Does the Histopathologic Pattern of the Ureteropelvic Junction Affect the Outcome of Pyeloplasty?

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Purpose: To investigate the effects of the histopathologic pattern of obstructed ureteropelvic junction (UPJ) specimens, including collagen type 3, elastin, fibrosis and Cajal cells, on the outcome of pyeloplasty.

Materials and Methods: Histopathological specimens obtained following Anderson-Hynes pyeloplasty from 52 patients with intrinsic ureteropelvic junction obstruction (UPJO) between January 2005 and January 2008 were evaluated histopathologically. Patients with extrinsic or secondary UPJO were excluded. Preoperative and postoperative radiographic evaluations were performed either via diuretic renography or intravenous pyelography, or both. Six months post-surgery the patients were divided into 2 groups, as successful surgery (group 1) and unsuccessful surgery (group 2). Histopathological findings (collagen type 3, elastin, fibrosis and Cajal cells) in each group were statistically compared.

Results: The study included 52 patients (21 female and 31 male). Mean age of the entire study population was 39.42 ± 14.5 years, versus 39.63 ± 14.9 years in group 1 (n = 47) and 37.4 ± 10.0 years in group 2 (n = 5). Median follow-up was 18 months. There weren't any significant differences in collagen type 3, elastin, fibrosis, or Cajal cells between the 2 groups ($P > .05$).

Conclusion: The histopathologic pattern of UPJ was not a factor associated with the success of pyeloplasty. Based on the present findings, we conclude that surgical technique is more important than the histopathologic pattern of UPJ for the successful treatment of UPJO.

Keywords: kidney pelvis; surgery; treatment outcome; ureteral obstruction; follow-up studies; physiopathology.

INTRODUCTION

Ureteropelvic junction obstruction (UPJO) is the most common congenital urinary tract obstruction, which occurs in 1 per 1000 newborns.[1] The underlying mechanism of UPJO remains unclear. A decrease in smooth muscle cells at the ureteropelvic junction (UPJ), abnormal muscle orientation, and collagen deposition, as well as a reduction in Cajal cells[2] and neural elements[3] have been suggested to play a role in the pathogenesis of congenital UPJO. Open pyeloplasty remains a viable treatment option for primary repair of primary UPJO, along with long-term follow-up.[4,5] Despite the efficacy of open pyeloplasty, in some patients the procedure is unsuccessful and additional intervention is required to treat persistent obstruction. The cause of pyeloplasty failure is not clear and the role of the histopathological pattern of the UPJ in this failure is contentious. The present study aimed to investigate the effect of the histopathological pattern of the UPJ on the outcome of pyeloplasty in patients with UPJO.

MATERIALS AND METHODS

Histopathological specimens obtained following Anderson-Hynes pyeloplasty in 52 patients with intrinsic UPJO between January 2005 and January 2008 were evaluated histopathologically. Patients with extrinsic UPJO and those with a history of surgical treatment were excluded. In preoperative evaluation, the patients whose ureters were visualized in intravenous urography (IVU) were excluded from the study. Patients whose ureters were not visualized in IVU were investigated via diuretic renogram. During diuretic renogram, intravenous furosemide was injected to the patients 20 minutes after radiotracer injection. Clearance half-time of the tracer (T1/2) from the collecting system was then measured. Patients who had T1/2 ≥ 20 min were accepted as having obstruction and then had pyeloplasty operation. In postoperative 3rd month evaluation while patients whose ureters were visualized in IVU were evaluated as successful surgery, patients whose ureters were not visualized in IVU were investigated via diuretic renogram. Also patients whose ureters were visualized in IVU and who had T1/2 < 20 min in diuretic renogram were evaluated as successful surgery (group 1, n = 47). The patients who had obstruction in post-operative 3th month were investigated via diuretic renogram again post-operative 6th month and patients who had T1/2 ≥ 20 min were accepted as having obstruction and evaluated as unsuccessful surgery (group 2, n = 5). All surgeries were performed by the same surgeon. All patients had an indwelling double pigtail stent placed intraoperatively, which was removed 4-6 weeks post-surgery. The UPJ segments excised in each group (successful surgery [group 1] and unsuccessful

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Table 1. Demographic characteristics of study patients.

Variables	Surgically Successful Group (n = 47)	Surgically Unsuccessful Group (n = 5)
Age, years (Mean ± SD)	39.63 ± 14.9	37.4 ± 10.0
Male, no	28	3
Female, no	19	2
Right side, no	26	3
Left side, no	21	2

surgery [group 2]) were compared histopathologically (collagen type 3, elastin, fibrosis, and Cajal cells).

Pathological Evaluation

All excised UPJ segments were examined at Dicle University, School of Medicine, Pathology Lab. Sections 4 µm thick were obtained from formalin-fixed paraffin blocks, stained with hematoxylin & eosin, and examined under a light microscope. Reticulin and Masson's trichrome staining was performed to determine collagen type 3 status in the submucosa and the presence of fibrosis.

Immunohistochemical Method

Cross sections 4 µm thick obtained from the paraffin blocks of selected patients were transferred to positively charged slides for immunohistochemical examination using a CD117/c-kit (catalogue no. CME 296 AK, Biocare Medical, Concord, CA, USA) and Elastin (catalog no. GTX29519 GeneTex, Inc. TX, USA antibodies). Sections were deparaffinized. Dehydration was performed in 96-degree ethyl alcohol and antigen recovery was carried out in a microwave oven in pH 6.0 citrate buffer solution. The sections were cooled for 20 min at room temperature and kept in phosphate buffered saline (PBS) solution for 10 min. The tissues were circled using a hydrophobic pen, and then maintained in protein block solution (Ultra V Block) for 5 min. The sections were then washed with PBS and incubated for 40 min using a CD117/c-kit and elastin. Next, they were washed with PBS, maintained at room temperature for 20 min with coenzyme Value Primer Antibody Enhancer, and then washed with PBS solution. Afterwards, they were treated with Value Horseradish Peroxidase (HRP) Polymer for 30 min in a dark environment. They were then washed with PBS, maintained in 3-amino-9-ethylcarbazol (AEC) single solution, and then washed with distilled water. Contrast staining was performed for 2 min using Mayer's hematoxylin. After drying at room temperature they were covered with aqueous mounting material (Ultramount, Labvision, Fremont, CA, USA), and then evaluated under a light microscope.

Evaluation of CD117, Elastin, Masson's Trichrome, and Reticulin Staining

Cajal cells between the muscle layers stained with CD117 were enumerated in the 10 Times Enlarging Area (TEA) and evaluated as follows: n = 0-1 (–); n = 2-5 (+); n = 6-10 (++); n = ≥ 11 (+++). Macrophages in the mucosa and submucosa were evaluated as positive controls. Evaluation of elastin staining was positive (+) or negative (–). The blood vessel wall was evaluated as a positive control. Masson's trichrome staining evaluation was performed according to fibrosis in the submucosa.

Table 2. The results of statistical analysis.

The Parameters Evaluated Histopathologically	Surgically Successful Group (group 1, n = 47)	Surgically Unsuccessful Group (group 2, n = 5)	*P* Value
Cajal cells			
–*	6 (12.8)	0 (0)	.910
+**	24 (51.1)	4 (80)	.446
++***	11 (23.4)	0 (0)	.521
+++****	6 (12.8)	1 (20.0)	1.000
Elastin (+)	8 (17.0)	0 (0)	.726
Elastin (-)	39 (83.0)	5 (100)	
Fibrosis (+)	13 (27.7)	2 (40.0)	.952
Fibrosis (-)	34 (72.3)	3 (60.0)	
Collagen type 3 (+)	6 (12.8)	2 (40.0)	.341
Collagen type 3 (-)	41(87.2)	3 (60.0)	

P = Chi-square test. Data are presented as no (%).
* = 0-1 Cajal cell
** = 2-5 Cajal cells
*** = 6-10 Cajal cells
**** = ≥ 11 Cajal cells

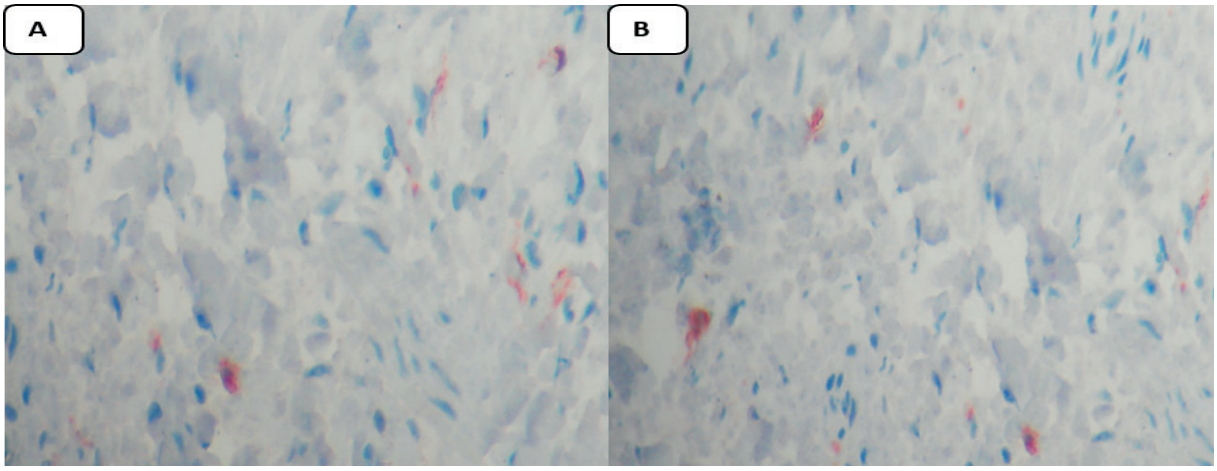

Figure. Immunoperoxidase × 400 Cd117 positive Cajal cells. **(A)** A 32 years old male patient with successful surgery; **(B)** A 38 years old male patient with unsuccessful surgery

Elastin couldn't be separated, as the collagen, elastin, and other connective tissues were stained blue; staining was considered positive (+) if there was blue coloring under the epithelium and negative (–) if there wasn't. Reticulin was evaluated according to the thickness of the fibers in the submucosa, as positive (+) or negative (–); reticulin fibers observed via low magnification were considered positive (+) and those that were not were considered negative (–).

Statistical Analysis

Statistical analysis of the data was performed using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 15.0. Frequencies and means for all data in both groups were calculated. Between-group comparisons were made using the chi-square test with Yates correction. The level of statistical significance was set at $P < .05$.

RESULTS

The study included 52 patients (21 female and 31 male). Mean age of the entire study population was 39.42 ± 14.5 years, versus 39.63 ± 14.9 years in group 1 (n = 47) and 37.4 ± 10.0 years in group 2 (n = 5). Median follow-up time was 18 months. Mean duration of surgery was 65 min and mean duration of hospitalization was 5 days. Intraoperative and early postoperative complications were not observed. In all, at 3 months post-surgery 47 patients were free of obstruction, whereas 5 had persistent obstruction, which persisted in all 5 at the 6-month post-surgery follow-up; these 5 patients with persistent obstruction constituted the group 2 (unsuccessful surgery group). Among the 5 patients in group 2, 1 underwent a second open pyeloplasty, 3 underwent antegrade endopyelotomy and 1 underwent nephrectomy. The case who underwent nephrectomy was determined as having decreased renal function (17%) in scintigraphy via techenetium-99m-labeled diethylenetriaminepentaacetic acid (99mTc-DMSA) in preoperative. The case underwent nephrectomy due to determining significantly decreased renal function (6%) in scintigraphy (via 99mTc-DMSA) in postoperative 6th month. Patient characteristics are given in **Table 1**. The UPJ segments in the 2 groups were examined histopathologically. There weren't any differences in the quantity of collagen type 3, elastin, fibrosis, or Cajal cells in the examined UPJ segments between the 2 groups ($P > .05$) (**Table 2, and Figure, A and B**).

DISCUSSION

Several open and minimally invasive surgical techniques are used for the treatment of UPJO. Although open surgery remains the gold standard, with a success rate as high as 97%,[6,7] alternative techniques have been developed in order to reduce the occurrence of morbidity associated open pyeloplasty while maintaining a high success rate. The overall success rate in the present study was 90.4%. The role of surgical technique and histopathological pattern of the UPJ in surgical success remains unclear. Many studies have compared the histopathological pattern of normal and obstructed UPJ segments, but none have examined the role of the histopathological pattern of UPJO segments in surgical success. To the best of our knowledge the present study is the first to investigate the role of the histopathological pattern of UPJO segments in surgical success. It is well known that Cajal cells are required to generate smooth muscle electrical slow waves.[8,9] Solari and colleagues[2] were the first to observe C-kit-positive Cajal cells in the normal human UPJ. As in gastrointestinal motility, Cajal cells may play an important role in the propagation, coordination and modulation of ureteropelvic peristalsis. Many studies have examined Cajal cells in the histopathologic examination of UPJ segments. Cajal cells were determined via CD117 tyrosine kinase receptor. This method is inadequate to determine all the Cajal cells and able to determine only functional active Cajal cells. Koleda and colleagues[10] reported that the number of Cajal cells in obstructed UPJ segments was higher than in normal UPJ segments, concluding that the observed increase in Cajal cells compensates for the effects of obstruction. Kuzgunbay and colleagues[11] reported that the number of Cajal cells increases during the early period of obstruction, as peristaltic activity increases, but that during the late period of obstruction as peristaltic activity decreases the number Cajal cells also decreases. In the same study, the number of Cajal cells were seen to decrease with increasing age in a pediatric group.[10] In our study, there were few cases in unsuccessful surgery group thus we thought that it was not essential to re-group the patients in unsuccessful surgery group

depending age range. In the present study there wasn't a significant difference in Cajal cells between the 2 groups. As all of the present study's specimens were obtained in the late period of obstruction when Cajal cells were decreased, we don't think that the number of Cajal cells will change and affect the surgical success. Kim and colleagues[12] reported that an increase in the collagen-smooth muscle ratio and an increase in elastin content in the obstructed UPJ contribute to inelasticity and low compliance, resulting in slower recovery of hydronephrosis following pyeloplasty. Kaselas and colleagues[14] studied the role of renal pelvis collagen, elastin and smooth muscle thickness in postoperative radiologic recovery, and reported that collagen and elastin did not play a role, whereas as an increase in smooth muscle thickness prolonged radiologic recovery. Similarly as Kaselas and colleagues,[14] in the present study there weren't any significant differences in collagen or elastin between the 2 groups. In an animal model of pyeloplasty Passerotti and colleagues[15] studied the histopathologic pattern of the UPJ 15 days post-surgery, and reported that fibrosis and accumulation of collagen type 3 were lower in the robotic-assisted laparoscopy group than in the open pyeloplasty and hand-assisted laparoscopy group. They concluded that the superior visual capability of robotic-assisted laparoscopy facilitates less traumatic surgery. In the present study there weren't any significant differences in collagen accumulation or fibrosis between the 2 groups, clearly indicating that they did not play a role in surgical success. As Passerotti and colleagues[15] reported, we also think that excessive dissection during pyeloplasty causes tissue hypoxia, resulting in fibrosis and accumulation of collagen. We think that the amount of fibrosis in the resected UPJ region does not have an effect on surgical success, but that fibrosis due to hypoxia and accumulation of collagen might negatively affect surgical success. Kim and colleagues[13] separated excised UPJs into 3 segments, as renal pelvis, UPJ and ureter, and examined elastin in each segment separately. They concluded that the amount of elastin in the remaining ureter and renal pelvis following excision of the UPJ could be an important factor affecting surgical success. In the present study the specimens were examined without separation. The effect of histopathology on surgical success would be better comprehended when histopathologic structure of remaining segments of ureter and pelvis that end to end anastomosis is done, is evaluated instead of histopathologic structure of excised segment.

CONCLUSION

The success of the surgical treatment of UPJO primarily depends on surgical technique and less so on the histopathological pattern of the UPJ. During surgery excessive dissection should be avoided and vascularization should be preserved: the resected amount should be in proper amount and the anastomosis should be tension free.

CONFLICT OF INTEREST

None declared.

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