Histological Variants of Colorectal Adenocarcinoma and Clinicomorphological Association

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Objective: *Besides TNM staging system, some special histological features of colonic carcinomas are associated with variable clinicopathological parameters. The objective was to provide new information of correlation between various histomorphological parameters together with available clinical data and each special feature*

Material and Method: *A retrospective study of 162 materials collected from subjects with first diagnosed as adenocarcinoma of colorectum in King Chulalongkorn Memorial Hospital over a period of 2 years from 2002 to 2003.*

Result: *One hundred and forty-seven cases of prominent cribiform feature are related to patient age (p = 0.025) and infiltrative margin (p = 0.006). Thirty-two cases with mucinous component are associated with patient age (p = 0.009) and tumor depth (p = 0.015). Thirteen cases with signet ring cell morphology are correlated with nodal and distant organ metastasis (p = 0.023 and p = 0.020, respectively) as well as angiolymphatic invasion (p = 0.015). In addition the size of signet ring cell containing carcinomas is also related to location (p = 0.036). It is larger in proximal site and smaller in distal counterpart. The authors did not find any statistical significance in 9 cases of medullary carcinoma. Notably, our 33 cases showed biphasic or triphasic feature.*

Conclusion: *Each distinct histological variant of colorectal adenocarcinoma is associated with some different clinicopathological variables, mostly effecting clinical outcome. Pathologists should be concerned with special histological subtypes of colorectal adeonocarcinomas and communicate with physicians for proper management.*

Keywords: *Colorectal neoplasia, Cribiform, Mucinous, Signet ring cell, Medullary*

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Colorectal cancers are a global oncologic problem challenging many physicians. Surgical resection is the essential primary treatment modality for colorectal carcinomas and pathological examination of the resected specimen and is the most powerful tool for assessing prognosis following surgery[1,2].

Careful evaluation of a surgically removed specimen is the strongest influence for further treatment[3]. Although the parameters that determine the pathologic stage are the most important predictors of postoperative outcome, each additive pathological feature possesses a potential as prognostic significance, regardless of tumor staging. These features are histologic grade, tumor border configuration, host lymphoid response facing along tumor, status of surgical resected margin, angiolymphatic invasions and neural invasions[4,5]. This is in line with recent documented special histologic patterns of colonic carcinomas that proved to be independent prognostic factors[6,7].

Most authors accept that mucinous, signet ring cell and medullary carcinomas are poor histologic subtypes, forecasting the worse outcomes despite vigorous management[7]. Ordinary adenocarcinoma is partly recognized as visible glandular formation. Cribiform pattern is referred to network of densely packed glands, arranged in round shape contours and sharp borders with recognizable several small glandular

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lumens. The amount of this pattern is quantified in many reports, determining possible new significant information[8,9].

Because these special features are associated with downward tend of outcome, the authors attempted to provide new information on the correlation between various histomorphological parameters, available clinical data and each special feature.

Material and Method

A retrospective study of 162 cases of sporadic colorectal adenocarcinoma from the pathology file of King Chulalongkorn Memorial Hospital between 2002 and 2003 was done. All subjects were first diagnosed with colorectal adenocarcinoma. The specimens were noted for the location, including ascending, transverse, descending and rectosigmoid regions, depth of tumor penetration, number of regional lymph node metastasis and distant organ spreading, according to TNM staging. Specimens with prior treatment of radiation or chemotherapy were excluded from the present study.

Microscopic examination was performed on 4-mm thick hematoxylin and eosin (H&E) stained sections. Three or more sections of the tumor were analyzed in each case. Tumor features were classified based on the variants according to the World Health Organization (WHO) histological classification of tumors of the colon and rectum. The classification consisted of mucinous, signet ring cell and medullary carcinomas[8]. The tumors were divided into one of three groups, < 10%, 10-50%, and > 50%[10]. Cribiforming growth pattern referred to complex glandular formation with sharp contour. They have been frequently recognized in the most recent literature. They were also recorded and stratified into < 10%, 10-50%, and > 50%[11]. Tumor margin, categorized as pushing or infiltrating, was also identified along with vascular and neural invasions.

Data were collected and analyzed with the statistical program SPSS for Windows, version 11.5. The relation between histologic variants and clinicomorphologic variables was assessed by means of the Spearman's rank correlation coefficient and Kruskall-Wallis test. Confidence intervals were 95%. A p value of < 0.05 was considered statistically significant.

Results

One hundred and sixty-two subjects consisted of 80 males (49%) and 82 females (51%) with a mean age of 62 years and 59 years, respectively. For microscopic characters, 147 cases showed cribiform arrangement (Fig. 1), 32 cases showed mucinous component (Fig. 2), 13 cases showed signet-ring cell feature (Fig. 3), and 9 cases showed medullary formation (Fig. 4). Notably, there were 33 cases that demonstrated biphasic or triphasic pattern. Signet ring cell carcinomas occurred in the youngest age group with a mean age of 52 years, while cribiforming growth pattern was found in the oldest mean age of 61 years (Table 1).

According to histopathologic parameters, cribiform feature and mucinous compartment were significantly increased with age ($p = 0.025$ and $p = 0.009$, respectively). Cribiform pattern was also associated with infiltrative margin ($p = 0.006$) whereas degree of mucinous compartment was correlated with depth of tumor invasion ($p = 0.015$). For signet ring cell configuration, it was not only related to vascular invasion ($p = 0.015$), number of nodal and distant organ metastases ($p = 0.023$ and $p = 0.020$, respectively), but it was significantly correlated with location ($P = 0.036$) as well. The signet ring cell carcinoma was smaller when situated in the distal part, and larger in the proximal part (Table 2).

Discussion

Cancers of the colon and rectum are world-

Table 1. Distribution of clinical information in each microscopic variant of colorectal cancers

Morphology	Mean age (yr)	Frequency*					
		Sex		Location			
		Male	Female	Ascending	Transverse	Descending	Rectosigmoid
Cribiform	61	59	88	27	11	12	97
Mucinous	54	19	13	10	3	3	16
Signet ring	52	4	9	6	2	0	5
Medullary	54	3	6	3	0	0	6

* There were 33 cases with combined two or three histologic features in each case

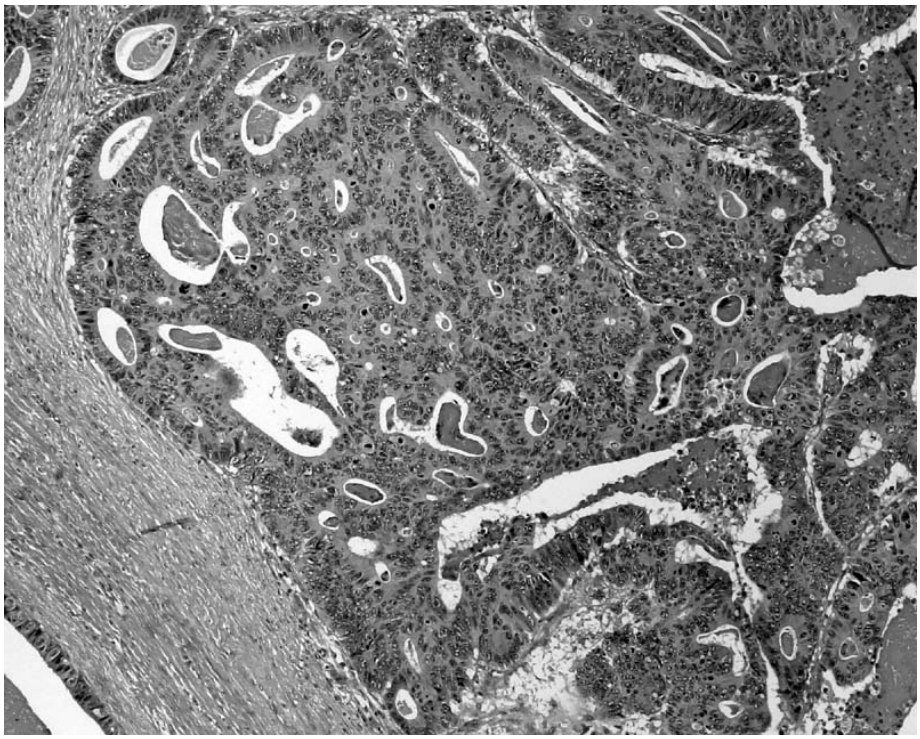

Fig. 1 Cribiform formation: Complex neoplastic glands bearing small glandular lumens with sharp contours

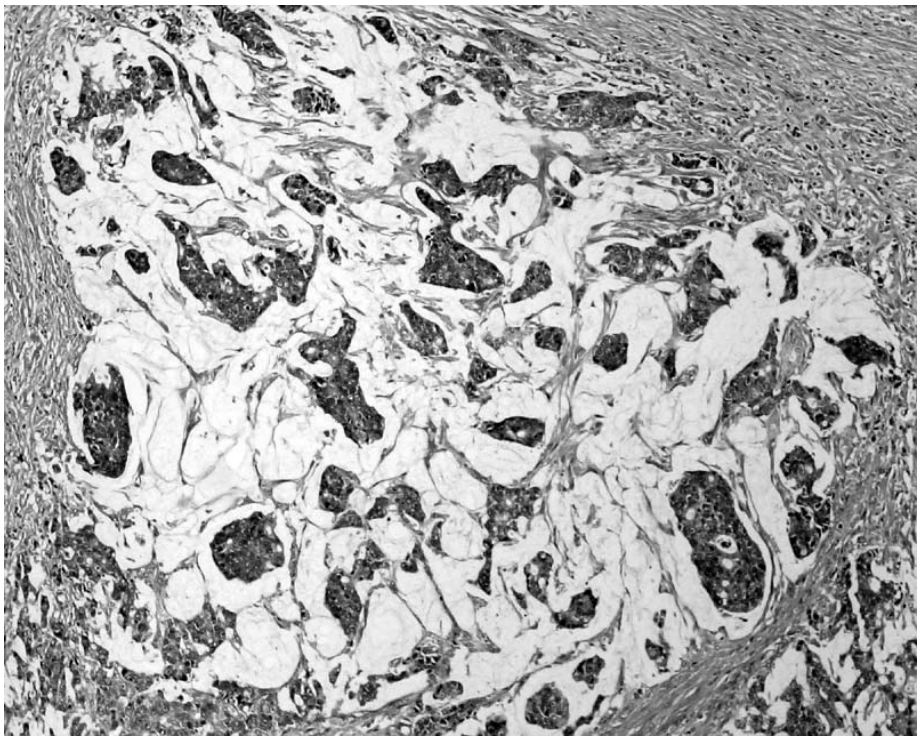

Fig. 2 Mucinous carcinoma: Several clusters of tumor cells floating in mucin lakes

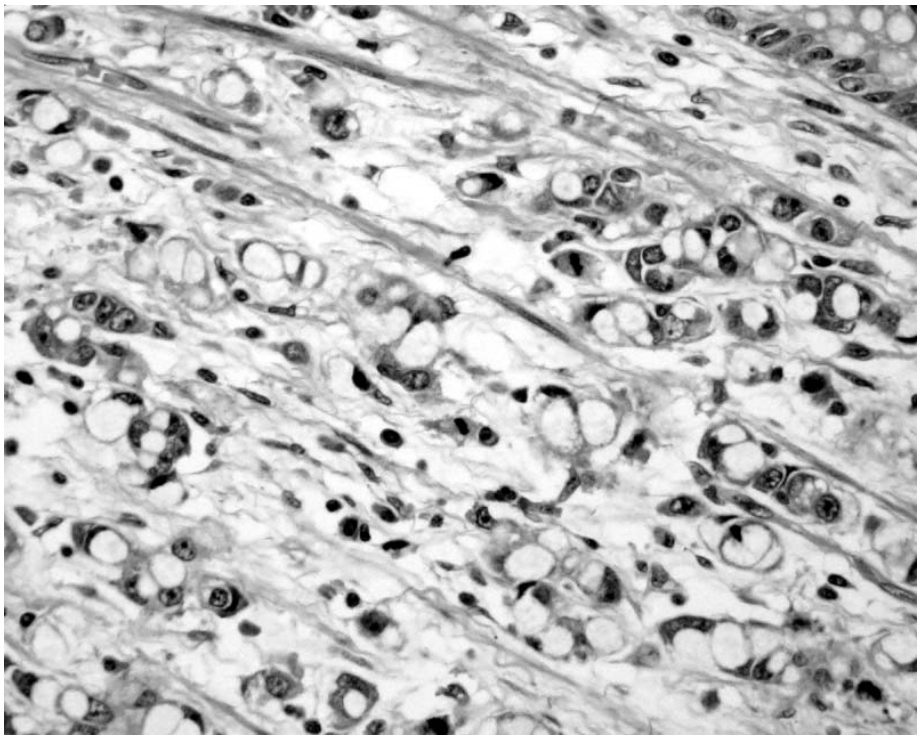

Fig. 3 Signet ring cell carcinoma: Individual neoplastic cells harboring intracytoplasmic vacuoles with eccentric pleomorphic nuclei

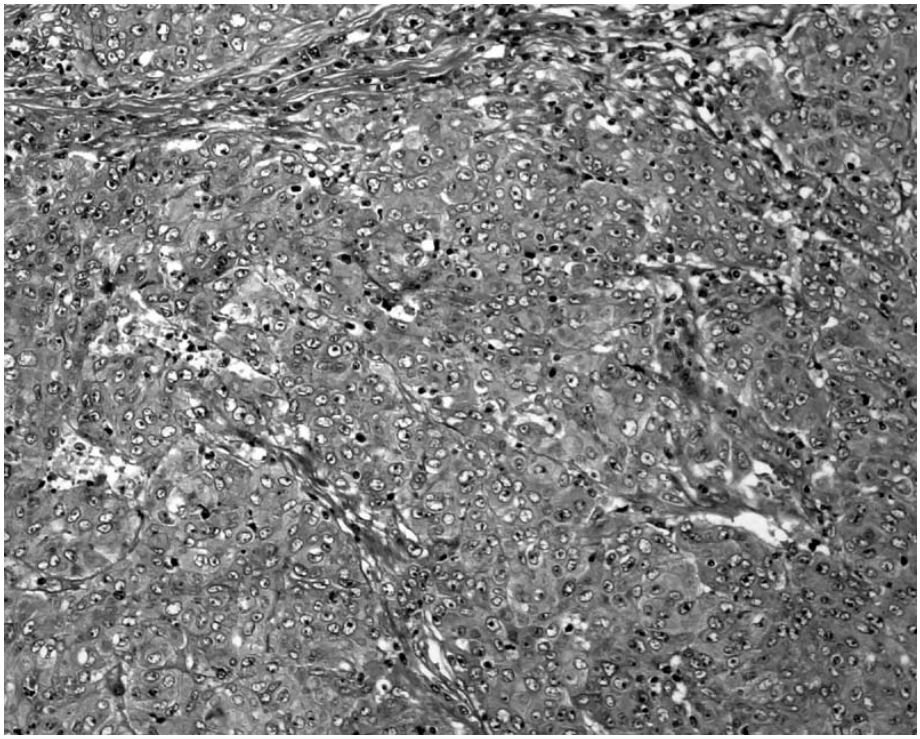

Fig. 4 Medullary carcinoma: Large solid sheets of malignant cells with syncytial cell borders, possessing vesicular nuclei and prominent nucleoli

Table 2. The correlation of variable parameters in each colorectal adenocarcinoma variant

Morphology	Age	Site	Tumor depth	Nodal involvement	Organ metastasis	Margin	Angiolymphatic invasion
Cribiform	$p = 0.025$	NS	NS	NS	NS	$p = 0.006$	NS
Mucinous	$p = 0.009$	NS	$p = 0.015$	NS	NS	NS	NS
Signet ring	NS	$p = 0.036$*	NS	$p = 0.023$	$p = 0.020$	NS	$p = 0.015$
Medullary	NS	NS	NS	NS	NS	NS	NS

*, inverse correlation; NS, not statistic significant

wide and is actually accepted that both genetic and environmental factors play a role in colorectal carcinogenesis. Currently, treatment options are mostly referred to tumor stage, which is associated with prognosis and clinical outcome[2,3]. However, tumor grade according to neoplastic differentiation including special micromorphologic characters such as signet ring cell, mucin-rich, medullary, sarcomatoid, and undifferentiated type also affects prognostic impact[6-8]. Nevertheless, association of clinicomor-phologic data in each histologic variant is seldom assessed in most publications.

Although cribiform formation is not separately classified into a particular group, this feature is usually apparent in conventional adenocarcinoma and some authors have stratified them semiquantitatively because tumor differentiation is downward if density of cribiform appearance is markedly increased[8]. The authors found that, besides being age related, cribiforming growth pattern was also associated with infiltrative growth margin.

Mucinous or colloid carcinoma is the tumor that produces copious extracellular mucin, accounting for 11% to 19% of colorectal cancers[7,12-14]. According to the World Health Organization (WHO) criteria, diagnosis with mucinous carcinomas is made when at least a half of tumor volume comprises mucin component[8]. Notably, mucinous carcinomas are disproportionately common in individuals younger than 40 years of age, patients with a history as chronic Inflammatory Bowel Disease (IBD), chronic anal fistula, previous abdominal radiation and residents of geographic zones with low endemic rates of colon cancer. Furthermore, mucinous carcinomas are by far the most common type of cancer arising within villous adenomas and villous dysplasia in the setting of IBD[14-17].

Concerning morphology, the mucinous type typically buds off from the deepest portions of the overlying adenomatous crypts, eliciting little desmoplasia of its penetrating wall. In many cases there seem to be a conventional adenocarcinoma in the superficial part, but mucinous character is identified in the deeper part of the tumor and along its advancing front. The important points published in many previous studies are poorer survival rate, lower percentages of resection for cure and higher recurrent rate compared with nonmucinous carcinomas[18,19]. However, poor outcomes attributed by mucinous carcinoma are largely due to their relatively advanced stage at diagnosis, similar to the present study. The authors found that the depth of mucinous tumor penetrating through the colonic wall is correlated with the amount of mucinous elements. Moreover, its quantity is also associated with patient age as the older the patient, the larger the amount of mucin.

Signet ring cell type is usually found in approximately 1% of all colorectal cancers with a peak incidence at younger than 40 years of age[1,20,21]. In a large population-based study, colonic carcinomas with signet ring cell characteristics accounted for 10% of patients younger than 20 years but 0.2% of those older than 40 years. For its biology, multifocal intramucosal tumor deposition is fairly common, usually representing metastatic involvement rather than new primary tumors. In the present study, signet ring cell variant itself was an independent factor, harboring aggressive behavior, both nodal and distant organ metastases. Angiolymphatic invasion, which was also significantly associated with this morphology, might be a possible potential mechanism. This fact is similar to other previous publications. Lymphatic invasion is common with frequent nodal involvement, seen in 75% to 90% of cases[22,23].

For tumor location of signet ring cell carcinoma, the tumor size in the rectosigmoid colon is significantly smaller than those in the proximal part, either ascending or transverse colon, at the time of diagnosis. For this reason, a tumor with signet ring cell morphology possibly possesses rapid growing potential plus physiologic manner of fecal formation. When

bowel content moves through the cecum and ascending colon, it is still liquefied and moves easily without warning signs, even though colonic lumen is partially occluded by carcinomatous mass. By contrast, fecal material is rather solidified in the distal part because of usual water absorption along intestinal mucosa. Thus, when feces move against the tumor, forming a narrowing colonic lumen, it causes the patients' experience of intestinal obstruction[2-4].

Considering colonic medullary carcinoma, this entity is outstanding in the female gender[8,22]. Cecum and ascending colon are the common locations as opposed to the present study. In this present study, six out of nine cases were discovered in the rectosigmoid region, whereas only three cases (33%) were situated in the proximal colon. The characteristic features of this type include sheets of malignant cells, containing vesicular nuclei, prominent nucleoli and eosinophilic cytoplasm, dispersedly infiltrated by prominent peritumoral and intratumoral lymphocytes. Medullary carcinomas occur either spontaneously or in individuals with the Hereditary NonPolyposis Cancer syndrome (HNPCC)[22,24]. However, there was no statistical significance between medullary carcinoma and clinicohistological parameters in the authors' experience.

To summarize, the authors conclude that each distinct histological variant of colorectal adenocarcinoma is associated with some different clinicopathological variables, mostly effecting clinical outcome. The authors are convinced that besides TNM staging system, pathologists must be concerned with special histological subtypes of colorectal adeonocarcinomas and communicate with physicians for proper management.

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ความสัมพันธ์ของจุลพยาธิสภาพที่หลากหลายกับลักษณะและความรุนแรงของโรคในมะเร็งลำไส้ใหญ่

นฤมล วิเศษโอภาส, ดวงเพ็ญ ถิระบัญชาศักดิ์, นฤดา จิรกาลวสาน, มานะ ทวีวิศิษฏ์

นอกจากการแบ่งระยะความรุนแรงของมะเร็งลำไส้ใหญ่ที่ใช้กันเป็นสากลแล้ว ยังมีลักษณะทางจุลพยาธิวิทยาบางอย่างที่สัมพันธ์กับลักษณะ ความรุนแรง และการดำเนินโรค รวมทั้งการตอบสนองต่อการรักษา เพื่อหาความสัมพันธ์นี้ คณะผู้ทำการศึกษาจึงรวบรวมชิ้นเนื้อมะเร็งลำไส้ใหญ่จำนวน 162 รายซึ่งถูกวินิจฉัยครั้งแรกที่โรงพยาบาลจุฬาลงกรณ์ระหว่างปี พ.ศ. 2545 ถึง พ.ศ.2546 เมื่ออิงตามนัยสำคัญทางสถิติปรากฏว่า เนื้อมะเร็ง 147 ราย ที่มีลักษณะเรียงเป็นรูปตะแกรงสัมพันธ์กับอายุผู้ป่วยและขอบของก้อนมะเร็งที่ไม่เรียบ เนื้อมะเร็งที่มีเมือกเป็นองค์ประกอบ 32 ราย สัมพันธ์กับอายุผู้ป่วยและความลึกของมะเร็งที่ลุกลามเข้าผนังลำไส้ เนื้อมะเร็ง 13 รายที่ให้ลักษณะรูปแหวนตราสัมพันธ์กับการกระจายเข้าสู่ท่อเลือด ต่อมน้ำเหลือง และอวัยวะห่างไกล มะเร็งลำไส้ใหญ่ที่มีลักษณะรูปแหวนตราดังกล่าวยังแปรผกผันกับตำแหน่งของลำไส้ กล่าวคือ ขนาดของก้อนมะเร็งจะเล็กกว่าถ้าเกิดที่ลำไส้ใหญ่ด้านซ้าย และใหญ่กว่าเมื่อเกิดที่ลำไส้ด้านขวา ส่วนมะเร็งลำไส้ใหญ่แบบเมดัลลารี่มี 9 ราย โดยไม่สัมพันธ์กับปัจจัยใด ทั้งนี้ มีอยู่ 33 รายที่มีลักษณะของมะเร็ง 2 หรือ 3 แบบในเนื้อมะเร็งก้อนเดียวกัน