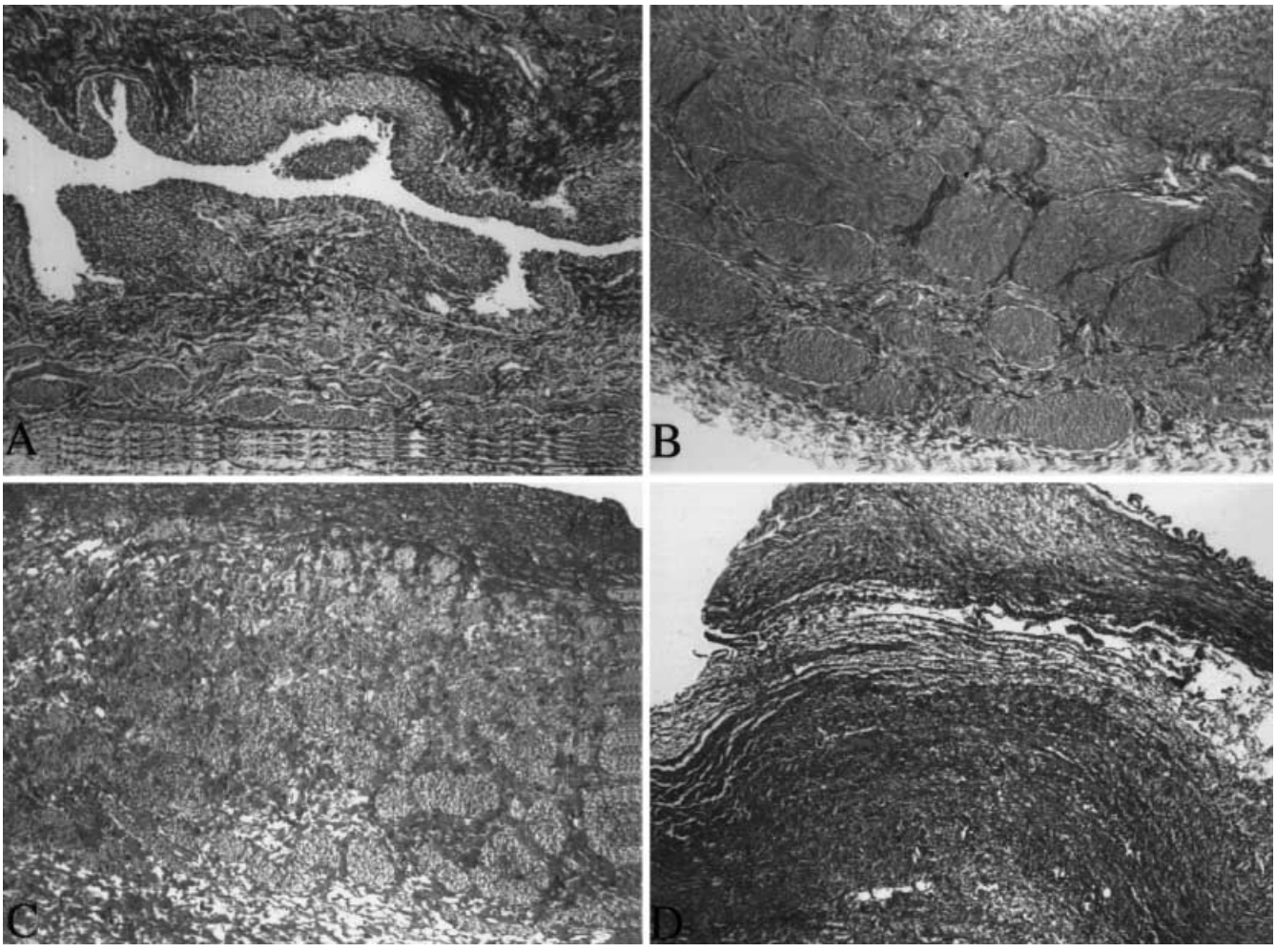

Fig. 4 The histological changes at the UPJ zone were graded (control in **A**). In **B**, the process was that of hypertrophy with limited fibrosis (grade 2). The fibrotic process was more extensive in **C** (grade 3) and in **D**, the fibrosis was severe so that the muscular component was markedly diminished (grade 4) (Masson's trichrome, ×125)

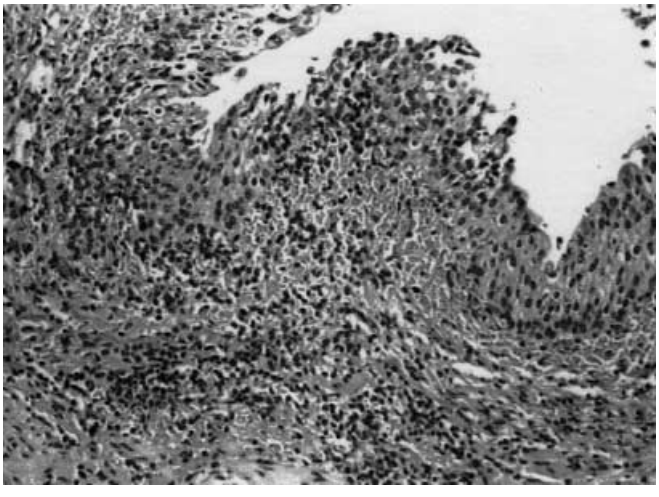

Fig. 5 Prominent chronic inflammation in the lamina propria (grade 3 inflammation) in patients with UPJ obstruction (hematoxylin and eosin, ×125)

the mural thickness of the UPJ (1.6±0.2 mm, $P<0.01$) was several times the average value of controls (0.3±0.05 mm) (Fig. 1C) and was formed mainly by the enlarged muscularis propria. Similarly, all controls had significantly less perifascicular fibrosis (grade 1.2±0.1) or muscular hypertrophy (grade 1.00±0.00) than patients with UPJ obstruction (grade 2.4±0.2 and 2.4±0.1, respectively; both $P<0.01$) (Fig. 4). Except for 1 case, controls had minimal inflammatory cells in the lamina propria (grade 1.2±0.1) compared with the UPJ obstruction group (2.1±0.1, $P<0.01$). Most patients with UPJ obstruction had grade 2 inflammation (mainly lymphocytes with some mast cells and plasma cells), whereas 3 patients had grade 3 inflammation (Fig. 5). Renal biopsies ($n=3$) and obstructed UPJ ($n=5$) due to extrinsic vessels showed no obvious difference from those in the "intrinsic" cases.

Discussion

Several studies have analyzed the relationship between changes in the renal biopsy and renal function as assessed by radionuclide scanning [11–14]. Stock et al. [11] found that patients with a differential function of

less than 35% have a high probability of "significant histological changes on biopsy" and limited post-operative improvement. Other workers also found that reduced renal function generally correlated with worse histological damage [12, 13], but there was a disparity between pre-operative differential renal function and renal biopsy findings in 25% of children [13]. In the present study, the histological changes in the renal biopsy were divided into four categories. Grade 1 and 2 were those of either no or minimal alterations; these could not be differentiated from control material or studies in the literature examining "normal" pediatric kidneys [15]. All these cases had normal pre-operative and post-operative renal function. In contrast, grade 4 changes were always associated with extensively compromised renal function and the histological alterations were all so severe that recovery of function was unlikely. In contrast, grade 3 changes showed great variation and did not correlate with renal function. In accordance with other studies, the current report showed that pre-operative renal function of less than of 30% correlated with worse renal damage (grade 3 or 4) and appeared irreversible following pyeloplasty. In our study, normal pre-operative renal function does not exclude the patients with mild-to-moderate renal damage, since 3 patients in the study had normal renal function before surgery but grade 3 changes in renal biopsies. Using a cutoff of 45% of pre-operative renal function for pyeloplasty, Tapia and Gonzalez [16] found a 54% increase in post-operative glomerular filtration rate in 16 pediatric patients with UPJ obstruction, and therefore recommended early surgery to prevent later irreversible changes. Large prospective studies are needed to determine whether early correction of UPJ obstruction will benefit patients the most.

In the current study, occasional glomerulosclerosis was seen in unremarkable renal biopsies, as observed by others [17]. From indirect evidence of glomerulosclerosis, dilation of Bowman's capsule and tubules, and proteinuria, Pascual et al. [14] proposed that glomerular hyperfiltration after the obstruction is the cause for subsequent renal damage. Causes for this glomerulosclerosis in our pathological material may be many: developmental phenomenon, hyperfiltration injury, or a glomerular extracapillary proliferative response that progresses to glomerulosclerosis. In the current study, we speculate that the glomerulosclerosis is related to the weakly PAS-positive material in the urinary space (? refluxed Tamm-Horsfall protein). Tamm-Horsfall protein has been noted in Bowman's space in a variety of circumstances that relate to intratubular reflux of urine, i.e., to tubulointerstitial injury [18] or obstruction [19]. In one study, this protein was seen in Bowman's space and in the interstitium in 42 renal biopsies; this abnormal distribution of Tamm-Horsfall protein did not correlate with the degree of tubulointerstitial damage or alteration of renal function [20]. We are not aware of extracapillary glomerular proliferation described in association with this protein. However, we have seen this relationship previously, in a partial nephrectomy performed because of an ectopic ureter draining into the vagina and in a case of UPJ obstruction not included in the present series. Staining for Tamm-Horsfall protein in these cases showed inconsistent results; specifically the putative protein when associated with glomerulosclerosis and crescent formation stained equivocally or not at all (N.R. Hannigan, J.T. Herrin, H.G. Rennke, S. Rosen; unpublished results). The PAS positivity of the Bowman space protein is clearly less than that for Tamm-Horsfall protein in casts within tubules or after extravasation into the interstitial tissues. It is conceivable that this material is indeed Tamm-Horsfall protein, which has been degraded so that epitopes are no longer easily available for detection.

The UPJ was examined in all of our patients in whom renal biopsies were obtained. This study differs from others in that control material was obtained and exact measurements of tissue thickness were performed. Semiquantitative analysis of fibrosis and muscular hypertrophy revealed that UPJ alterations could be categorized into groups with increasing perifascicular fibrosis associated with muscular hypertrophy. The most-severe changes were those of severe fibrosis with muscle atrophy, possibly the final evolution of the latter.

There appear to be at least two types of UPJ obstruction, one resulting from compression by aberrant vessels and the other being idiopathic or due to "intrinsic" factors. Early descriptions of the UPJ alterations were those of extensive fibrosis and muscular attenuation [1–8]. In our study the changes in the UPJ could not be distinguished by etiology (extrinsic or intrinsic), at least in part due to the fact that some of our cases had extensive perifascicular fibrosis and made the distinction impossible at this apparent late stage. Some cases with muscular hypertrophy with limited fibrosis may be considered as in a "proliferative stage". In recent years, advanced radiological techniques may have allowed early detection and treatment of an abnormality at the UPJ, so that progression to severe fibrosis may have been diminished. Innervation abnormalities at the UJP have been suggested as another cause for the UPJ obstruction, based on findings of reduced nerve distribution at this location [9, 10]. It is, however, not certain whether the diminished nerve distribution at the obstructed UPJ [9, 10] results from a primary defect or is secondary to considerable distortion by hypertrophic muscle and fibrosis.

In the current study, a significant inflammatory component was seen in the lamina propria of UPJ in most obstruction cases, whereas only occasional inflammatory cells in the lamina propria were seen in controls. With UPJ obstruction, the inflammatory cells were mainly lymphocytes, with some plasma cells and mast cells. Regardless of the primary cause of idiopathic UPJ obstruction, chronic inflammatory components indicate chronic injury at this obstructed zone. It would be interesting to investigate whether the chronic inflammatory process at the obstructed UPJ is important in the genesis of the muscular hypertrophy and fibrogenesis, as seen at a "proliferative stage," or a final "fibrotic stage" with limited remaining muscle.

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