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Experimental gastrocystoplasty in rats: Risk of developing ECLoma

Reidar Alexander Vigen [a,*], Carl-Jørgen Arum [a,b], Trond Viset [c], Duan Chen [a], Chun-Mei Zhao [a]

[a] *Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Erling Skjalgssons Gate 1, NO-7006 Trondheim, Norway*
[b] *Department of Surgery, St. Olav's Hospital, Trondheim, Norway*
[c] *Department of Pathology and Genetics, St. Olav's Hospital, Trondheim, Norway*

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Abstract *Objective:* There are no clinical reports on the risk of carcinoids in the gastric segment following gastrocystoplasty. The aim of the present study was to examine whether gastric carcinoids could develop in a rat model of gastrocystoplasty.
Materials and methods: Rats were subjected to gastrocystoplasty in which 10% of the oxyntic part of the stomach was removed (i.e. 10% fundectomy), gastrocystoplasty with 90% fundectomy (known to induce hypergastrinemia), sham operation, or no operation, and were followed up for 6 months. Tissue specimens of bladder and stomach were analyzed by means of pathology and immunohistochemistry.
Results: Atrophy of gastric glands in the augmented bladders was found after gastrocystoplasty with either 10% or 90% fundectomy. Gastrocystoplasty with 90% fundectomy resulted in hyperplasia of the oxyntic mucosa, enterochromaffin-like (ECL) cell hyperplasia and ECLoma in the remnant stomach, and atrophy of the oxyntic mucosa and ECLoma in the gastric segment of the bladder.
Conclusions: ECLoma could develop in the gastric segment of the bladder after gastrocystoplasty, particularly in the setting of hypergastrinemia. The tumorigenesis of ECLoma seems to follow the same pathological pathway regardless of whether the oxyntic mucosa is located in the stomach or the bladder.

* Corresponding author. Tel.: +47 72826062; fax: +47 72576412.
E-mail addresses: reidar.a.vigen@ntnu.no (R.A. Vigen), carl-jorgen.arum@ntnu.no (C.-J. Arum), trond.viset@stolav.no (T. Viset), duan.chen@ntnu.no (D. Chen), chun-mei.zhao@ntnu.no (C.-M. Zhao).

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Introduction

Intestinocystoplasty is the gold standard of urinary bladder augmentation. However, gastrocystoplasty has been reported to have certain advantages over intestinal segment augmentation, such as reduced chloride reabsorption, decreased mucus production, fewer urinary tract infections in the presence of acidic urine and a lower incidence of stones [1]. Disadvantages of gastrocystoplasty include the hematuria–dysuria syndrome and hypochloremic alkalosis. Gastrocystoplasty is preferred in the presence of kidney failure, due to protection against hyperchloremic acidosis, and in short bowel syndrome.

During recent years, there have been several reports of malignancy following gastrocystoplasty, mostly adenocarcinomas in the gastric segment near the anastomosis [2–8]. For instance, Vemulakonda and colleagues reported a 2.8% malignancy rate after 14–18 years [6]. Castellan and colleagues reported a 3.4% malignancy rate after 11–14 years [4]. In the experimental setting, hyperplastic, metaplastic and neoplastic lesions in the bladders have been found [9–11]. None of these reports indicated the risk of carcinoids.

An increased risk of gastric carcinoids after long-term hypergastrinemia has been well recognized in both experimental and clinical settings [12–14], and about 5% of carcinoids have malignant transformation potential [13]. Gastric carcinoids are composed of endocrine cells, most frequently the enterochromaffin-like (ECL) cells, which constitute 65–75% of the endocrine cells in rats and 30–35% in humans. Other endocrine cells in this location are D cells (5–10% in rats), A-like cells (20–30% in rats) and enterochromaffin (EC) cells [15].

The rat stomach is anatomically divided into forestomach (also called rumen), fundus (sometimes called corpus, the oxyntic part) and antrum. Fundectomy in rats, corresponding to partial gastrectomy (removal of the oxyntic part) in humans, is known to induce hypergastrinemia, depending on the proportion of tissue removal. A 90% fundectomy induces hypergastrinemia by removing the most parietal cells and thereby inhibiting a negative feedback loop of gastric acid – gastrin, while 10% fundectomy has no effect on the serum gastrin levels [16,17].

The circulating gastrin levels could be elevated after gastrocystoplasty, due to the degree of tissue removal rather than the gastrocystoplasty *per se* [18]. The aim of the present study was to examine whether the gastric carcinoids could develop after gastrocystoplasty. To this end, we utilized a rat model of gastrocystoplasty in which the fundus of the stomach was used as a gastric patch augmentation to the bladder, and 10% or 90% fundectomy was performed simultaneously with gastrocystoplasty.

Materials and methods

Thirty-five male Sprague–Dawley rats were obtained at 2 months of age from Taconic M&B (Skensved, Denmark), and divided into four groups consisting of 10 rats undergoing gastrocystoplasty with 10% fundectomy, 10 gastrocystoplasty with 90% fundectomy, 10 sham operation (laparotomy, and cystotomy before closure of bladder and abdomen), and 5 non-operated controls. Gastrocystoplasty was performed by isolating a wedge-shaped patch from the gastric fundus (about 10% fundectomy) on a distally based gastroepiploic vascular pedicle, and anastomosing this to the longitudinally opened bladder. A 90% fundectomy was performed by keeping a thin brim of oxyntic mucosa next to the rumen. Fundectomy was performed immediately after gastrocystoplasty. In the initial experiment, there was high mortality following 90% fundectomy. This was due to gastroparesis as a result of vagal nerve damage. Hence, pyloroplasty was thereafter performed on the rats subjected to 90% fundectomy. For details on the surgery see Vigen et al. [19].

Tissue samples from the bladders and the remnant fundus were collected 6 months postoperatively, after the rats were euthanized by an overdose of anesthetics. The samples were fixed in 4% formaldehyde, dehydrated and embedded in paraffin for routine histopathology and immunohistochemistry. The specimens were stained with hematoxylin, eosin and saffron. Immunocytochemistry was performed by the avidin–biotin–peroxidase complex (ABC) method using commercial ABC kits (Vector Laboratories, Burlingame, USA). The following primary antibodies were used: pancreastatin, a fragment of chromogranin A (Euro-Diagnostica, Malmö, Sweden) as a marker of endocrine cells in general at a final dilution of 1:3000; histidine decarboxylase (HDC) as ECL cell marker at final dilution of 1:3000; somatostatin as a D-cell marker at a final dilution of 1:600 (DAKO, Glostrup, Denmark); ghrelin as A-like-cell marker at a final dilution of 1:7000 (Phoenix Pharmaceuticals, CA, USA), and β-subunit of H^+/K^+-ATPase as parietal cell marker at a final dilution of 1:100 (a gift from Dr Lennart Friis-Hansen, Copenhagen University Hospital).

Results

Histopathology

Histopathological evaluation revealed chronic inflammation at the anastomotic site, flat urothelial hyperplasia in widespread areas, and papillary urothelial hyperplasia in smaller areas. Atrophy of gastric glands in all augmented bladders was found regardless of whether 10% or 90% fundectomy (Fig. 1). No malignancy was found in any of the rats after a 6-month follow up.

Gastrocystoplasty with 10% fundectomy was without any effect on the stomach, whereas gastrocystoplasty with 90% fundectomy resulted in hyperplasia of the oxyntic mucosa in the remnant stomach (Fig. 2A and B).

Immunohistochemistry

Immunostaining with antibody to pancreastatin showed normal distribution of the endocrine cells in the stomach and in the translocated mucosa of augmented bladders in non-operated or sham-operated rats, and rats undergoing gastrocystoplasty with 10% fundectomy (Fig. 2C and E). In rats undergoing gastrocystoplasty and 90% fundectomy, linear as well as nodular ECL cell hyperplasia and carcinoids consisting of ECL cells, i.e. ECLomas, were found in the stomach (Fig. 2D). ECL cell hyperplasia and ECLomas were also found in the augmented bladders (Fig. 2F). This was confirmed by immunostaining with antibody to HDC (data