



Microtubular Colorectal Adenoma an Aggressive Histologic Phenotype with Propensity to Evolve into Invasive Carcinoma

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Abstract: Colorectal carcinoma, the third most commonly diagnosed type of cancer in Europe and the USA, usually originates in colorectal adenomas (CRA). Two main histological phenotypes of CRA are usually recognized: conventional (tubular or villous) adenomas and traditional serrated (serrated and microtubular) adenomas. Microtubular adenomas (MTA) are histologically typified by dysplastic epithelium arranged in closed rings (microtubules), sideways along elongated outgrowth. We investigated 4446 CRA diagnosed at this Department during a 10-year period (2001-2010). Out of the 4446 CRA, 68 (1.5%) were MTA; of these, 38 (55.9%) had low-grade dysplasia (LGD), 17 (25.0%) high-grade-dysplasia (HGD), two (2.9%) intraepithelial carcinoma (IEC), three (4.4%) intramucosal carcinoma (IMC), and eight (11.8%) submucosal carcinoma (SMC). Ninety-four per cent (64/68) of the MTAs were left-sided adenomas. Cell proliferation in MTA occurred initially in the dysplastic microtubules. In contrast, cell proliferation occurred initially at the luminal aspect of the dysplastic crypts in conventional (tubular or villous) adenomas, and initially at the bottom of the dysplastic crypts in serrated adenomas. Because of distinctive microscopic characteristics, and cell proliferative attributes, it is submitted that MTA is a particular CRA phenotype, at variance with conventional (tubular or villous) adenomas and serrated adenomas. The high frequency of submucosal invasion strongly suggests that MTA is an aggressive phenotype of CRA.

Keywords: Advanced adenomas, microtubular configurations, invasive carcinoma

1. INTRODUCTION

Colorectal carcinoma (CRC) is the third most commonly diagnosed type of cancer in Europe and the USA [1]. Main risk factors include advanced age, family history, male sex, lifestyle factors natural exposures to dietary/environmental factors, genome differences, obesity, type 2 diabetes, and the colonic microbiome [2]. CRC usually originates in mucosal foci of mutated cells with proliferative, biochemical and molecular aberrations, referred to as colorectal adenomas (CRA)[3]. Less frequently, CRC develops from dysplastic crypts in flat mucosa in patients with ulcerative colitis[4], from epithelial cells covering gut-associated lymphoid tissue [5], or from mucosa without any recognizable preceding dysplastic alteration (*de novo* carcinoma)[6, 7].

CRA have been classically classified into conventional (tubular or villous) adenomas

(CTVA) [8], and serrated (SA) adenomas (typified by dysplastic, teeth-like outlines that resemble serrations in a saw) [9].

In 1997, we found in Japanese patients a CRA that was at variance with the aforementioned histological phenotypes, as it displayed closed dysplastic microtubules arranged in a sequential fashion along the slopes of epithelial outgrowths [10]. Initially called villo-microglandular adenoma it was later re-named microtubular adenoma (MTA) by the WHO in 2000 [11]. Since its description in Japanese patients, MTAs were also reported in Swedish [3], Italian [12], English [6] and Icelander [13] patients. MTA and SA are being referred to as traditional serrated adenoma (TSA)[14, 13].

Based on the degree of cellular dysplasia, some authors have classified CRA into those exhibiting slight, moderate or severe dysplasia [15], and others showing low and high-grade dysplasia (LGD and HGD, respectively)[16].

More recently, the concept of advanced CRA (ACRC) [17] has received wide acceptance due to its propensity to progress to invasive carcinoma [18, 19]. It should be pointed out, however, that the definition of ACRC varies in the literature. Some authors regard as ACRC those adenomas measuring >1cm in diameter [20, 21], others >1cm in diameter with villous histology [22-24]; others require the presence of HGD [25-27]; others, at least 1 cm or with villous elements at a frequency greater than 20% or with HGD [28]; and others as carcinoma *in situ* (intraepithelial carcinoma, IEC)[29-31]. Finally, some authors require the presence of intramucosal carcinoma (IMC) [19, 32-34].

In early work, we investigated 92 consecutive CRAs with submucosal carcinoma (SMC) having HGD or IEC in the remnant adenomatous tissue[35]. Although submucosal invasion occurred more frequently in CRA with IEC than in those with HGD, as many as 42% of the SMCs arose in CRA with HGD exclusively. Despite morphological, histochemical and immunohistochemical dissimilarities between the two lesions [35-37] it was concluded that both HGD and IEC have a particular propensity to invade host tissue.

The purpose of the present work was to assess the frequency of MTA in a cohort of CRAs diagnosed between 2001 and 2010 at this Department.

2. MATERIAL AND METHODS

The material comprised 4446 polypectomies exhibiting CRA at histology, diagnosed at the Department of Pathology, Karolinska University Hospital during a 10-year period (2001-2010). A total of 3456 CRAs were diagnosed by the author (CR); and the remaining 990 CRAs by other pathologists at the Department. Sections from these 990 CRA were retrieved from the files and reviewed; the aim was to detect possible unreported cases of MTA.

Conventional (tubular and villous) adenomas, SA and sessile serrated polyp/adenoma (SSA/P) were excluded from the study.

Definitions

MTA: CRA exhibiting closed rings (microtubules) of dysplastic epithelium arranged

lengthwise along the slopes of elongated outgrowths present in >50% of the adenomatous tissue (Figure 1).

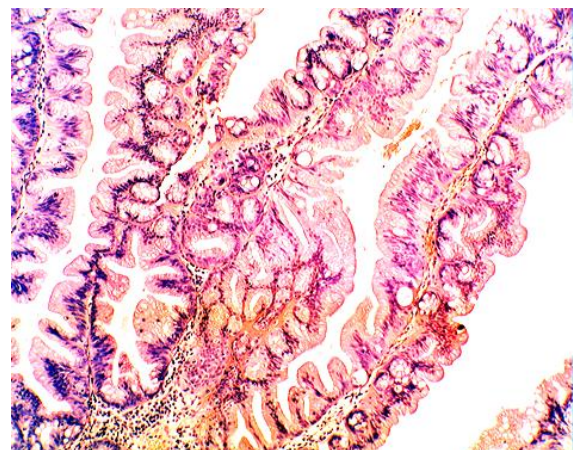


Figure1. Microtubular adenoma showing sideways dysplastic microtubules (H&E, X4).

Classification of MTA according to the degree of neoplastic severity

- i) **LGD:** Dysplastic epithelium lined with spindle-shaped, rather uniform hyperchromatic nuclei, with regular nuclear membrane. Chromatin particles are uniformly small and the stratified nuclei do not exceed the deeper half of the epithelial thickness.
- ii) **HGD:** Dysplastic epithelium lined with spindle-shaped cells with hyperchromatic, pleomorphic nuclei. Chromatin particles are irregular with angular shapes, and the nuclear membrane is regular. Stratified nuclei exceed the superficial half of the epithelium often reaching< the luminal epithelial border. Atypical mitoses are often present (Figure 2).

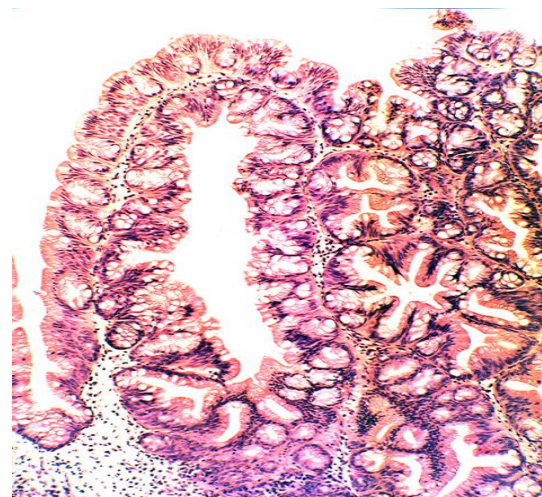


Figure2. Another microtubular adenoma showing sideways dysplastic microtubules (H&E4)

iii) *IEC*: Intraepithelialneoplastic epithelium exhibiting marked pleomorphic cells with swollen large vesicular (oval or round-shaped) nuclei, with bridges of nucleolus-associated chromatin reaching angular chromatin deposits both in the nucleus and on the nuclear membrane. Nucleolus is conspicuous ($\geq 2.5 \mu\text{m}$ in diameter) and irregular and the nuclear membrane is often notched. The nuclear polarity is disrupted and atypical mitoses are found. Structural glandular alterations consist of budding or branching crypts or tubules with epithelial septa, back-to-back glands and cribriform growth. The glands are often arrayed obliquely to the basement membrane (Figure 3).

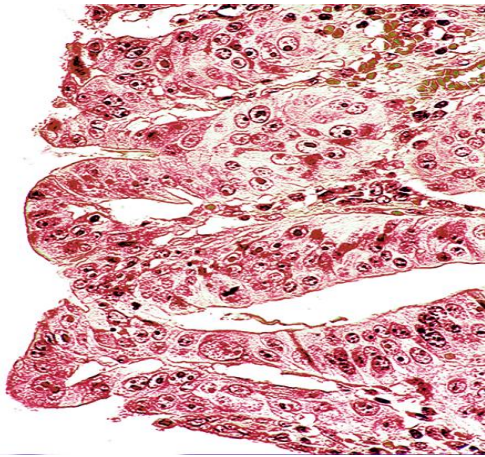


Figure3. Microtubular adenoma with high-grade dysplasia. Note large pleomorphic, pale vesicular nuclei with large, prominent, irregular nucleoli (H&E, X40).

iv) *IMC*: Adenoma with neoplastic cells with unquestionable invasion into the *lamina propria mucosae*. A desmoplastic reaction in the juxtaposing *lamina propria* and/or a neutrophilic infiltration occurred at the site of invasion (Figure 4).

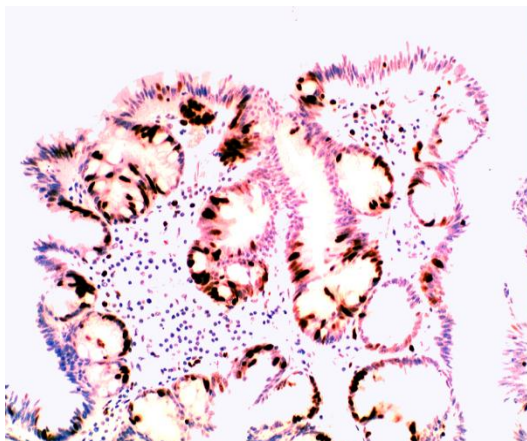


Figure4. Microtubular adenoma immunostained with revealing that cell proliferation initially occurs in microtubules (Ki67, batch MIB1 x20)

v) *SMC*: Adenoma with neoplastic cells invading across the *muscularis mucosae* and unquestionably reaching the submucosal layer (Figure 5).

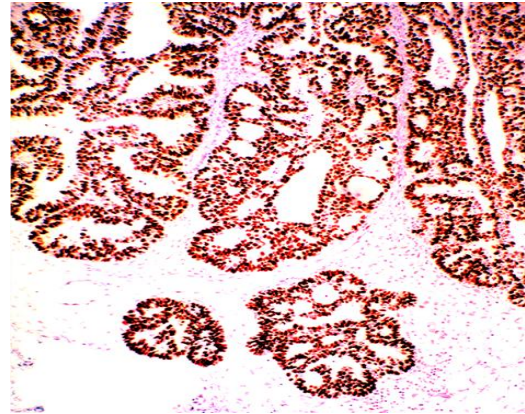


Figure5. Invasive carcinoma evolving from microtubular adenoma.

Note that the invading tumour retains the microtubular features (p53, X4).

Statistical analysis. The non-parametric Kruskal-Wallis test was applied, to compare difference between groups. Statistical significance was defined as $P < 0.05$.

This study was approved by the Ethics Committee, Department of Pathology, Karolinska University Hospital.

3. RESULTS

Out of 68 MTAs, 37 (54%) were found in males and the remaining 31 (46%) in females. The mean age of patients with MTA was 59 years (range= 25-82 years); 25 (37%) were ≤ 59 years of age and the remaining 43 (63%), ≥ 60 years of age.

Of the 68 MTA, 64 (94.1%) were located in the left colon-rectum and the remaining four (5.9%) in the right colon ($p < 0.05$).

Histological Evaluation. Out of the 3456 CRAs reviewed by CR, 58 (1.7%) were MTA. The review of the remaining 990 CRAs diagnosed by other pathologists at the Department revealed that 10 CRAs initially diagnosed as TA (n=2), VA (n=5), or SA (n=3) were MTA at review. Hence, MTA accounted for 1.5% (n=68) of all CRAs (n=4446) seen at this Department between 2001 and 2010. Out of 68 MTAs, 55.9% had LGD, 25.0% HGD, 2.9% IEC, 4.4% IMCs and the remaining 11.8% SMCs.

4. DISCUSSION

In this survey, MTA accounted for 1.5% of 4446 CRA; of those, histology showed LGD in 55.9%, HGD in 25.0%, IEC in 2.9%, IMC in 4.4% and SMC in the remaining 11.8%. These results validate previous results obtained in 1552 CRA in Florence, Italy [12] where 35.7% of the MTAs had HGD, IEC and IMCs; SMC were recorded in 7.1%. Accordingly, previous and present findings strongly indicate that MTAs are aggressive lesions, with propensity to evolve into invasive carcinoma.

Fifty-four percent of the patients with MTA were males, and 63% were ≥ 60 years of age. These percentages are similar to those recorded in a cohort of Swedish patients with CRA where all phenotypes of CRA were investigated [3]. In that work, 52% of 3135 CRAs were males and 65% were ≥ 60 years of age. It would appear that the development of MTA is neither influenced by the gender nor by the age of the patients.

The degree of cellular dysplasia and invasion into the *lamina propria* into the submucosa were separately analysed. This was done since progression of cellular neoplastic aberrations requires accumulation of genetic cell mutations [38], whereas penetration of the basement membrane by neoplastic cells requires collagen-degrading proteolytic enzymes, such as collagenase, plasminogen activator [39], heparanase [40], and matrilysin [41].

In 2008, Torlakovic *et al.* noted morphological features in TSA, such as filiform projections and ectopic crypt formations [14]. The criteria and illustrations in TSA with ectopic crypt formations in that publication are identical to those previously reported for MTA in Japanese patients in 1997 [10], endorsed by the WHO in 2000 [11], and subsequently in Swedish patients in 2002 [3], in Italian patients in 2003 [12] and in English patients in 2007 [6]. We prefer the descriptive term microtubular to 'ECF' [14], in as much as microtubular configurations are also present in invasive areas [42].

Since the age of the patients was similar in MTA to other adenoma phenotypes, there was no indication that TA, VA or SA had chronologically 're-modelled' into MTA, or that MTA, TA, VA and SA were transitional patterns capable of converting into a different phenotype with increasing age.

In previous work we found that cell-proliferation occurred initially in the dysplastic

microtubules of MTA, initially in the luminal dysplastic epithelium in CTVA initially, and initially at the bottom of the crypts in SA [4, 42-44]. Because of the distinctive microscopic and cell proliferative attributes, it is submitted that MTA is as a specific CRA phenotype, at variance with TA, VA, and SA. The high frequency of SMC strongly suggests that MTA is an aggressive phenotype of CRA.

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Citation: Carlos A Rubio, Lorand Kis, Denis Nastic, Peter T Schmidt. *Microtubular Colorectal Adenoma an Aggressive Histologic Phenotype with Propensity to Evolve into Invasive Carcinoma*. *ARC Journal of Cancer Science* 2017; 3(2):31-36. DOI: <http://dx.doi.org/10.20431/2455-6009.0302005>

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