Sporadic Medullary Carcinoma of the Colon

A Clinicopathologic Comparison With Nonhereditary Poorly Differentiated Enteric-Type Adenocarcinoma and Neuroendocrine Colorectal Carcinoma

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Abstract

We studied 68 sporadic colorectal carcinomas (CRCs) with medullary features (MCRCs) and compared them with 35 poorly differentiated purely “enteric” CRCs (ECRCs) and 15 purely neuroendocrine carcinomas (NECs) of grades II and III, all in patients lacking a family history of CRC. Potential clinicopathologic differences between the study groups were assessed. MCRCs were significantly more common in the ascending colon than were ECRCs, but there was no significant dissimilarity to NECs. ECRCs occurred more often in the rectosigmoid than MCRCs or NECs. MCRCs arose in older patients, and a marked sex difference also was noted. Despite an infiltrative growth pattern, MCRC was less likely than ECRC to manifest with stage III or IV disease, but there was no stage-related difference from NECs. Although the histologic images of MCRCs were evocative of neuroendocrine differentiation, chromogranin positivity and synaptophysin reactivity in that group did not differ meaningfully from that of ECRCs but was dissimilar to the 100% labeling of NECs. p53 immunolabeling was similar in the 3 tumor groups. Follow-up data in the study cases showed that 5-year mortality was 40% (27/68) for MCRC, 59% (19/32) for ECRC, and 93% (14/15) for NEC. Medullary CRC seems to be a distinct clinicopathologic variant of CRC, which does not have a neuroendocrine lineage. The biologic behavior of MCRC was better than that of ECRC or NEC.

During the past 25 years, several distinct morphologic variants of colorectal carcinoma (CRC) have been identified, including such patterns as mucinous (colloid) carcinoma,1 signet-ring cell adenocarcinoma,2 “anaplastic” large-cell carcinoma,3,4 neuroendocrine carcinoma,5 “amphicrine” carcinoma,6 sarcomatoid carcinoma (“carcinosarcoma”),7 squamous cell carcinoma,8 lymphoepithelioma-like carcinoma,9 and “medullary” (undifferentiated) carcinoma.10,11 Aside from having clinical evolutions that are potentially different from those of conventional forms of CRC, these other morphotypes also evoke dissimilar differential diagnoses and raise various questions about correlations between their histologic images and basic cellular properties. In particular, substantial attention has been focused on the presence of “occult” neuroendocrine differentiation in poorly differentiated carcinomas in various organ sites.12-22 This phenomenon is seemingly a common one, but its prognostic significance, if any, is unsettled for many tumors in several anatomic locations. In particular, studies of poorly differentiated colonic carcinomas with partially neuroendocrine phenotypes have yielded conflicting conclusions about their biologic features.13,14

Medullary adenocarcinoma of the large intestine,10 also termed large cell carcinoma with minimal differentiation,23 is a variant of colonic cancer that has been recognized as a separate entity only during the last decade. In an effort to further characterize the clinicopathologic attributes of that tumor type in its sporadic form, the present study was undertaken to compare its morphologic, immunocytochemical, and behavioral features with those of poorly differentiated cases of conventional (“enteric”) CRC (ECRC) and cases of “pure” neuroendocrine carcinoma (NEC).
Materials and Methods

We searched our institutional surgical pathology files to retrieve all cases of CRC that had been coded as “undifferentiated,” “poorly differentiated,” “anaplastic,” “small cell,” “large cell,” “neuroendocrine,” and “carcinoma, not further specified.” We reviewed in a consensus manner the H&E-stained sections of each lesion obtained by such means, and cases thought to meet the criteria for medullary, pure neuroendocrine, and poorly differentiated enteric carcinomas were retained for further study. Only resection specimens were included in the analysis.

The morphologic features of each of the 3 study groups were as follows: Medullary CRCs (MCRCs) were required to demonstrate sheets, nests, and trabeculae of large polygonal cells with high nuclear/cytoplasmic (N/C) ratios and amorphophilic cytoplasm, with variably interspersed mature lymphocytes. Nuclei were vesicular, with prominent nucleoli. Focal cytoplasmic vacuolization and a minor admixture of an enteric-type adenocarcinoma component were allowed in such lesions. NECs were accepted as such if they showed organoid growth—with insulae, trabecular formations, and cellular rosettes—as well as high N/C ratios, nuclear monomorphism, dispersed nuclear chromatin with inconspicuous or absent nucleoli, necrosis, and brisk mitotic and apoptotic activity. Finally, requisite attributes of poorly differentiated ECRCs included rudimentary but definite gland formation, infiltrative growth, basal orientation of nuclei within tumor glands, vesicular chromatin, discernible nucleoli, and foci of so-called dirty geographic necrosis.

The age and sex of each patient in the study group, the anatomic locations of the tumors, their stages (according to American Joint Committee on Cancer definitions),24 and follow-up information was recorded for all cases. Only cases of nonhereditary colorectal neoplasia were accepted into the final study group, and tumors arising in the context of inflammatory bowel disease also were excluded.

Paraffin sections of each case chosen for study were cut at 5 μm, mounted on adhesive slides, and rehydrated in a standard manner for immunohistochemical analysis. They were subjected to microwave-mediated epitope retrieval after immersion in citrate buffer25 and labeled with antibodies to keratin, chromogranin A, synaptophysin, and mutant p53 protein. Avidin-biotin-peroxidase complex immunodetection ensued, with development of chromogenic precipitates in a solution of diaminobenzidine hydrochloride (0.25 mg/mL). Slides were counterstained with hematoxylin and examined by light microscopy. Immunostaining was scored as positive if at least 10% of the tumor cells demonstrated labeling for the determinants in question. That cut point was chosen to parallel emerging convention in diagnostic immunohistology in general.

Statistical comparisons of selected clinicopathologic features of the 3 tumor groups were undertaken with a commercial computer application (EpiStat for Windows, EpiStat Services, Richardson, TX), using the χ² method. Results were considered significant at a P value of .05 or less.

Results

Clinical Characteristics

Patients with MCRCs in this series had a mean age of 71 years, and 45 (66%) of 68 were women. Their tumors were located in the ascending colon in 41 (60%) of 68 cases, with the cecum predominating as the site of origin in that subgroup. The remaining MCRCs were distributed equally throughout the rest of the colon. Stage III or stage IV disease was seen in 44 cases (65%), and tumor-related mortality at 5 years was 40% (27/68) in the entire group. All patients had surgical resections of their tumors, and those with stage III or IV lesions also received chemotherapy.

Individuals with colorectal NEC were slightly younger, with an average age of 63 years, and 8 (53%) of 15 patients were men. One third of the tumors in this group had an ascending colonic localization, again favoring the cecum, and 87% (13/15) of the lesions were stage III or stage IV at diagnosis. Tumor-related mortality in the entire group was 93% (14/15) at 5 years after diagnosis. All patients with NEC were treated with surgery and adjuvant chemotherapy.

The group of patients with ECRC had a mean age of 61 years, and only 11 of 32 were women. Of the 32 tumors in this diagnostic category, 27 (84%) were stage III or stage IV at diagnosis, and 7 (22%) were located in the ascending colon. Of the

<table>
<thead>
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<th>Antibody</th>
<th>Manufacturer</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin</td>
<td>Becton-Dickinson Laboratories, Mountain View, CA</td>
<td>1:40</td>
</tr>
<tr>
<td>Clones CAM5.2</td>
<td>Zymed Laboratories, South San Francisco, CA</td>
<td>1:150</td>
</tr>
<tr>
<td>Clones AE1 and AE3</td>
<td>Zymed Laboratories</td>
<td>1:100</td>
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<tr>
<td>Clones KA4/UCD/PR10.11 (MAK-6)</td>
<td>Novocastra Laboratories, Newcastle upon Tyne, England</td>
<td>1:250</td>
</tr>
<tr>
<td>Mutant p53 protein (clone Pab1801)</td>
<td>Research Diagnostics, Flanders, NJ</td>
<td>1:20</td>
</tr>
<tr>
<td>Chromogranin A (clone LK2H10)</td>
<td>DakoCytomation, Dublin, CA</td>
<td>1:20</td>
</tr>
<tr>
<td>Synaptophysin (clone SY38)</td>
<td>DakoCytomation, Dublin, CA</td>
<td>1:20</td>
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</tbody>
</table>
patients with ECRC, 19 (59%) had died of their tumors at 5 years after diagnosis. Each patient in this group had a surgical resection of his or her tumor, and those with stage III or IV disease also were given adjunctive chemotherapy.

Demographic findings for the 3 tumor groups are summarized in Table 2. The topographic distribution of the lesions is depicted in Figure 1.

**Table 2**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Age Range (Mean) (y)</th>
<th>Male/Female Ratio</th>
<th>Stage III or IV Disease</th>
<th>5-Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary carcinoma (n = 68)</td>
<td>48-82 (71)</td>
<td>23:45</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma (n = 15)</td>
<td>35-71 (63)</td>
<td>8:7</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Enteric-type adenocarcinoma (n = 32)</td>
<td>42-68 (61)</td>
<td>21:11</td>
<td>27</td>
<td>19</td>
</tr>
</tbody>
</table>

*Data are given as number of patients unless otherwise indicated.

**Morphologic Findings**

**Medullary Colorectal Carcinoma**

All MCRCs demonstrated an ulcerated mucosal component grossly, but they were situated principally in the submucosa and often grew through the entirety of the bowel wall Image II. Histologically, these lesions featured a distinctive

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**Figure 1** Anatomic distribution of medullary carcinomas (n = 68) (A), neuroendocrine carcinomas (n = 15) (B), and poorly differentiated enteric-type adenocarcinomas (n = 32) (C) of the colon and rectum in this series.

**Image II** A, Gross photograph of medullary colorectal carcinoma, showing a fleshy, partially ulcerated mucosal mass in the cecum. B, A scanning microscopic image of the same tumor shows predominant growth in the bowel wall, with cellular arrangement in solid cords and nests (H&E, x60).
image on scanning microscopy, with the tumor cells being arranged in nests, cords, and sheets Image 2. The neoplastic elements infiltrated widely through the mural intestinal connective tissue; perineural and angiolymphatic invasion also were common Image 3. Foci of geographic necrosis were scattered throughout the lesions Image 4, but there was no evidence of the Azzopardi phenomenon. A peritumoral and intratumoral lymphoid infiltrate was observed at least focally in 60 (88%) of the 68 lesions. Individual tumor cells had high N/C ratios, round to oval nuclear contours, vesicular chromatin, and easily seen amphophilic nucleoli Image 5. Mitotic figures were numerous, as were apoptotic bodies.

There was no difference in the microscopic appearance of lymph nodal tumor deposits vis-à-vis that of the primary neoplasms. Tubular or tubulovillous adenomas also were present in 65 (96%) of the MCRC cases, but the carcinomas did not demonstrate a direct connection with any of them.

**Neuroendocrine Colorectal Carcinoma**

NECs had limited mucosal components and were situated principally in the bowel wall; only 50% demonstrated gross ulceration of the mucosa Image 6. On the other hand, several of them showed peripheral growth in the submucosa that undermined intact overlying mucosa, and 10 of 15

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**Image 2** A. Cords, nests, and ill-defined trabecular profiles of tumor cells are present in this medullary colorectal carcinoma (H&E, ×60). B. The medullary nature of the tumor is seen to better advantage in this photograph (H&E, ×200).

**Image 3** Angiolymphatic invasion by tumor is apparent in this medullary colorectal carcinoma (right side of figure) (H&E, ×160).

**Image 4** Clustered cellular growth in medullary colorectal carcinoma, with foci of spontaneous tumor necrosis (upper central portion of figure) (H&E, ×160).
exhibited a connection to, and apparent origin in, tubular or tubulovillous adenomas.

Histologically, all of the NECs showed organoid growth with insular, trabecular, or sheet-like cellular growth [Image 7]; similar to pulmonary neuroendocrine tumors, 7 were classified as grade II tumors because they demonstrated well-defined organoid growth and only moderately increased N/C ratios but showed nuclear pleomorphism, more than 5 mitotic figures per 10 high-power (×400) microscopic fields, and foci of spontaneous tumor necrosis [Image 8]. The remaining tumors were all grade III lesions, exhibiting high N/C ratios, mitoses in excess of 10 per 10 high-power microscopic fields, obvious and multifocal geographic necrosis, nuclear pleomorphism, and prominent apoptosis. Of 8 grade III neoplasms, 6 were of the small cell type, whereas the others were of the large cell type [Image 9]. Angiolympathic and perineural invasion were common in the colonic NECs. There was no appreciable lymphoid infiltrate within or around these lesions. Cytologic characteristics included round to oval nuclear contours, dispersed chromatin, inconspicuous nucleoli, and amphophilic cytoplasm in all cases. Again, lymph nodal deposits and the primary neoplasms were comparable histologically. NECs originating in tubular or tubulovillous adenomas demonstrated a sharp interface with those lesions.

[Image 5 A and B], The cytologic features of the neoplastic cells in medullary colorectal carcinoma include open chromatin, easily discernible nucleoli, amphophilic cytoplasm, and numerous mitotic figures (A, H&E, ×250; B, H&E, ×400).

[Image 6 A], Gross photograph of neuroendocrine carcinoma of the cecum, demonstrating a partially endoluminal and ulcerated mass. The bowel also demonstrates the changes of melanosis coli. B, Another case of colonic neuroendocrine carcinoma shows localization of the tumor in tissue deep to the mucosa (H&E, ×60).
Poorly Differentiated Enteric-Type Adenocarcinoma

The ECRCs in this series all were exophytic endoluminal masses or mucosal ulcers with “heaped-up” margins. They infiltrated irregularly into the bowel wall, and 31 (97%) of 32 were associated with tubular or tubulovillous adenomas in the resection specimens. Histologically, these neoplasms were typified by small glands with basally oriented nuclei, alternating with sheets or nests of solidly cellular tumor elements. Organoid growth patterns were not apparent on scanning microscopy. Dirty necrosis in glandular profiles, characterized by karyorrhectic cellular debris, was common, but foci of geographic necrosis were not, and the Azzopardi phenomenon was absent. Angiolymphatic or perineural invasion was evident in 28 cases, and a peritumoral or intratumoral lymphoid infiltrate was seen in 18. The tumor cells showed a modest quantity of amphophilic or eosinophilic cytoplasm, coarse chromatin, discernible nucleoli, and easily seen mitotic figures. None of the ECRCs demonstrated direct apposition to colonic adenomas as seen in cases of NEC. Lymph nodal metastases of the former tumors were comparable histologically to the primary neoplasms.

Image 7: Cellular growth in trabecular profiles is evident in this colonic neuroendocrine carcinoma (H&E, ×200).

Image 8: Grade II neuroendocrine carcinoma of the colon, in which the tumor cells contain a moderate amount of cytoplasm and retain a medullary growth pattern, yet exhibit spontaneous necrosis and brisk mitotic activity (H&E, ×160).

Image 9: A, Large cell neuroendocrine colonic carcinoma showing numerous mitoses and necrosis but relatively generous size of individual tumor cells (H&E, ×160). B, Cytologic features of the tumor include nuclear molding and dispersed chromatin (H&E, ×600).
Immunohistochemical Findings

All tumors in this series were reactive for keratin, establishing the basic antigenic integrity of the substrate tissues. Cytoplasmic immunoreactivity for chromogranin A and synaptophysin was apparent multifocally in MCRCs in 22 (32%) of 68 cases Image 11. In general, those reactants were seen in widely separated groups of tumor cells, with the intervening elements being negative. Similar findings were observed in ECRC cases, among which 19% (6/32) showed conjoint chromogranin and synaptophysin positivity. In contrast, the great majority of neoplastic cells in all NECs were labeled for those 2 markers. Immunostains for putatively mutant p53 protein showed nuclear reactivity in 36 (53%) of 68 MCRCs, 22 (69%) of 32 ECRCs, and 10 (67%) of 15 NECs Image 12. More than 50% of the neoplastic cells were strongly labeled in each of the p53+ lesions.

Statistical Comparisons Between Tumor Groups

Statistical comparisons were made using MCRC cases as the control group. There were significantly more women in that cohort than in the ECRC case cluster ($P = .008$), and

■ Image 10. Poorly differentiated enteric-type adenocarcinoma of the colon showing disorganized growth of nests and cords of tumor cells (A) but with multifocal primitive glandular differentiation (B) (A, H&E, x100; B, H&E, x250).


■ Image 12. Diffuse nuclear immunopositivity for p53 protein is seen in this poorly differentiated enteric-type colonic adenocarcinoma (avidin-biotin-peroxidase complex immunostain for p53, x300).
MCRCs also were more likely to arise in the ascending colon (P < .001). The likelihood of stage III or IV disease in MCRC also was statistically less than that seen with ECRC (P = .001). Moreover, death due to tumor was significantly more likely in the ECRC group than in the MCRC cohort (P < .001). There was no meaningful dissimilarity in chromogranin or synaptophysin immunoreactivity in the MCRC and ECRC cases (P = .26), and the same was true of p53 protein immunolabeling (P = .25). Similar comparisons of MCRC and NEC showed a significant difference in the 2 groups only with respect to a greater likelihood of death due to neoplastic disease (P < .001) and the incidence of positivity for chromogranin and synaptophysin (P < .001) in NEC cases.

Discussion

As used in this report, the term medullary CRC is intended to represent an organoid architecture in that tumor type on scanning microscopic examination—that is, a growth pattern that simulates that of developing embryonic organs. The designation of medullary is now well established, but that name has the disadvantage of previous use in other organ systems such as the thyroid and breast in reference to completely dissimilar tumor types which should not be confused with the lesions discussed herein. The morphologic similarity between MCRC and NEC of the gut initiated this contemporaneous analysis of those 2 tumor types in an effort to revisit the conclusions of Jessurun et al., who stated that endocrine differentiation was lacking in MCRC. We also compared MCRC with poorly differentiated “conventional” colonic carcinoma to extend the results of previous parallel studies on those tumor entities.

In contrast with earlier reports on medullary colonic carcinoma, immunohistologic evidence of neuroendocrine differentiation was found in 32% of MCRC cases (22/68) in the present series. That observation is notable for 2 reasons. First, it corroborates that developing embryonic organs. The designation of medullary is now well established, but that name has the disadvantage of previous use in other organ systems such as the thyroid and breast in reference to completely dissimilar tumor types which should not be confused with the lesions discussed herein. The morphologic similarity between MCRC and NEC of the gut initiated this contemporaneous analysis of those 2 tumor types in an effort to revisit the conclusions of Jessurun et al., who stated that endocrine differentiation was lacking in MCRC. We also compared MCRC with poorly differentiated “conventional” colonic carcinoma to extend the results of previous parallel studies on those tumor entities.

In contrast with earlier reports on medullary colonic carcinoma, immunohistologic evidence of neuroendocrine differentiation was found in 32% of MCRC cases (22/68) in the present series. That observation is notable for 2 reasons. First, it corroborates that MCRCs are definably more aggressive than other colonic carcinomas discussed herein, at a statistically significant level. Moreover, as Gaffey et al. have written, there are no appreciable differences in behavior between grade II and grade III NECs.

On the other hand, MCRC is paradoxical biologically. Its histologic appearance is that of an undifferentiated neoplasm, yet it is associated with less mortality than poorly differentiated ECRC or NEC. That observation further validates a premise advanced by Alexander and colleagues, who stated that the medullary histotype in colon cancer is an effective predictor of microsatellite instability; that attribute, in turn, is thought to confer a better prognosis on advanced-stage colorectal carcinomas, with a heightened response to chemotherapy. In an analysis by Hinoi et al., 60% of MCRCs demonstrated molecular evidence of high-frequency microsatellite instability.

Another proffered contention in the literature on CRC is that microsatellite instability and p53 gene mutation (usually correlating with immunoreactivity for p53 protein) are correlated inversely with one another in the pathogenesis of those neoplasms. Although the focus of our study admittedly was not the molecular profiling of the tumors in question, comparable p53-immunostaining results that were obtained in the MCRC and ECRC groups might call the aforementioned mechanistic paradigm into some question with specific reference to MCRC.

Rather surprisingly, there have been few specific reports heretofore on the clinical outcome of patients with MCRC. However, the results of the present series clearly show that it behaves more favorably than poorly differentiated ECRC in regard to the likelihood of high-stage disease at diagnosis and in overall risk of death due to tumor growth.

Sporadic MCRC seems to be a distinctive clinicopathologic variant of large intestinal carcinoma, with a predilection for the large intestine, and its likelihood probably is related simply and directly to tumor grade.

Staren et al. suggested that one can subclassify poorly differentiated CRCs into 4 groups: lesions with a clearly neuroendocrine morphotype and global immunoreactivity for endocrine markers, others with a purely enteric histologic and immunophenotypic image, a third assemblage with mixed enteric and neuroendocrine components at morphologic and immunohistologic levels, and a fourth subset that has a purely nonneuroendocrine morphologic appearance but a partially neuroendocrine immunophenotype. MCRC represents yet another variation on this construct, because its histologic image suggests possible endocrine differentiation, and yet it shows only partial neuroendocrine composition in a minority of cases. The practical value of this information lies in the assertion that only the lesions that have a neuroendocrine morphotype and global immunoreactivity for endocrine determinants should be classified as NECs. As so defined, NECs are definably more aggressive than other colonic carcinomas discussed herein, at a statistically significant level. Moreover, as Gaffey et al.
for origin in the ascending colon in female patients and the organoid growth of relatively monotonous large polygonal tumor cells. Despite its histologic image, it does not demonstrate any neuroendocrine differentiation in the great majority of cases and has a better prognosis than that of poorly differentiated enteric-type adenocarcinoma or pure NEC of the colon and rectum.

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References


