Evaluation of the Prognostic Significance of Micropapillary Component in Colorectal Carcinoma

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Research Article

Abstract: **Background:** Micropapillary carcinoma (MP)has been described in several organs as an aggressive variant where it is associated with frequent lymphovascular invasion and poor clinical outcome.**AIM:** To classify colorectal carcinoma based on presence or absence of Micropapillary component and to evaluate the prognostic significance of Micropapillary pattern in colorectal carcinoma.**Settings and Design:** The study was undertaken on samples received at the Department of Pathology from 2003-2005. **Materials and Methods:** 100 cases of colorectal carcinoma with 43 cases showing micropapillary component were noted. The following parameters were assessed, histological grade, peritumoral lymphocytic infiltration, lymphovascular invasion, perineural invasion, tumorbudding, lymph node metastasis, distantmetastasis, depth of invasion, and TNM staging. Statistical analysis used was Fisher's exact test. **Results:** Colorectal carcinoma with micropapillary component was associated with high-grademorphology, with increased peritumoral lymphocytic infiltration, lymphovascularinvasion, perineuralinvasion, tumorbudding, lymph node metastasis and distant metastasis in comparison with colorectal carcinoma without micropapillary component. **Conclusion:** The diagnosis of patients with micropapillary component would be valuable in identifying high risk patients in TNM stages I and II .Colorectal carcinoma with micropapillary carcinoma differs from carcinoma without micropapillary component by shorter survival time in TNM stages I and II, more lymph node metastasis, distant metastasis, more aggressive behavior and lower differentiation status.

Keywords: colorectal carcinoma, micropapillary component, prognosis, TNM stage.

Introduction

Colorectal carcinomas (CRC) are amongst the most common malignant neoplasm and are the second and third most common cause of cancer death in men and women in the United States, respectively.[1]In India, they account for major cause of cancer relatedmortality in men and women respectively.[2] Though many putative prognostic factors affect the outcome of colorectal carcinoma, the most important prognostic factors are the depth of invasion, lymph node status and distant metastasis.[3,4,5,6] Currently, the therapeutic decisions are mainly based on the Tumor Node Metastasis(TNM) staging of cancer. No other reliable histomorphologic features are available for prognostication.

Micropapillary carcinoma (MP) has recently been described in several organs such as breast, bladder, lung and salivary glands.[3,4,5,6,7] Micropapillary structure is identified as a tight neoplastic cell tufts which lack central fibro vascular cores and are surrounded by cleft-like spaces. The tumor cells have eosinophilic cytoplasm and pleomorphic nuclei.[8] Pure micropapillary carcinoma is extremely rare and is usually associated with conventional carcinoma.[8]Colorectal carcinoma with a micropapillary component seems to be an aggressive variant of adenocarcinoma, due to its prevalence with high tumor stage as well as more frequent nodal and distal metastasis.[8] Colorectal carcinoma with a micropapillary component seemed to have a lower differentiation status, increased tumor budding more frequent lymphovascular and perineural invasion, more frequent lymph node metastasis and a higher tumor node metastasis (TNM) stage.[8]

Materials and Methods

A Prospective study was conducted on 100 cases of colorectal carcinoma from2008-2011,ranging from20-70years of age. Of the 100 cases of colorectal carcinoma,43 cases of colorectal carcinoma had micropapillary component. Included in the study group were 2 paraffin embedded tissue blocks were processed according to standard histological procedures and sections stained with hematoxylin and eosin. The diagnosis of H and E stained slides was categorized as colorectal carcinoma with micropapillary component and without micropapillary component. The following pathological indicators were assessed: (1) MP:carcinoma with MP when micropapillary tufts, lacking true fibro vascular cores, and surrounded by empty lacunar spaces, represented at least 5% of the tumor area in histologic sections (2) histologic type:
tubular adenocarcinoma, papillary carcinoma, mucinous adenocarcinoma, signet ring-cellcarcinoma, and undifferentiated carcinoma; (3) histologic grade: low grade (gland formation>50% in tubular adenocarcinoma

and papillary carcinoma) and high-grade (gland formation<50% in tubular adenocarcinoma, mucinous adenocarcinoma, signet ring-cell carcinoma, and undifferentiated carcinoma); (4) lymphovascular invasion;(5) perineural invasion; (6) tumor budding: this refers to microscopic clusters of undifferentiated cancer cells ahead of the invasive front of the tumor. The grade of budding was determined according to Morodomi'sdefinition: an average count of 0 to 4 in an area of500_2500 mm was considered negative, Z5 was positive (+:5 to 14 and ++:Z15)12; (7) peritumoral-lymphocyticinfiltration: peritumoral lymphocytes were counted in4 high-power fields (HPF) (40_) from surface to invasivefront, and mean values were calculated. Mean value<50/HPF was defined as negative, Z50/HPF was positive;(8) The depth of infiltration: T1 and T2, T3 and T4; (9)metastasis in lymph node: _ and +; (10) distantmetastasis; and (11) TNM stage. Excluded in the study were; patients on chemotherapy and radiotherapy before surgery and deaths due to causes other than colorectal carcinoma.

Statistical analysis

Statistical analysis was performed with SPSS16.0 soft ware for windows. Categorical variables such as age, grade of the tumor, tumor location, and nodal status were studied by frequencies and percentages. Fisher exact test or chi-square test was used to compare categorical Variables among colorectal carcinomas with and without micro-papillary (MP) component. Results were considered statistically significant when p<0.005.

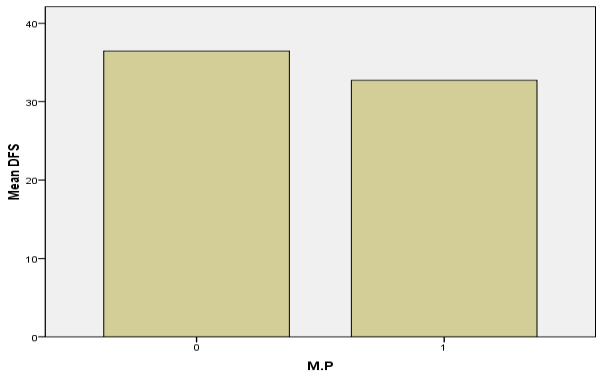
Results

Clinical and Histologic Evaluation

Of the 100 carcinomas, 43 cases presented with a MP: 21 were males and 22 females. The median age was 55 years, with a range of 20 to 86 years. 42 were alive at the time of last follow-up. The MP ranged from 5% to75% of the tumor area in histologic sections. Of these 43carcinomas with MP, 19 were tubular adenocarcinoma, 10 was mucinous adenocarcinoma, 1 was signet ring cell carcinoma, 3 were neuroendocrine type and 10 combined type. TNM stages I- II, III-IV accounted for 33% (n=14), 67% (n=29) respectively. Carcinoma with MP compared with those without MP revealed a higher percentage of high-grade tumors (33% vs. 25%) and higher levels of lymphovascular Invasion (98% vs. 49%), perineural invasion (30% vs.16%), positive tumor budding (81% vs. 42%), positivelymph node metastasis (56% vs. 33%), and TNM stages III and IV (67% vs. 40%) . No statistical differences were observed between carcinomas with and without MP with respect to age, sex, anatomic location, depth of infiltration, peritumoral-lymphocytic infiltration, histologic grade, perineural invasion, depth of invasion, and distant metastasis. However, the results stratified by T stage indicated that the presence of MPpredicted more frequent positive lymph node metastasis (24 out of 43, 56%) than the absence of MP (19 out of 57, 33%).

Survival Analysis

Among the 100 patients, none died of disease bythe end of 5years of follow-up. All the cases of CRC had a follow up ranging from 2 months to 76 months. Disease free survival (DFS) was calculated from time of diagnosis to first recurrence. Carcinomas with MP had a worseprognosis compared with those without MP.



Graph 1: Comparison of disease free survival (DFS) interval of colorectal carcinoma with MP and without MP

On X axis, 0 indicates CRC without MP component and 1 indicates CRC with MP component.

Table 1: Comparison of pathological indicators between colorectal carcinoma with and without MP

Variable	With MP(%)	Without MP(%)	p	Variable	With MP(%)	Without MP(%)	P
Age(yrs)				**PNI**			
<60	26(60%)	35(61%)	.544	**Negative**	30(70%)	48(84%)	.070
>60	17(40%)	22(39%)		**Positive**	13(30%)	9(16%)	
Sex				**Tumor budding**			
Male	21(47%)	40(70%)	.025	**Negative**	8(19%)	33(58%)	.0001
Female	22(53%)	17(30%)		**Positive**	35(81%)	24(42%)	
Location				**D.O.I**			
Colon	29(67%)	27(47%)	.117	**T1-T2**	4(9%)	10(18%)	.189
Rectum	13(30%)	29(51%)		**T3-T4**	39(91%)	47(82%)	
Both	1(3%)	1(3%)					

Histologic Grade				LNM			
Low	29(67%)	43(75%)	.255	Negative	19(44%)	38(67%)	.020
High	14(33%)	14(25%)		Positive	24(56%)	19(33%)	
PLI				DM			
<50/HPF	4(9%)	12(21%)	.093	Negative	32(74%)	49(86%)	.115
>50/HPF	39(91%)	45(79%)		Positive	11(26%)	8(14%)	
LVI				TNM stage			
Absent	1(2%)	29(51%)	.001	I-II	14(33%)	34(60%)	.006
Present	42(98%)	28(49%)		III-IV	29(67%)	23(40%)	

HPF- High power field, MP-micropapillary component, PLI-Peritumoral lymphocytic infiltration, LVI-Lymphovascular invasion, PNI-Perineural invasion, D.O.I-degree of infiltration, LNM-lymph node metastasis, D.M-distant metastasis.

Discussion

It has been demonstrated that the MP of some carcinomas, easily identified by pathologists in hematoxylin and eosin stained sections, is associated with biologic behavior[9,10,11,12,13,14] and in particular has been documentedas being an adverse prognostic factor for carcinomasin several organs such as lung, breast, and bladder.[3,10.15]However, in colorectal carcinoma, the significance of MP for survival has not been investigated. This study revealsthat the presence of MP has independent importance for survival in TNM stages and its aggressive behavior in comparison to colorectal carcinoma without MP component. TNM stage is always used to predict prognosis butthe patients in the same stage exhibit highly variable survival after curative resection. Although patients in TNM stage I and II have an overall favorable prognosis, they still show varying survival times after surgery. Ourresults demonstrate that MP predicts poorer survival in patients. The comparisons of clinicopathologic markers incarcinoma with and without MP are outlined in Table 1. Xu *et al.*[8] documented 30 cases with micropapillary pattern among a total of 221 (13.5%) cases of colorectal carcinomas. In their study, they found, Colorectal carcinoma with MP was characterized by higher histologic grade, higher levels of lymphovascular and perineural invasion, more frequent lymph node metastasis in T1 and T2 stage, and higher TNM stage than carcinoma without MP. Haup*et al.*[16] found MP to be an independent predictor of regional nodal metastasis in a series study of 34 colorectal carcinomas with MP among178 cases (19.1%), and the percentage of MP in whole tumor area was not associated with lymph node metastasis. Kim *et al.*,[7] studied 55 cases CRC with MP component and compared them with 119 of conventional adenocarcinoma and found MP component is associated with higher levels of lymphovascular 1 invasion, more frequent lymph node and distant metastasis in T1 and T2 stage, and higher TNM stage than carcinoma without MP. Although our results are similar to those of Haup *et al.*[16],Xu *et al.*[8] and Kim *et al.*[7] in MP component having higher levels of lymphovascular and perineural invasion, tumor budding, more frequent lymph node and distant metastasis and higher TNM stage than carcinoma without MP. This result, together with the outcome by survival analysis, indicates that colorectal carcinoma with MP is a distinctive variant, associated with shorter disease free survival and aggressive behavior.

1)AstlerColler (AC) staging in Colorectal carcinoma

Table 2: AC stages in colorectal carcinomawith and without MP component in present study

AC stage	AC-A	AC-B1	AC-B2	AC-C1	AC-C2	AC-D	Total
MP +ve	0	0	17(40%)	2(4.5%)	22(51%)	2(4.5%)	43
MP –ve	1(1.5%)	6(10.5%)	28(49%)	5(8.5%)	15(26%)	2(3.5%)	57
Total	1	6	45	7	37	4	100

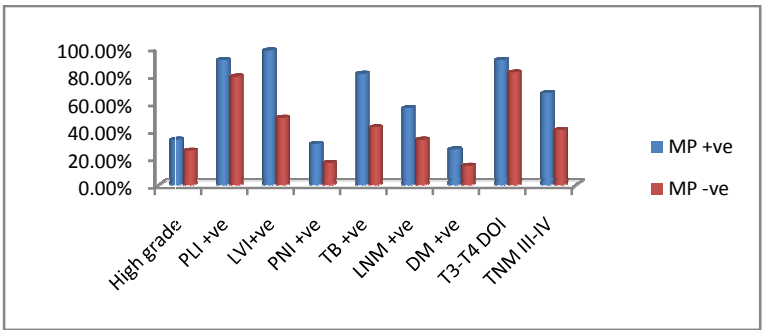
From the above table it can be seen that 45% of cases were staged as B2 while 37% were staged as C2. Among the cases of CRC with MP, maximum number of cases (51%) was in C2 stage, while 49% of CRC without MP component were in B2 stage. This suggests that CRC harboring MP component have a higher depth of mucosal and serosal invasion and higher grade of lymphovascular invasion as compared to CRC without MP component.

3) Degree of differentiation (DOD)

Table 3: Degree of differentiation in colorectal carcinoma with and without MP component in present study

DOD	WD	MD	PD	Total
MP +ve	9(21%)	21(49%)	13(30%)	43
MP -ve	37(65%)	6(11%)	14(25%)	57

Most of the cases of CRC with MP were well differentiated (WD-65%*)* in comparison to CRC without MP where majority of them were moderately to poorly differentiate (79%). It can be inferred that CRC with MP are less differentiated tumors as compared to CRC without MP.



Graph 2: Comparison of various pathological parameters among colorectal carcinomas with MP and colorectal carcinoma without MP

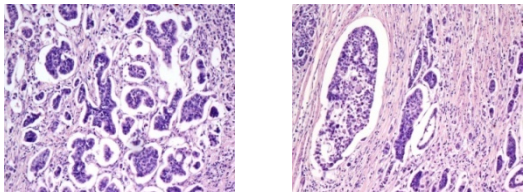


Figure 1: colorectal carcinoma with micropapillary component with tight cluster of neoplastic cells without central fibrovascular cores, surrounded by cleft like spaces.

Figure 2: Micropapillae showing tumor budding at the invasive edge of the tumor.

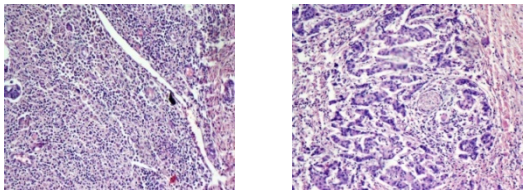


Figure 3: Micropapillae surrounded by dense lymphocytes and plasma cells.

Figure 4: Micropapillae showing perineural invasion.

Conclusion

Colorectal carcinoma with MP as compared with CRC without MP revealed a higher percentage of lymphovascular invasion (98% vs. 49%), positive tumor budding (81% vs. 42%), positive lymph node metastasis (56% vs.33%), and TNM stages III and IV (67% vs. 40%). No statistical differences were observed between carcinomas with and without MP with respect to age, sex, anatomic location, histologic grade, perineural invasion, depth of infiltration, peritumoral-lymphocytic infiltration, and distant metastasis.

Limitations of the Study

1. Kaplan Meir survival curves were not obtained since none of the patients died during the follow up period, which ranged from 2-76 months.
2. As only two sections from the tumor were taken for each case, micropapillary areas may not have been sampled.
3. As the sample size was small and limited to only 100 cases, the conclusions drawn from the study may not represent the true biological behavior of colorectal carcinoma with micropapillary component.

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