

## Gut-associated Lymphoid Tissue (GALT) Carcinoma in Ulcerative Colitis

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**Abstract.** *Background:* In ulcerative colitis (UC), the majority of colorectal carcinomas (CRC) arise in the vast colorectal mucosal domain built with mucus-producing goblet cells and columnar cells. Conversely, CRC in UC rarely evolve in the tiny, spotty gut-associated lymphoid tissue (GALT) mucosal domain. Here we review the four reported cases of colonic carcinoma developing in GALT mucosa in UC, searching for possible precursor lesions connected with the evolution of these tumours. *Materials and Methods:* The clinical history, age, gender, endoscopic descriptions, and the pathology (localization, gross and histological descriptions of the luminal surface) of the four UC-GALT carcinomas reported in the literature were reviewed. *Results:* The luminal surface in three out of the four carcinomas revealed conventional (tubular/villous) adenomas or high-grade dysplasia. All four UC-GALT-carcinomas were detected at an early stage (T1N0). *Conclusion:* GALT carcinomas do occur, albeit infrequently, in patients with UC. The finding that three out of the four GALT carcinomas on record were covered by conventional adenomas or by high-grade dysplasia strongly suggests that non-invasive conventional neoplasias might often precede GALT carcinomas in UC.

The currently accepted consensus is that sporadic colorectal carcinomas (CRC) develop *via* the conventional (tubular or villous) adenoma–carcinoma pathway (1) or the serrated

adenoma–carcinoma pathway (2). Both these trails of progression evolve in the vast colorectal mucosal domain built with mucus-producing goblet cells and columnar cells. Sporadic CRC evolving in the remnant, tiny and spotty, gut-associated lymphoid tissue (GALT) mucosa are rare, a trail recently referred to as the third pathway of colorectal carcinogenesis (3).

Patients with UC are at increased risk of developing CRC, particularly those with early onset or with total-longstanding colitis (4). In contrast to sporadic CRC, CRC in UC might be preceded by different epithelial lesions: i) dysplasia in flat mucosa (5), ii) UC-related conventional (tubular or villous) adenomatous growth (6), iii) UC-related serrated adenomatous growth (7, 8), iv) dysplasia in UC-related subtle villous changes (9), v) conventional (tubular or villous) adenomas on top of GALT (3), or vi) UC-unrelated, synchronously growing, age-dependent, sporadic conventional or serrated adenomas (8). It should be understood that these precursor lesions also develop in the vast colorectal mucosa built with mucus-producing goblet cells and columnar cells. When no precursor lesions are found in early UC carcinomas, the term *de novo* carcinoma has been used (8, 10). In similarity to the sporadic counterpart, CRC in UC rarely evolves in GALT mucosal domains. In a lecture 114 years ago, at gross examination, Ball suspected a carcinoma arising in an organized lymphoid follicle: These were his words: “We occasionally meet with small tumours which clinically resemble closely simple adenomata, but which upon microscopic examination prove to be composed of lymphoid tissue instead of the epithelial elements” (11).

In 1954, Cuthbert Dukes described a histological lesion in the submucosa characterized by “misplaced” colonic epithelium in patients with UC (12). Dukes submitted that the misplaced epithelium was the result of mucosal repair following regeneration of a mucosal ulcer, and that the epithelium detached and buried in the submucosal would encourage cancer development (12). Following the suggestion of Dukes, the frequency of misplaced (*i.e.* ectopic) colonic mucosa in 62 colectomy specimens was

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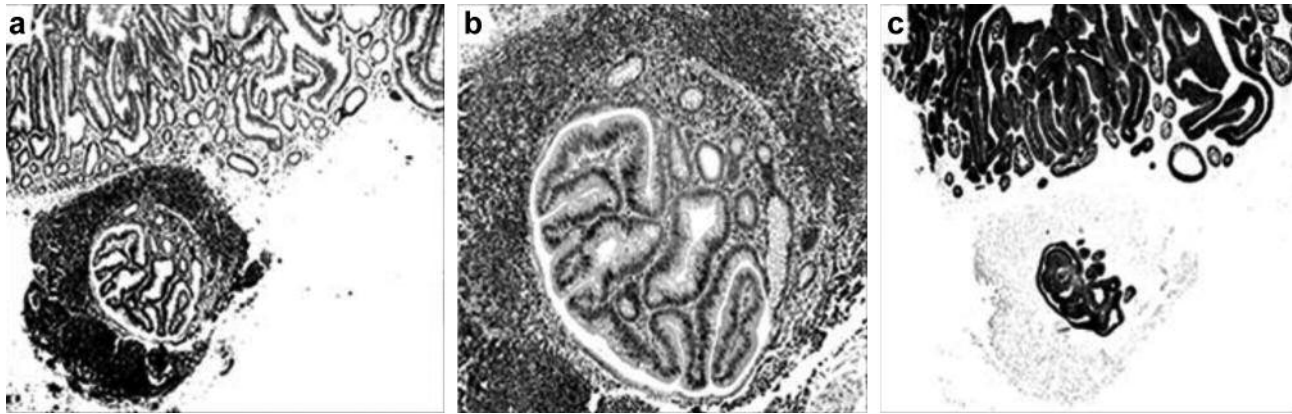


Figure 1. a: Villous adenoma on top of a gut-associated lymphoid tissue (GALT) carcinoma (H&E magnification  $\times 4$ ). b: Detail from GALT carcinoma (H&E magnification  $\times 10$ ). c: GALT carcinoma immunostained with the anti-cytokeratin antibody MNF 116 to highlight the epithelial structures of the villous adenoma on top and the GALT carcinoma in the submucosa (MNF 116 magnification  $\times 4$ ).

Table I. Clinical data and descriptive characteristics in four carcinomas arising in gut-associated lymphoid tissue in four patients with ulcerative colitis reported in the literature.

Year (ref.)	Senior author	Localization	Gross description of the surface	Histology at the surface	Age, years/gender
1984 (13)	Rubio	Left colon	Irregular plaque-like lesion	Chronic inflammation	57/M
2002 (14)	Rubio	Right colon	Sessile polyp	Adenoma HGD	53/F
2008 (15)	Stewart	Right colon	Polypoid lesion	HGD	70/M
2013 (16)	Rubio	Transverse colon	Polypoid lesion	Adenoma HGD	68/F

HGD: High-grade dysplasia.

reported in 1984 (13). One or more foci of misplaced mucosa was found in 72% of the 22 colectomies from patients with UC, in 55% of 20 from patients with Crohn's disease-associated colitis, and in none of 20 from patients without inflammatory bowel disease. In one patient with UC, an adenocarcinoma surrounded by nodular lymphoid tissue invading the submucosa was found. This histological characteristic fulfilled the criteria of colonic GALT carcinoma (13). Since then, three additional cases of GALT carcinomas evolving in UC have been reported (14-16).

The purpose of this communication was to review the four cases of GALT carcinoma in patients with UC in the literature, searching for possible precursor lesions connected with the evolution of this carcinoma in UC.

**Materials and Methods**

*Literature review.* The search was performed using the PubMed electronic database.

The narratives of the clinical history (age, gender, endoscopic descriptions), and the pathology (localization, gross and histological

descriptions of the luminal surface) of the four cases of colorectal GALT carcinomas in UC on record, were reviewed.

**Results**

The results are presented in Table I.

*Clinical data.* The mean age of the four patients was 62 years (range=53-70 years). Two out of the four cases were males and the remaining two, females. All four cases had protracted UC.

*Pathological description.* Localization. In two out of the four cases, the GALT carcinoma was located in the right colon, one in the transverse colon and the remaining one in the left colon.

*Gross description of the surface.* Out of the four GALT carcinomas, three were reported at endoscopic examination as being polyp/polypoid lesions and the remaining one as an irregular plaque-like lesion.

*Histology of the luminal surface.* Histology of the luminal surface covering the GALT carcinoma in two out of the four cases revealed conventional adenomas (Figure 1), one disclosed high-grade dysplasia, and the remaining one mucosa with chronic inflammation. The four GALT carcinomas were confined to the submucosa. Neither of the two adenomas described in Table I showed poor glandular differentiation, budding or lymphovascular invasion.

## Discussion

In patients with UC, the vast majority of CRCs evolve in the GALT-free mucosa. In contrast, CRC arising in GALT domains in patients with UC occur much less frequently (17).

The first colonic GALT carcinoma in a patient with UC was reported in 1984 (13). Since then, three additional cases of GALT carcinoma in patients with UC have been published (14-16). Notably, three out of the four UC-GALT carcinomas were covered by conventional adenomas or high-grade dysplasia, strongly suggesting that non-invasive conventional neoplasias might precede GALT carcinoma in UC. All four UC-GALT carcinomas were detected at an early phase (T1N0).

The low frequency of UC-GALT-carcinomas could be due to the fact that only minute areas of the colorectal mucosa are occupied by GALT domains (17).

As a corollary, GALT carcinomas do occur, albeit infrequently, in patients with UC. Studies of the molecular pathway in GALT carcinomas in UC are limited by the rarity of these tumours. As a light at the end of the tunnel, it should be mentioned that GALT carcinomas were found in 53% of colonic GALT mucosal domains in Sprague-Dawley rats treated with the colonotropic carcinogen 1,2 dimethylhydrazine (18). This animal model would permit further investigation into the molecular signals required for the development of GALT carcinomas in rats having synchronously experimentally induced ulcerative colitis (19, 20).

## Conflicts of Interest

The Authors have no conflict of interest to declare in regard to this study.

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