

Early morphological and histochemical alterations in rats subjected to ileocystoplasty¹

Alterações morfológicas e histoquímicas precoces em ratos submetidos à ileocistoplastia

Edinaldo Gonçalves de Miranda^I, Marcelo Ribeiro de Sousa Bizerra^{II}, Daniel Reis Waisberg^{III}, José Carnevale^{IV}, José Figueredo Silva^V, Jaques Waisberg^{VI}

^I MD, Assistant Professor, Head Division of Pediatric Surgery and Experimental Surgery, FACIME/UESPI, Piauí, Brazil.

^{II} Graduate student, FACIME/UESPI, Piauí, Brazil.

^{III} Graduate student, Faculty of Medicine, University of Sao Paulo (FMUSP), Brazil.

^{IV} PhD, Volunteer, FACIME/UESPI, Piauí, Brazil.

^V PhD, Full Professor, Head Division Pathology, FACIME/UESPI, Piauí, Brazil.

^{VI} PhD, Associate Professor, Faculty of Medicine of ABC and Department of Surgery, Hospital do Servidor Público Estadual, Sao Paulo, Brazil.

ABSTRACT

Purpose: To study morphologic and histochemical alterations arising at the ileocystoplasty site. **Methods:** Sixteen Wistar female rats were subjected to ileocystoplasty and sacrificed after eight weeks. Material collected was divided into four groups for histological and histochemical studies: Group I (control) – isolated ileum segment removed during ileocystoplasty; Group II – ileoileal anastomosis; Group III – ileovesical anastomosis and Group IV – ileal segment from the neobladder. Histological and histochemical study assessed dysplasia, metaplasia, acute and chronic inflammation, fibrosis, atrophy, hypertrophy, total mucins, sialomucins and sulfomucins. The non-parametric Wilcoxon and Mann-Whitney tests were employed in statistical analysis. **Results:** None of the groups presented dysplasia. Acute inflammation and atrophy occurred in Groups II, III and IV, not reaching statistical significance. Metaplasia was significant only in Group III (p=0.012). Chronic inflammation, fibrosis and hypertrophy were significant in Groups II, III and IV. There was a significant increase in total mucin content in Group IV (p=0.014) and a reduction in Group III (p=0.016). Increases in sialomucins were observed in samples for Groups III (p=0.003) and IV (p=0.002) along with reduced sulfomucins in samples from Groups III (p=0.013) and IV (p=0.008). **Conclusion:** Ileocystoplasty in female rats caused squamous metaplasia, chronic inflammatory infiltration, fibrosis, hypertrophy, increase in sialomucin content, reduction in sulfomucins, and alterations in total mucin content with statistical significance, as well acute inflammatory infiltration and muscular atrophy with less intensity.

Key words: Urinary Diversion. Neoplasm. Mucins. Sialomucins. Urinary Bladder. Ileum.

RESUMO

Objetivo: Estudar alterações morfológicas e histoquímicas nas ileocistoplastias em ratos fêmea. **Métodos:** 16 ratos fêmea foram submetidos à ileocistoplastia, sacrificadas após oito semanas. O material coletado foi e dividido em quatro grupos para análise morfológica e histoquímica: Grupo I (controle) biópsia intestinal no momento da cirurgia; Grupo II – anastomose íleo-íleo; Grupo III – anastomose íleo-vesical e Grupo IV – segmento intestinal da neobexiga. Os parâmetros avaliados foram: displasia, metaplasia, processo inflamatório agudo e crônico, fibrose, atrofia, hipertrofia, conteúdo total de mucinas, sialomucinas e sulfomucinas. Utilizou-se os testes não-paramétricos de Wilcoxon e Mann-Whitney para estudo estatístico. **Resultados:** Não houve displasia. Processo inflamatório agudo e atrofia ocorreram nos grupos II, III e IV, sem significância estatística. Metaplasia com significância estatística ocorreu somente no grupo III (p=0.012). Processo inflamatório crônico, fibrose e hipertrofia foram significantes nos grupos II, III e IV. Observou-se aumento significativo no conteúdo total de mucinas no grupo IV (p=0.014) e redução no grupo III (p=0.013). Aumento significativo de sialomucinas foi observado nos grupos III (p=0.003) e IV (p=0.002) e redução significativa das sulfomucinas nos grupos III (p=0.013) e IV (p=0.008). **Conclusão:** Nas ileocistoplastias em ratos fêmea observou-se metaplasia escamosa, processo inflamatório crônico, fibrose, hipertrofia, aumento do conteúdo de sialomucinas, redução das sulfomucinas e alterações no conteúdo total de mucinas com significância estatística, bem como atrofia e processo inflamatório agudo em menor intensidade.

Descritores: Derivação Urinária. Neoplasias. Mucinas. Sialomucinas. Bexiga Urinária. Íleo.

¹Research performed at Department of Pediatric Surgery, Faculty of Medical Sciences, State University of Piauí (FACIME/UESPI) and Department of Surgery, Hospital do Servidor Público Estadual, Sao Paulo, Brazil.

Introduction

Diseases affecting the lower urinary tract, whether congenital or acquired, can alter miction due to loss of anatomical or functional vesical sphincter coordination and lead to high pressure

bladder requiring bladder augmentation or even replacement by low pressure reservoir in order to preserve the upper urinary tract¹.

Choice of surgical technique depends on the extent of lower urinary tract compromise, that is, the state of the detrusor in part or whole, of the bladder neck and urethra¹. Depending on the

degree of compromise of these structures, the option elected will be bladder augmentation associated or otherwise with vesical coloplasty or orthotopic reservoir construction coupled to the emptying mechanism for clean intermittent catheterism. Reconstruction of the lower urinary tract using segments of the digestive tract has been increasingly used after popularizing of clean intermittent catheterism. All segments have been used in reconstruction ranging from the stomach to the colon, each having specific indications, advantages and disadvantages^{2,3}.

The ileum has remained the most commonly used segment in bladder augmentations and replacements⁴. However, although compliance is improved thereby providing urinary continence and protecting renal function, complications may arise such as urethral stenosis, urinary lithiasis, metabolic disturbances, repeated urinary infections, neobladder perforations and neoplasia.

Morphological and histochemical alterations occur during carcinogenesis although its physiopathology has yet to be fully elucidated¹⁻⁴. The objective of the present study was to analyze early alterations in neobladder ileal segments and at the anastomosis site with the detrusor in Wistar rats subjected to ileocystoplasty, and compare these alterations with the whole intestinal segment and ileo-ileal anastomosis to evaluate the influence of surgical, thread, surgical trauma and fecal bolus at the absence of urine.

Methods

Following approval by the Ethics Committee for Animal Research of the Medical Sciences Faculty of Piau , 16 *Wistar* female rats (*Rattus norvegicus*) aged between 100 and 120 days (mean=108.3 days) weighing from 130 to 230g (mean=190g), kept at suitable temperatures and under ambient light, fed with balanced feed and given free access to water, received a prophylactic dose of cefalexin (3mg/100g weight) and kept on the same dose of antibiotic until experiment end point. The rats were anesthetized with ethylic ether. After asepsis using iodated topical solution, the animals underwent laparotomy by longitudinal median 3cm incision. The ileal segment was exteriorized followed by enterectomy of a 3cm pedicled segment, 10cm proximal from the cecum whereby 1cm of this segment at its proximal portion was resected and collected for use in the control group (Group I). Subsequently, termino-terminal ileo-ileal anastomosis was performed and the vesical dome was removed. The remaining 2cm of the ileal segment was anastomosed isoperistaltically to the

bladder. The sutures were applied along a single, continuous plane using polypropylene thread and an atraumatic needle.

Eight weeks later the animals were sacrificed with ethylic ether and autopsied, during which neobladder and the intestinal segment containing the ileo-ileal anastomosis were collected for exams. All material collected was washed with isotonic saline solution, fixed in 10% formalin, and embedded in paraffin.

Serial 4µm-thick slices were obtained for histologic assessment after staining with hematoxylin-eosin. For the histochemical study, staining was carried out using Masson's trichrome, Periodic Acid Schiff (PAS), Alcian Blue and High-iron-diamine-Alcian Blue (HID-AB).

Samples collected were divided into four groups: Group I (control) – ileum segment resected on ileocystoplasty; Group II – ileo-ileal anastomosis; Group III – anastomosis of ileum with detrusor muscle and Group IV – ileal segment from the neobladder and examined for two independent Pathologists.

Histological study performed on epithelial cells assessed for the presence of dysplasia and squamous metaplasia, intensity of tissular reaction. The inflammatory process was checked, while occurrence of atrophy and hypertrophy was observed in tunic muscularis; total mucin, sialomucin and sulfomucin content were evaluated in goblet cells.

Alterations were quantified using a 6-tier classification and scored between -2 and +4, excluding zero, using the following scale: -2 = moderately reduced; -1 = slightly reduced; +1 = normal; +2 = slightly increased; +3 = moderately increased and +4 = significantly increased.

The non-parametric Wilcoxon tests were employed for intra-group statistical analysis while the Mann-Whitney test was used for intergroup comparisons. The level for rejection of the null hypothesis was set at 5% ($P < 0.05$).

Results

Disagreement did not have between the Pathologists. No dysplasia was found in the groups studied. Squamous metaplasia (Figure 1A) however, occurred across all groups except the control and reached statistical significance in Group III ($p=0.012$) (Figure 2). Acute inflammation statistically insignificant was observed in Groups II ($p=0.180$), III ($p=0.178$) and IV ($p=0.593$) (Figure 2). Significant levels of chronic inflammation (Figure 1A and 1B) were seen in groups II, III and IV (Group II: $p=0.003$, Group III: $p=0.001$, and Group IV: $p=0.002$) (Figure 2).

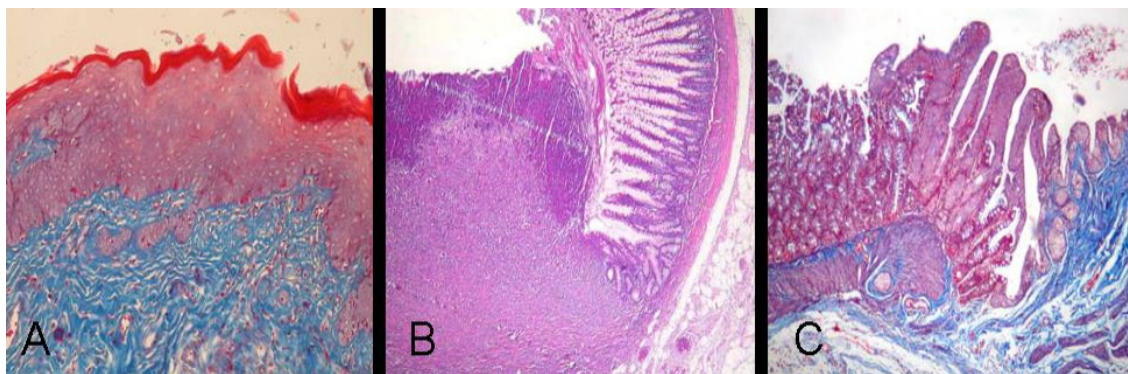


FIGURE 1 – A. Metaplasia at urointestinal anastomosis, staining with Masson's trichrome, 400X magnification; B. Fibrosis at urointestinal anastomosis, staining with hematoxylin-eosin, 200X magnification; C. Hypertrophy at urointestinal anastomosis, staining with Masson's trichrome, 100X magnification

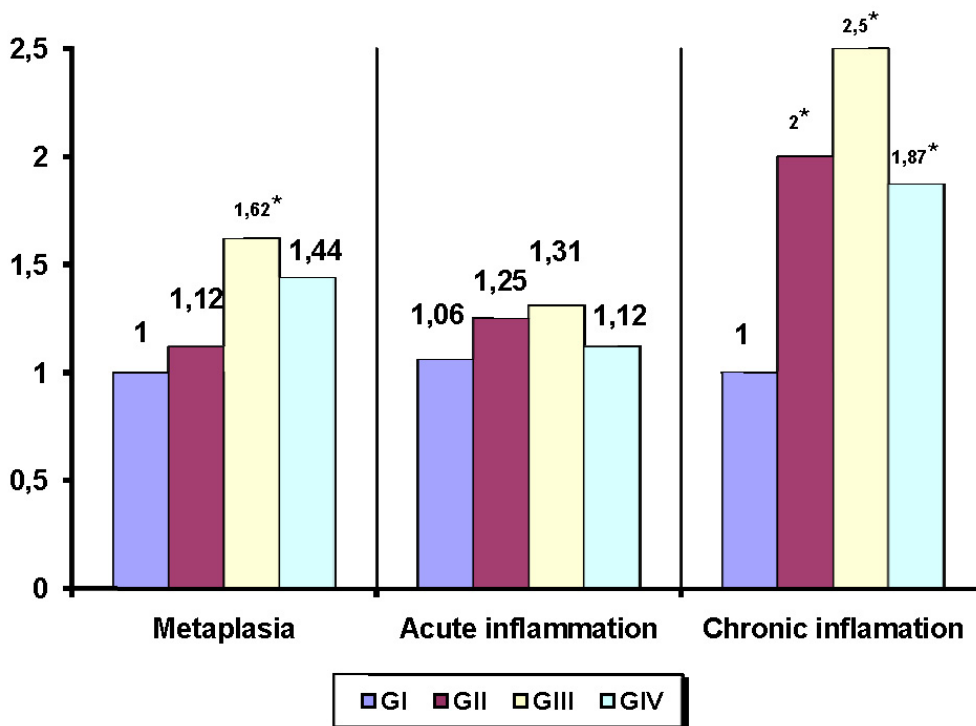


FIGURE 2 - Medium value of metaplasia, acute inflammatory process and chronic inflammatory process in control intestine (GI), at ileo-ileal anastomosis (GII), ileo-vesical anastomosis (GIII) and in intestinal tissue of neobladder (GIV). *p<0,05 (p with statistical significance)

Fibrosis (Group II: p=0.002, group III: p=0.001, and Group IV: p=0.008) (Figure 1B; Figure 3), hypertrophy (Group II: p=0.028, Group III: p=0.008, and Group IV: p=0.003) (Figure 1C;

Figure 3) and atrophy of the muscular layer (Group II: p=0.310, Group III: p=0.310 and Group IV: p=0.109) (Figure 3) were also present in all groups, except the control.

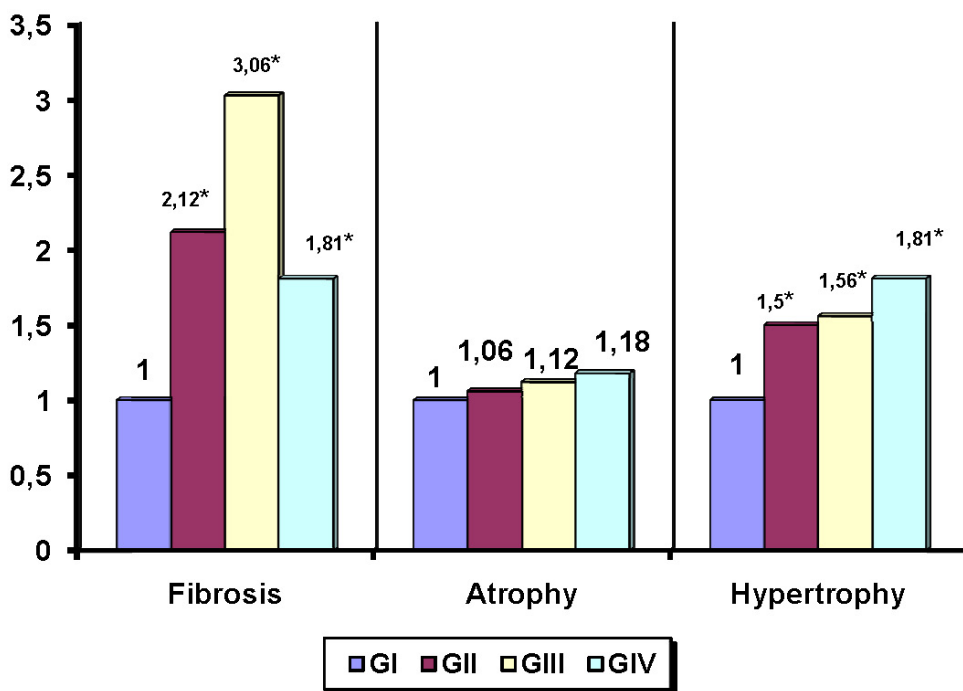


FIGURE 3 - Medium value of fibrosis, atrophy and hypertrophy in control intestine (GI), at ileo-ileal anastomosis (GII), ileo-vesical anastomosis (GIII) and in intestinal tissue of neobladder (GIV). *p<0,05 (p with significance statistical)

In terms of total mucin content (Figure 4A), levels were increased in Groups II and IV, reaching significance only in Group

IV (p=0.014) (Figure 4B; Figure 5) and was significantly reduced in Group III (p=0.016) (Figure 4C; Figure 5).

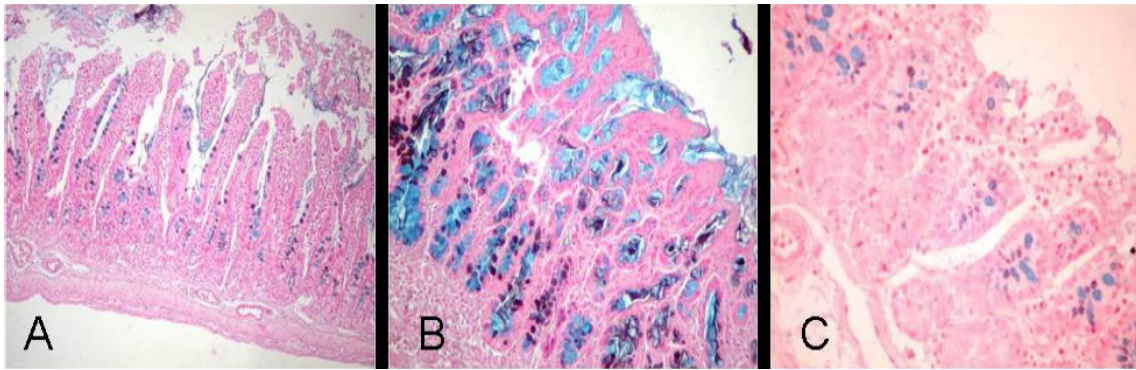


FIGURE 4 – A. Total normal mucin content at intestine of neobladder, staining with PA (neutral mucins, in red) and with Alcian blue (acid mucins, in blue), 100X magnification; B. Increased total mucin content, in intestine of neobladder, staining with PAS (neutral mucins, in red) and with Alcian blue (acid mucins, in blue), 200X magnification; C. Reduced total mucking content at urointestinal anastomosis, staining with PAS (neutral mucins, in red) and with Alcian blue (acid mucins, in blue), 200X magnification

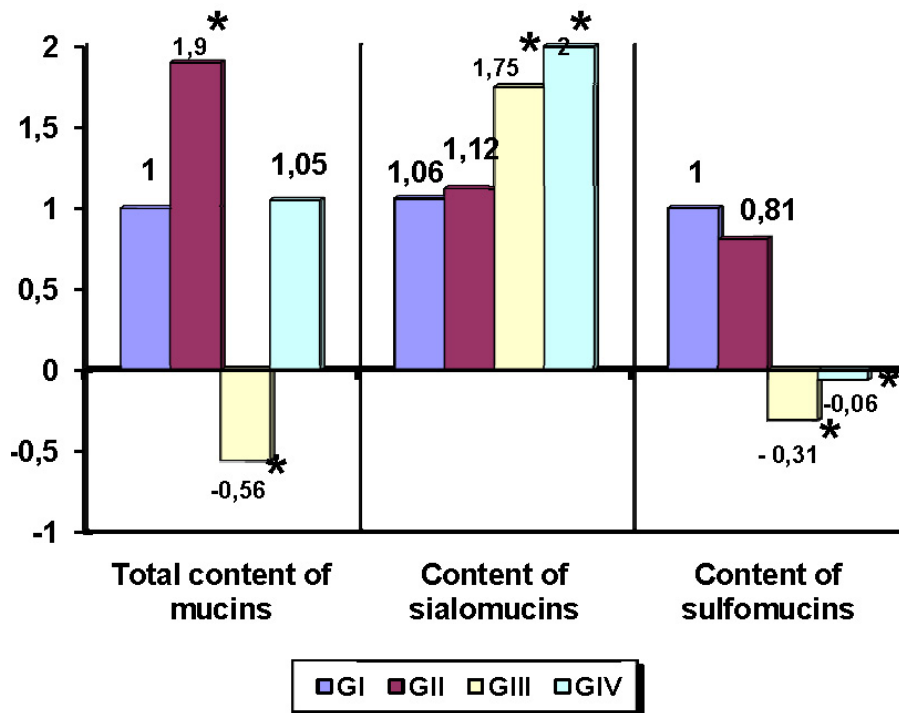


FIGURE 5 - Medium value of total content of mucins, sialomucins and sulfomucins in control intestine (GI), at ileo-ileal anastomosis (GII), ileo-vesical anastomosis (GIII) and in intestinal tissue of neobladder (GIV). *p<0,05 (p with significance statistical)

Sialomucins were increased in all groups (Figure 6B and 6C), except the control (Figure 6A), reaching statistical significance in Groups III (p=0.003) and IV (p=0.002) (Figure 5). However, sulfomucins were reduced in groups II, III and IV

(Figure 5B and 5C), except the control (Figure 5A), where this reached significance in Groups III (p=0.013) and IV (p=0.008) (Figure 5).

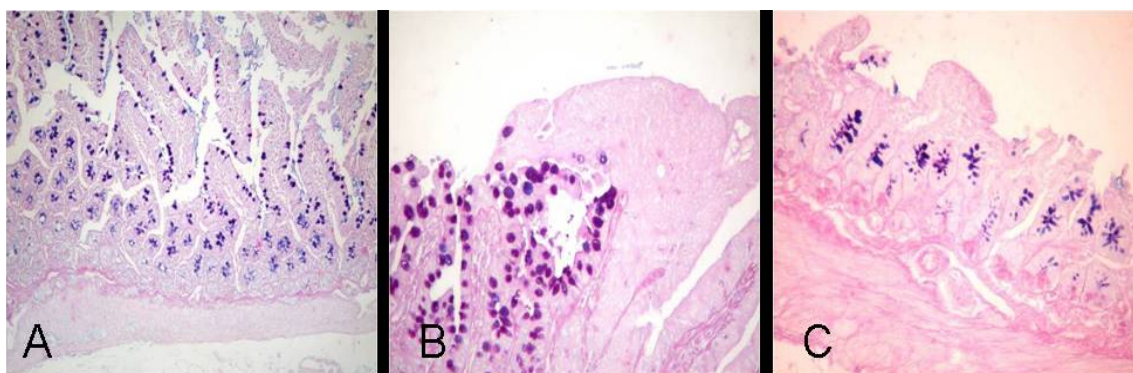


FIGURE 6 – A. Increased sialomucins at urointestinal anastomosis, staining with HIDAB, light bluish purple, 200X magnification; B. Normal sialomucins and sulfomucins, staining with HIDAB, light bluish purple, 100X magnification; C. Reduced sulfomucins at urointestinal anastomosis, staining with HIDAB, brownish grey, 200X magnification

Discussion

The presence of benign and malignant tumors has been reported following incorporation of intestinal segment in urinary tract reconstruction⁵ and it's more frequently found along the uro-intestinal anastomosis line⁶ and the risk of malignancy, is greater in the younger patient^{4,7}. The latency time prior to the emergence of such lesions has been described within the range of five to 30 years, averaging 19 years post operatively. However, pre-malignant lesions and neoplasias have been reported within two to five years of surgical intervention⁴. The most frequently described neoplasia is adenocarcinoma⁸.

In the light of the controversy over the etiology of the carcinogenesis, it is necessary to study those early alterations in urinary tract reconstructions which may be considered pre-malignant. To this end, the study of mucins in goblet cells is a consistent and feasible alternative for use in clinical practice³.

The present study sought to assess early, morphologic and histochemical alterations in ileocystoplasty focusing on concentrations and distribution of mucins in intestinal glands. To date, few studies have considered these aspects, particularly the content and distribution of sialomucins⁹ in experimental models analogous to those carried out in humans, and without fecal stream. Observation time was eight weeks to correspond with a five-year period in humans¹⁰, this being the time required for onset of neoplasia^{7,8}.

The absence of dysplasia could be due to the fact these appear only after 12 to 80 weeks in experimental studies¹⁰⁻¹². However, in patients observed for more time, dysplasia also did not occur^{4,13}.

Squamous metaplasia was observed in all three groups of samples, reaching statistical significance in Group III (urointestinal anastomosis), stemming from increased proliferative epithelial activity induced by inflammation and chemical and/or mechanical irritation^{14,15}. In contrast to earlier studies¹⁶, the presence of squamous metaplasia in the neobladder (Group IV) in the absence of feces, is most likely due to the action of urine aggravating the chronic inflammation present both in ileo-vesical anastomosis and the intestinal segment of the neobladder, given that practically no metaplasia was seen in ileo-ileal anastomosis^{8,9,16}. Squamous and columnar metaplasia in ileal conduits are considered signs of the

commencement of structural alterations which culminate with the appearance of dysplasia and adenocarcinoma in humans^{12,15}. In rats, these alterations manifest at between eight and 12 weeks after vesico-colic anastomosis or in the colic segment¹⁴.

The acute inflammatory process, observed in all groups without reaching statistical significance, is probably due to surgical trauma, the action of surgical thread or the presence of urine. In the absence of a constant irritating factor, the acute inflammatory process is transitory and does not trigger carcinogenesis¹¹, being limited to polymorphonuclear infiltration with increased cellular proliferation and renewal¹³. In enterocystoplasty and ureterosigmoidostomy, infection may evolve to chronic inflammation facilitating the process of carcinogenesis¹⁷⁻¹⁹.

The chronic inflammatory process, observed significantly in all groups, suggests that surgical trauma and the presence of suture thread may have caused the local acute reaction. The constant presence of urine or other carcinogens may have caused chronic reaction in stroma tissue with severe infiltration of monocytic cells^{15,20}. The suture thread may also shorten latency time to carcinogenesis while the fecal bolus may act as a continuous and prolonged aggression¹⁷. These changes, also present in the intestinal segment of the neobladder, suggest isolated action of urine as a cause of lymphoid depletion in intestinal segments, which could in turn promote the carcinogenesis process^{16,20}.

Atrophy of tunic muscularis, although found in all groups, was mild and non-significant, mirroring the observations of other studies¹⁹. This takes place due to the deeper localization of the muscle layer compared to mucosa, thereby avoiding direct contact with urine, as well as shorter exposure time to aggression factors¹⁷.

Hyperplasia and hypertrophy of the tunic muscular in ileo-vesical anastomosis and in the intestinal segment of the neobladder was significant and most likely the result of local surgical trauma aggravated by the presence of urine. Several authors have observed only muscular hyperplasia^{11,21} while others have found muscular hypertrophy arising from probable bladder strength^{7,20,22,23}.

Fibrosis, which proved statistically significant in all groups, reflected the chronic response of tissues to initial aggression of surgical trauma, aggravated by other continuous aggressions¹⁷.

Study of mucins is possible by employing three different stains: Periodic Acid *Schiff* (PAS) which discriminates for neutral

mucins (red), *alcian blue* (AB), which discriminates acid mucins (blue) and *high iron diamine alcian blue* pH2.5 (HIDAB) which separates acid mucins into sulfomucins (brownish grey) and sialomucins (light bluish purple)^{5,24}.

Villi of intestinal mucosa contain goblet cells which produce mucin-rich mucosa. Mucous is a protector against abrasions caused by solid feces and facilitates progression of the fecal bolus hampering bacterial adherence, reducing the transformation of nitrosamides into nitrosamines and reducing the carcinogenic effect of repeated and chronic infections. In the urinary tract, the mucus reduces bacterial adhesion and the effect of urine contact with the intestinal epithelium¹⁷.

The mucins can be either acid or neutral and are spread throughout the digestive tract, being scarce in the duodenum but progressively more frequent toward the ileum and colon²⁴. The acids are subdivided into several types, the main types being sialomucins and sulfomucins. Sulfomucins tend to predominate in normal intestine and are concentrated in the lower 2/3 of the crypts, while sialomucins are concentrated in the upper 1/3^{16,21}.

The mucins are altered in intestinal neoplasms and the area adjacent to the tumor known as transitional mucosa – TM^{21,22} which constitutes the tissue between the neoplasm and normal intestine. Reduced or absence of sialomucins can be observed in neoplastic tissue, along with increased sulfomucins. In TM however, there are increased numbers of sialomucins and lower levels or absence of sulfomucins. Such changes in mucin content may indicate risk to the presence of pre-malignant lesions²⁵⁻²⁸. Sialomucins are scarce in normal ileum yet significantly increased levels are seen in neoplastic lesions²⁸. Another phenomenon observed is inversion of mucin distribution in villi of TM, with sulfomucins, normally more concentrated in the lower 2/3, becoming predominant in the upper 1/3²¹.

Neutral and total mucins in urinary tract reconstructions have been little studied and thus their importance in the presence of neoplasms remains unknown. Previous studies have found no alterations in mucin in intestinal segments used in such reconstructions^{11,13,24}. Nevertheless, mucins have been shown to be reduced in more aggressive experimental models using feces and urine mixtures¹⁷.

The present study evidenced a significant increase in total mucin content in ileo-ileal anastomosis and in the intestine of the neobladder, coupled with significant decreases in total mucin in the ileo-vesical anastomosis.

The mechanical trauma seems to have contributed to increase total mucin content at the absence of urine and also for its reduction in the presence of urine. Initial increase in mucins suggests a tendency toward cellular differentiation, whilst involution and reduction only occur when aggression is maintained¹⁷. Lower levels of neutral mucins, as occur in TM of intestinal neoplasias, might be indicative of pre-malignant lesion, where as increased levels are seen in neoplastic tissue^{10,21}.

Mucin levels may also drop over time, even in the absence of feces, as a result of functional changes in goblet cells, dysplasias and carcinomas²¹. This suggests that urine is the principal triggering factor of carcinogenesis while feces alone, or mixed with urine, constitute exacerbating factors¹⁴.

Reduced sulfomucins in conjunction with increased sialomucin levels in the three groups of samples of the present study support the notion that surgical trauma contributes to the

emergence of these alterations and points to the existence of other factors beyond those of surgical trauma and fecal bolus^{9,11,13}. Another factor to explain the histochemical changes seen in ileo-ileal anastomosis is the presence of stitching thread exposed to feces. Thus, mechanisms and carcinogens other than those which are urinary in nature may trigger the neoplastic process, while greater aggressiveness in the groups with urine but not feces suggests that different factors may be at play to those present in fecal content.

These alterations constitute the earliest observed in TM and evolve to radical reduction or even absence of sialomucins in areas with neoplasms, being more marked with greater lesion severity: metaplasia, adenoma or carcinoma. This initial increase in sialomucins have a prognostic value in intestinal neoplasias, having an inverse relationship between presence at resection margins and survival, as well as recurrence rates, independently of staging or histological type¹⁷, a situation observed in all post-ureterosigmoidostomies and ileocystoplasty cases studied¹⁴.

While alternatives such as bladder transplant, tissue culture, vesical pacemaker and artificial bladder remain unavailable and intestinal segments are being used routinely for lower urinary tract reconstruction, qualitative studies of mucins in intestinal goblet cells should be encouraged, since the importance of recognizing pre-malignant lesions is clear and shall certainly contribute to longer and improved quality of life in patients requiring this type of surgical procedure.

Conclusion

Ileocystoplasty in female rats caused squamous metaplasia, chronic inflammatory infiltration, fibrosis, hypertrophy, increase in sialomucin content, reduction in sulfomucins, and alterations in total mucin content with statistical significance, as well acute inflammatory infiltration and muscular atrophy with less intensity.

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Correspondence:

Edinaldo Gonçalves de Miranda
Rua Jaime da Botica, 3442
64052-200 Teresina – Piauí Brazil
Phone: (55 86)9982-2987
edinaldomiranda@hotmail.com

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