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Urothelium damage as the primary cause of ureteropelvic junction obstruction: a new hypothesis

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Abstract Ten infants under 6 months old underwent surgery for obstruction of the ureteropelvic junction. Craniocaudal light microscopy showed subdivision of the resected ureteropelvic junction into three portions: prestenotic, stenotic, and poststenotic. The prestenotic portion was characterized by dilatation of the ureteral lumen, flattening of its mucosal folds and thinning of the urothelium; the stenotic tract showed partial or total loss of the epithelium and fibrosis of the mucosal and fibromuscular coats. No modifications were detected in the poststenotic portion. We advance the hypothesis that a primary epithelial break might cause urine to spread inside the ureteral wall and consequently the mastocytes to migrate and degranulate within the mucosal and fibromuscular coats. The histamine and prostaglandins produced by the mastocytes could induce prolonged muscular spasm, in turn responsible for increasing the intrapelvic pressure and so causing enlargement of the epithelial break. A connective tissue reaction of the ureteral wall would thus occur, which should be considered a secondary event leading to fibrotic stenosis of the ureteropelvic junction.

Key words Ureteropelvic junction obstruction · Pathogenesis · Children · Histology

Introduction

Congenital obstruction of the ureteropelvic junction (upj-o), is usually observed in children and its detection is considered the result of manifestation of a progressive malfunction disorder which began in fetal life [9]. The main histological alterations described for upj-o are fibrosis of the mucosa and fibromuscularis tunicae, in both the stenotic and prestenotic tract [4, 6, 7, 12, 13], together with changes in the number, distribution, and size of the muscle cells in the ureteral wall, which seem numerically increased in the prestenotic tract and reduced in the stenotic one [7].

In idiopathic hydronephrosis, investigators have reported an alteration in the specialized muscle cells of the pyeloureteral pacemaker system, whereby there is a reduction in the number of cell-to-cell junctions involved in the electric coupling of the muscle cells [4]. A previous study on upj-o has suggested that myocytes of the ureteropelvic wall may stimulate the production of a surplus of collagen fibres in the fibromuscularis tunica [6].

The pathogenesis of upj-o is still unknown despite considerable research in this field. This may be due in part to failure to make serial sections of prestenotic, stenotic, and poststenotic ureteric segments and to the early occurrence of urinary tract infections, which may have complicated microscopic observation. The aim of this work was to provide further information on the etiopathogenesis of upj-o, by means of a morphological study of serially cut sections of the ureteropelvic junction (upj) in children affected by upj-o uncomplicated by urinary tract infection.

Materials and methods

The ureteropelvic junctions of ten children under 6 months of age were analyzed. Nine had monolateral upj-o and in the remaining patient a monolateral upj-o was associated with ipsilateral vesicoureteral reflux. In all cases, a prenatal diagnosis of upj-o had been made with ultrasonography and subsequently confirmed by cystography, intravenous pyelography, and a renogram. The last two tests were performed at 3 weeks of age with diuretic stimulation (furosemide 0.3 mg/kg i.v. bolus), to discriminate obstructive from

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nonobstructive hydronephrosis. In all cases, diuretic stimulation failed to force a passage, confirming the obstructive nature of the upj-o.

The resection specimens (obtained during surgery performed according to the Anderson-Hynes technique), included the upj and a portion of the adjacent pelvis and the upper ureter. In all specimens, narrowing of the upj was evident. The fragments were fixed in Bouin's fluid, dehydrated in alcohol, embedded in paraffin, and serially cut in 7-μm-thick sections, in a proximodistal direction, orthogonally to the longitudinal axis of the ureter. During both the surgical and the histological procedures, care was taken to preserve the anatomy of the specimen. The sections were stained with hematoxylin-eosin and with metachromatic substances such as alcian blue-safranin and toluidine blue, to detect the presence of mastocytes in the ureteral wall.

The upj of three deceased children (a two-year-old child, who died of cardiovascular disease, a two-month-old who died of necrotizing enterocolitis, and a five-month-old who died of intracerebral hemorrhage secondary to child abuse), were used as controls. Mastocyte counts were performed using morphometric software (Analysis kontron electronic/Carl Zeiss image analysis system/VIDAS), and the parametric *t*-test was used to compare means.

Results

Control cases

In the histological sections of the control specimens, the mucosa showed longitudinal folds, giving a typical star-like configuration to the lumen. In all control upj, a normal transitional epithelium completely covered the tunica propria. The latter was composed of closely woven connective tissue, which became progressively looser nearing the tunica fibromuscularis. In the fibromuscular coat, thin bundles of connective fibers were interposed among the smooth muscle cells, which were arranged in two layers, inner and outer, of similar thickness, with longitudinal and circular orientation of the myocytes, respectively. The adventitial coat consisted of loose connective tissue containing blood vessels and nerve fibers (Fig. 1).

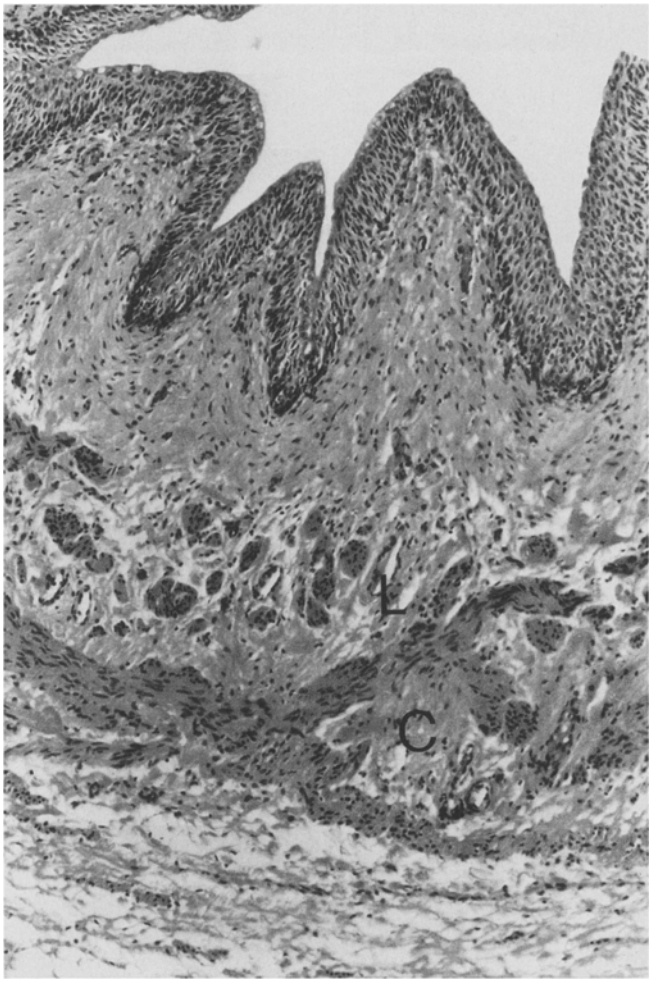

Fig. 1 *Control ureter.* The mucosa, made up of a thick urothelium and a dense connective layer, forms longitudinal folds jutting out into the lumen. The muscular coat is formed by two layers, an inner longitudinal (*L*) and an outer circular (*C*) layer. Hematoxylin-eosin, ×75

Upj-o specimens

In all specimens, three morphologically different segments: (A) prestenotic, (B) stenotic, and (C) poststenotic, were easily recognized:

A. In the prestenotic tract, the ureteral lumen was dilated and the mucosa folds were absent. The epithelium was thin throughout and some cells in its superficial and intermediate layers were detached or injured. The fibromuscular coat was built up of thick, closely packed muscular layers, where circular muscle bundles are more represented than longitudinal ones. In two cases, the circularly oriented smooth muscle bundles were dissociated, while the longitudinally directed ones were reduced. The adventitial layer showed no morphological changes (Fig. 2A).

B. Proceeding in a caudal direction, the ureteral lumen progressively narrowed (stenotic tract). The urothelium was lacking almost everywhere, being preserved only in small areas, so that the subjacent, thickened tunica propria was uncovered. The connective tissue of the fibromuscular coat was abundant, and damaged smooth muscle cells were also apparent. The tunica adventitia had a normal structure (Fig. 2B).

C. In the poststenotic tract, the ureteral lumen contour was star-shaped, due to numerous mucosal folds; the covering epithelium was multilayered and continuous. The fibromuscular wall had a normal structure made up of two laminae of myocytes arranged longitudinally (inner layer) and circularly (outer layer). No significant changes in the adventitia were observed (Fig. 2C).

In the control cases, mastocytes were present in both the tunicae mucosa and the fibromuscularis ($10.7 \pm 4.1/75.440\ \mu m^2$). In the upj-o specimens,

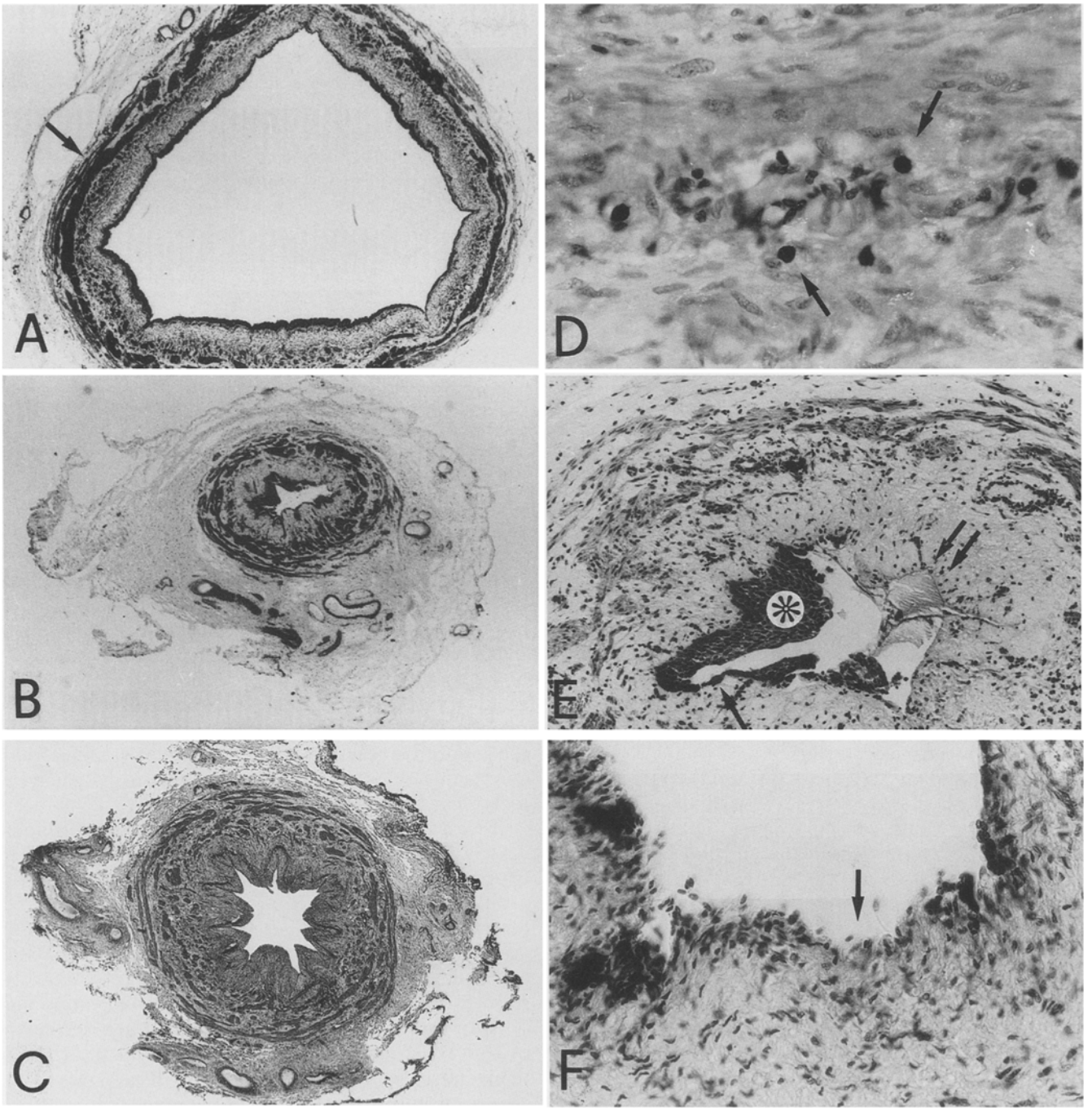

Fig. 2 **A** *Prestenotic tract.* The ureteral lumen is dilated, mucosal folds are absent, and the urothelium is thin, but preserved everywhere. The tunica fibromuscularis is thick with closely packed smooth cells (*arrow*), mainly in its circular layer. Alcian blue-safranine, × 25. **B** *Stenotic tract.* The lumen is highly stenotic and the covering epithelium appears damaged or absent. Connective tissue is abundant in both tunica propria and tunica fibromuscularis. Alcian blue-safranine, × 25. **C** *Poststenotic tract.* Mucosal folds are present and the transitional epithelium is continuous and intact everywhere. The tunica propria is thin. Both the circular and the longitudinal muscular layers are present and regularly arranged. Hematoxyline-eosin, × 25. **D** *Prestenotic tract.* Granulated mastocytes are apparent around blood vessels and smooth muscle cells (*arrows*). Alcian blue-safranine, × 270. **E** *Stenotic tract.* The lumen is narrow and the covering epithelium is partly preserved (*asterix*), partly thin (*arrow*), or lacking (*double arrow*). Connective tissue is abundant in both tunica propria and tunica fibromuscularis. Muscular tissue is poorly represented. No mastocytes are recognizable. Alcian blue-safranine, × 75. **F** *Stenotic tract.* The urothelium is lacking (*arrow*); the tunica propria connective tissue directly bordering on the lumen is dense and rich in fibrocytes; no mastocytes are recognizable. Alcian blue-safranine, × 100

numerous granulated mastocytes were recognizable in the mucosal and fibromuscular coats of the prestenotic tract ($15 \pm 1.4/75.440\ \mu m^2$), either located near the blood or intermingled with smooth muscle cells among the collagen fiber bundles (Fig. 2D). Mastocytes were rare or absent in the stenotic tract ($2.5 \pm 3.5/75.440\ \mu m^2$), where the urothelium was severely injured (Fig. 2E, F). They are normally present in both the tunica propria and the fibromuscular coat of the poststenotic tract ($12.5 \pm 6.4/75.440\ \mu m^2$). The number of mastocytes were significant reduced ($P < 0.001$) in the stenotic tract with respect both to controls and to the pre- and post-stenotic portions.

Discussion

Our histological findings confirm the results of the instrumental tests performed before surgery and show that the ureteropelvic junction of the upj-o specimens is characterized by remarkable morphological alterations. Most significant was the lack of covering epithelium in the stenotic segment. Epithelial modifications were also observed in the prestenotic tract, where the urothelium appeared slightly thinned and contained damaged cells in the superficial and intermediate layers. These structural upj modifications suggest that the epithelial loss is primary in the stenotic segment and secondary in the prestenotic one, where it might be consequent to urinary stasis.

It is well known that the transitional epithelium of the upj consists of three layers, in which the cells of the superficial layer are welded by junctional complexes, zonulae occludens (tight junctions), zonulae adherens, and desmosomes, which contribute to the constitution of the ureteral barrier, preventing free diffusion of urine in the subepithelial layers [8, 18]. This barrier system can be altered not only by various pathological conditions such as renal stones [16], bilharziasis [17], pyelonephritis [17, 5], and urinary stasis [17] but also during fetal and neonatal development, owing to the peculiar sensitiveness of the immature junctional complexes. It seems possible that breaks in the epithelial junctions, occurring for any reason during intrauterine life, or any defects in maturation, may result in an ineffective ureteral barrier with consequent diffusion of small amounts of urine in the underlying tunicae propria and fibromuscularis. Urine diffusion through the connective interstitium could stimulate mastocyte migration and degranulation, releasing histamine and prostaglandin, in turn responsible for spastic contraction of the smooth muscle cells [16]. By causing a transitory obstruction to urinary flow, the muscular spasm could increase intrapelvic pressure and consequently enlarge the primary epithelial break. The progressive breakage of the epithelial barrier might increase the spread of urine through the ureter wall, causing further structural changes in the mucosal and fibromuscular coats, such as dissociation of the collagen fiber bundles, degeneration of myocytes, and disappearance of mastocytes, most probably caused by the cytotoxic effect of the urine. The modifications in the connective interstitium of the tunicae propria and fibromuscularis, together with the myocyte damage, might trigger a connective tissue reaction ultimately leading to fibrosis of the stenotic tract. Thus, upj-o would be functional at onset and then become morphological and irreversible, depending upon the fibrosis building up in the ureteral wall. It seems likely that the final fibrosis might also cause damage to the ureteropelvic pacemaker system [3].

The pathogenetic mechanism of upj-o suggested in this paper would also account for the fact that this disease can manifest itself during adult life [1], since the connective and muscular tissue reactions are obviously long-term and progressive processes. The passing of time may, in fact, play an important role in the increase in volume of the obstructed urinary system which leads to large-scale hydronephrosis [2]. This hypothesis also implies that intermittent hydronephrosis, believed to be transitory and functional, should be considered the initial expression of evolving obstructive processes affecting the ureteral wall [10]. It could help to explain the development of upj-o in patients affected by ipsilateral vesicoureteral reflux or megaureter [11, 14]. In these situations, urinary stasis or recurrent infections might cause breakage of the ureteral barrier and trigger the connective reactions. Another unanswered question concerning upj-o is why the obstruction is generally located at the level of the upj.

If we assume the pelvis and ureter to be continuous vessels, having different diameters only, the following explanation can be proposed. It is known that the radius (R) of a vessel is strongly influenced by three forces: (1) the pressure (P) inside the lumen of the vessel; (2) the elastic tension (ET) produced by elastic and collagen fibers (this is the force that automatically restores the R of the vessel to its native state); and (3) the vasomotor tone, which generates active tension (AT) in the wall of the vessel (when this force increases it can provoke vessel constriction). When AT overcomes ET and P, a reduction in the vessel caliber takes place (according to Laplace's law). This model can be further elaborated by considering the P effect resulting from a decrease in the vessel R. Bernoulli's law indicates that a reduced cross-sectional flow area produces higher flow velocity and lower P in that area, thus reducing the amount of AT force necessary to cause vessel R reduction. So, as vessel R decreases, P increases above the obstruction and, eventually, forces the vessel to reopen [15].

If this model is applied to our hypothesis, the suggestion may be made that the spastic contraction of smooth muscle cells generated by the liberation of histamine and prostaglandin from mastocytes increases

the AT in the ureteral wall, in turn causing closure of the ureteral lumen. The increasing P generated in the pelvis to overcome the functional obstruction may increase the epithelial break and thus trigger the progressive damage leading to stenosis. The upj, which is the first segment of the urinary tract with a small R, is probably the most affected by these events.

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