Mucinous Colorectal Carcinoma Arising in Nonulcerated Villous Adenoma (MAVA) – A Distinct Pathologic Entity

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INTRODUCTION

The association of mucinous with villous adenoma of the colon and rectum has been reported.[13,14] Mucinous epithelial inclusions at the base of colonic adenomas have been observed by various authors, being considered nonmalignant epithelial displacements into the colorectal submucosa, [10,8] also known as pseudocarcinomatous invasion in polyps.

In a series of colectomies and rectocolectomies for adenocarcinomas invading the *muscularis propria,* we found a group of tumors with superficial areas of villous and tubulovillous adenoma and deep areas of mucinous carcinoma. Adenocarcinomatous areas were morphologically similar to those reported in submucous pseudocarcinomatous invasion of polyps, but there was invasion in the *muscularis propria* and subserous layer.

The object of this paper is to report the pathologic findings in this group of lesions, comparing them with other colonic adenocarcinomas and with mucinous tumors not associated with adenoma.

MATERIAL AND METHODS

209 colectomies and rectocolectomies performed because of primary adenocarcinoma of the rectum and colon with spread into the *muscularis propria* or through it (Stages B1, B2, C1 and C2 in Kirklin's modification of Dukes' staging,[1,5] were examined retrospectively.

Macroscopic examination records were reviewed and 2 to 5 microsections (mean 2.82) of the primary tumor were histologically examined.

The sections of the primary tumor had been selected from areas of deeper macroscopic invasion, when processing the surgical specimen. They included part of the normal-appearing mucosa around the tumor.

In each case the maximum tumor diameter, existence of adenoma over or at the periphery of the adenocarcinoma, intramural spread, lymph-node status, location, age and sex, were determined.

Adenocarcinomas were classified as mucinous when a minimum of the estimated carcinomatous volume consisted of mucin, according to criteria previously described.[14]

The mucinous carcinomas were further classified into three subgroups:
a) Mucinous carcinoma wi-

thout adenoma (with a necrotic or ulcerated surface).

b) Mucinous carcinoma associated with adenoma at the periphery (with necrotic or ulcerated surface areas).

c) Mucinous carcinoma arising in non-ulcerated villous or tubulovillous adenoma (MAVA).

Mucinous areas were divided into three subtypes, according to Morson and Dawson.[7]

I — Mucus-filled cysts with a peripheral epithelium coating, incomplete in many cases.

II — Cellular cords and groups surrounded by extracellular mucin.

III — Diffuse infiltrative mucocellular form with signet-ring cells.

RESULTS

Of the 209 patients examined, 35 mucinous carcinomas were identified (16.7%). Of these, 19 were not associated with adenomas (subgroup a). 16 of these consisted mainly of mucinous extracellular deposits with cellular cords (subtype II). In three patients, the diffuse infiltrative pattern (subtype III) was predominant. There was superposition of these two morphologic subtypes in individual patients.

Seven of the mucinous carcinomas showed villous or tubulovillous adenoma at the periphery, the remaining surface being ulcerated or necrotic (subgroup b). In these patients, pools of mucus with epithelial coating (subtype I) were predominant at the base of the peripheral adenomas, but in the ulcerated areas six of the tumors showed semi-differentiated common type (nonmucinous) carcinoma, and one a mucinous diffuse infiltrative adenocarcinoma (subtype III).
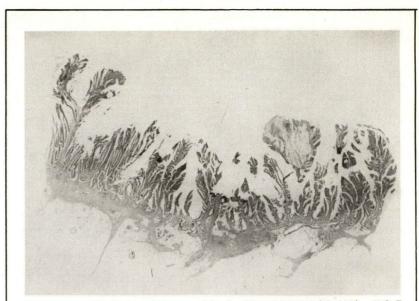
Nine patients had a regularly repeated morphology

Figura 1 — *Mucinous carcinoma arising in villous adenoma (MAVA) — H & E, x 6. Note that deep portions of the interpapillary crypts are projected up to the muscular wall of the colon. From the crypt bases arise pools of mucus, infiltrating the extramuscular fat. At the center and in the right side there are lakes of mucus with superficial epithelial coating, but without epithelia in their deepest areas.*

Figura 2 — *Deep portion of a MAMA — H & E x 100. The villous adenoma crypts are going through the muscular wall, into the subserous layer, with moderate stromal reaction, showing mild dysplasia. In the upper part of the field there are muscular bundles preserved within the epithelial crypts and lacking of stromal reaction.*

Figura 3 — MAVA — H & E x 6. Pools of mucus spreading from the base of villous crypts, infiltrating profusely the extramuscular fattissue. Note the incomplete epithelial coating (predominantly near the base of the adenoma) of many mucinous lakes.

(Fig. 1), with features of a villous or tubulovillous adenoma, flattened and nonpeduculated, on the surface (subgroup c). The villi were separated by deep crypts and showed variable degrees of intraepithelial dysplasia with scant mucin production, though isolated hypersecretory areas could be identified.

Intervillous crypts deepened at the base of the lesion, surpassing the submucous layer. Moreover, misplaced epithelial structures at the *muscularis propria* and subserous layer, in direct continuity with the adenoma's crypts, were found.

In some areas, this deepening of the crypts occupied the interstices of the *muscularis propria,* with preservation of the interposed muscular fascicles (Fig. 2). Pools of mucus, spreading from the bases of the crypts, were observed infiltrating profusely the muscular and subserous layers. Near the crypts' bases of the adenoma, these pools of mucus frequently showed an epithelial coating (subtype I), while the deepest portion

of the pools was uncoated (Fig. 3).

The mucous accumulations did not generate stromal inflammatory response, or desmoplastic reaction; the cellular elements of the lakes of mucus had a cytologic degree of dysplasia that could be classified as mild to moderate according to previously reported criteria (Fig. 2).

The mean diameter of the tumors is shown in Table 1.

They were 13 mucinous tumors in men and 22 in women. Six of the MAVA cases were in men and three in women.

The relation of tumor type to location is given in Table 2

In Table 3 the type of tumor is correlated with Dukes' grades. Note that there is only one MAVA with lymph node metastasis.

DISCUSSION

Submucosal inclusions, considered nonmalignant epithelial displacements, have been described in villous adenomas.[8],[10] The degree of

dysplasia has been considered the most important distinctive parameter between authentic malignant invasion and these submucosal inclusions (also known as pseudocarcinomatous invasion). Frequently these epithelial displacements adopted a mucus-filled cystic appearance.[10]

In our series, we consider it possible to define a group of mucinous colorectal tumors with a nonulcerated adenomatous coating, infiltrating the *muscularis propria* and even the subserous layer (MAVA).

The areas of invasion consisted of pools of mucus similar to those observed at the submucous inclusions of villous adenomas, though they were located more deeply. These mucinous inclusions showed mild or moderate cytologic dysplasia, even in a subserous location. This invasion showed no tendency to be surrounded by secondary inflammation or to generate desmoplastic reaction in the stroma, as in the case of common colorectal carcinoma.

The epithelial inclusion was sometimes located at the interstice of the colonic muscular wall, similarly by to acquired colonic diverticulosis, not destroying the muscular bundles even in the presence of transmural spread. This suggests that the process of parietal invasion in the MAVA is a displacement of the base of the adenoma's crypts, implying a mechanism of carcinomatous invasion different from common colorectal carcinomas. Nonmalignant glandular structures placed in the underlying muscular layer are observed in other organs (uterine endometriosis, Rokitansky-Aschoff sinuses in the gallbladder), and in the colon itself (diverticulosis). The lack of surface ulceration, with preservation of the adenomatous lesion which generates the process may imply that

there is no restriction in the irrigation of the submucous vascular plexus of the MAVA, due to the absence of an actual carcinomatous invasion.

A lesion similar to MAVA is illustrated in figures 3 and 4 of the paper by Symonds et al.[14] These authors considered this lesion as a mucinous carcinoma "originating within the center of a large sessile villous adenoma", suggesting that there exists a sequence between nonmalignant papillary lesions and mucinous carcinoma though the relation of the tumor with the pseudoinvasion in polyps nor the mechanism of the wall invasion is not discussed.

Villous and tubulovillous cystadenomas have been described in the cecal appendix, with mild, moderate or severe dysplasia, that may develop a mucocele.[6,9] In general, they secret a great amount of mucin, causing a distortion in the organ, with displacement of the mucinous tumor in the appendix wall and adjacent tissues. The result is a pseudoinvasion, whose differential diagnosis with actual malignancy becomes very difficult.[7] The morphology described for the mucinous areas of these appendiceal tumors is similar to that of some ovarian tumors, the peritoneal pseudomyxoma and the MAVA.

In mucious ovarian tumors there are descriptions of invasive mucious pools with a nonmalignant epithelial coating, but with unlimited growing capacity.[11] This suggests that the cells producing extracellular mucin may acquire invasive properties and spread following the mucinous pools, which tend to dissect the surrounding tissues. This mechanism seems to be different from that of the usual carcinomatous infiltration. Frequently in our series of MAVA, mucious pools

were observed to have an epithelial coating near the base of the adenoma and noncellular mucius lakes projecting on the subserous layer (Fig. 3).

Only one of the nine MAVA observed showed lymph-node metastasis, differing from the total of tumors examined, which have nodal metastasis in 45.9% of the patients, and from the other mucinous tumors, with metastasis in 50% of the patients. The only MAVA with metastasis showed the same pattern in the lymph-nodes and in the primary tumor, pools of mucus being predominant. Due to the retrospective character of the investigation we can not discard the possibility of existence of areas of the common or undifferentiated infiltrative carcinoma type, not included when processing the surgical specimen. Anyway these data suggest that, for similar tumor sizes, MAVA has less frequent nodal metastasis than common colorectal tumors and other mucinous carcinomas, the average maximum diameter 4.85 cm for MAVA and 5.65 cm for all tumors of the series.

Most of the partially ulcerated carcinomas associated with adenomas at the periphery (subgroup b) showed an usual nonmucinous carcinoma at the base of the ulceration. We believe that in these cases the adenoma acquires actual malignancy, similar to that observed in the usual adenoma-carcinoma sequence,[4] and is more likely to develop nodal metastasis (four patients out of seven). This variety and MAVA, showing the association of mucinous carcinoma with adenoma, were found in 45.6% of all mucinous carcinomas in this series. This figure is somewhat higher than the 31% found by Symonds et al.[14]

54,2% of all mucinous carcinomas were located in the right colon, confirming what has been found in other series.[3] MAVA, however, followed the general distribution of colorectal tumors (five in the sigmoid and two in the rectum, of nine patients). The MAVA showed predominance in men (six of nine patients), while, in general, mucinous carcinoma was predominant in women, in this series (62.8%).

Diagnosis of MAVA, in spite of being a tumor of sufficient size and having a parietal involvement as to possess clear radiologic and clinical expression, cannot be established as malignant by means of endoscopic biopsy, since its endoluminal expression is the same as an adenoma. This fact has already been described in a very similar tumor of the urethra, where there exists misdiagnosis by superficial transurethral biopsy, which can only take papillary areas, nor showing the deep infiltrating pools of mucus.[12]

We consider mucinous carcinoma arising in a nonulcerated villous of tubulovillous adenoma to be a definite pathologic entity, which probably has a better prognosis than common adenocarcinoma. It may take place at an advanced stage of a sequence including the adenoma with a villous component and the villous adenoma with submucosal epithelial inclusion. It is probably incapable of developing lymph-node metastasis by itself, and may be the result of a displacement of epithelium and pools of mucus similar to the peritoneal pseudomyxoma.

The usual criteria for histologic malignancy, such as cellular atypism and stromal reaction, were not found. In spite of it, we approve the designation of "carcinoma" to this lesion, because it is able

to completely invade the colon or rectum wall.

SUMMARY

Among 209 surgical specimens of resectable colorectal adenocarcinomas, nine mucinous carcinomas arising in nonulcerated villous adenoma (MAVA) were identified. They showed infiltration in the colorectal muscularis propria or through it. However, their morphology was similar to the so-called pseudocarcinomatous submucous foci of villous adenomas. Only one of these tumors had lymph-node metastasis. We suggest that the mechanism of invasion of the colorectal wall in MAMA is different from that of the common adenocarcinoma, not implying an authentic carcinomatous transformation at cellular level.

TABLE 1:
AVERAGE MAXIMUM DIAMETER ACCORDING TO TUMOR TYPE

	Number of patients	Average (cm)
All the series	209	5.65
Mucinous Ca without adenoma	19	5.89
Mucinous Ca with periph. adenoma	7	6.00
MAVA	9	4.85

TABLE 2:
LOCATION ACCORDING TO TUMOR TYPE

	Right Colon	Sigmoid	Rectum	Other Location
All series	58 (27.7%)	80 (38.3%)	37 (17.7%)	35 (16.7%)
Mucinous Ca without adenoma	13	5	1	—
Mucinous Ca with periph. adenoma	3	3	1	—
MAVA	2	5	2	—
All the mucinous tumors	18 (54.2% #)	13	4	

: Percentage of incidence of mucinous tumors in right colon.

TABLE 3:
CORRELATION BETWEEN TUMOR TYPE AND DUKES' GRADE

	Dukes' B	Dukes' C
All the series	113 (54.1%)	96 (45.9%)
Mucinous Ca without adenoma	10	9
Mucinous Ca with periph. adenoma	3	4
MAVA	8	1

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