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Original Research Article

Clinicohistopathological study and expression of CK7 and CK20 in mucinous tumors of gastrointestinal tract and ovary

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ABSTRACT

Background: Mucinous ovarian tumors differ from other types of epithelial ovarian cancers in their clinical behaviour and the need for innovative treatment approaches to achieve improved patient outcomes. Immunohistochemistry plays an important role in diagnosis and differentiates primary and secondary mucinous tumors. To know the distribution and expression of CK7 and CK20 in mucinous tumors of ovary and gastrointestinal tract.
Methods: Ninety eight cases of mucinous tumors of ovary and gastrointestinal tract were analysed as per standard protocol out of which malignant mucinous tumors constituted forty five cases. All 45 cases of mucinous carcinoma of ovary and gastrointestinal tract were subjected to IHC CK7 and CK20. The results were analysed.
Results: Total mucinous tumors of ovary were 64 cases and total mucinous tumors of gastrointestinal tract were 34 cases. Predominant expression in primary mucinous carcinoma of ovary was CK7 positive and CK20 positive, in metastatic mucinous ovarian carcinoma of gastric origin was CK7 positive and CK20 positive and from colorectal origin was CK7 negative and CK20 positive. Signet ring cell carcinoma of stomach showed CK7 diffuse positivity with focal CK20 positivity. Colorectal mucinous carcinoma was CK7 negative and CK20 positive. The expression varied with the stage of the disease.
Conclusions: CK7 and CK20 plays an important role in differentiating primary mucinous carcinoma of ovary from metastatic ovarian carcinoma arising from lower gastrointestinal tract.CK7 and CK 20 expression is variable with stage of disease hence should be interpreted in the background of histopathology.

Keywords: Mucinous carcinoma of ovary, Mucinous carcinoma of GIT, CK7, CK20

INTRODUCTION

Mucinous ovarian tumors differ from other types of epithelial ovarian cancers in their clinical behaviour and the need for innovative treatment approaches to achieve improved patient outcomes.[1] Primary mucinous ovarian carcinomas constitute approximately 10% of all primary ovarian malignant neoplasms. Mucinous carcinomas involving the ovary are, more likely to be secondary neoplasms, originating most commonly in the large intestine and stomach. Differentiating primary mucinous ovarian tumors from metastatic mucinous lesions can be more problematic and needs the help of immunohistochemistry especially in cases of unknown primary.[2] Mucinous gastrointestinal tumors can be differentiated by their unique immunohistochemical profile which has therapeutic implications.[3] The aim and objectives of the study are to know the distribution of mucinous tumors of the ovary and gastrointestinal tract and to know the expression of CK7 and CK20 in primary,

secondary mucinous carcinoma of ovary and mucinous carcinoma of gastrointestinal tract.

METHODS

Study setting

Tertiary care centre, Andhra Medical College, Visakhapatnam, Andhra Pradesh.

Study duration

Study duration was period of 2 years from November 2018 to October 2020.

Study design

The study design was hospital based observational study.

Sample size

98 cases of mucinous tumors of ovary and gastrointestinal tract received for histopathological examination.

Inclusion criteria

Specimens of mucinous tumors of ovary and gastrointestinal tract received in the department of pathology for histopathological examination during this period.

Exclusion criteria

Cases with recurrent lesions, who are on therapy and non mucinous tumors of ovary and gastrointestinal tract.

Clinical data recorded as per protocol.

Malignant tumors were grossed and representative bits were taken and subjected for paraffin embedded processing. The sections were stained with Hematoxylin and Eosin and interpretation done as per standard reporting protocol.

Forty five cases of malignant mucinous tumors of ovary and gastrointestinal tract were subjected to immunohistochemistry by CK7 and CK20 (Company: Dako) and their expression recorded.

Ethical considerations

Prior permission was taken from institutional ethics committee.

Statistical considerations

Data is recorded in Microsoft Excel sheet and percentage distribution calculated. P value is calculated by t test and comparison of means.

RESULTS

Total mucinous tumors of ovary and gastrointestinal tract analysed are 98. Total mucinous tumors of ovary analysed are 64 (65.31%). Total mucinous tumors of gastrointestinal tract analysed are 34 (34.69%). All the malignant tumors of ovary and gastrointestinal tract are subjected to immunohistochemistry by CK7 and CK20.

Number of cases subjected for IHC study CK7 and CK20 are 45.

These cases are: 1) primary mucinous carcinoma of ovary (8 cases), 2) secondary mucinous carcinoma of ovary (Krukenberg tumor) (5 cases), 3) mucinous carcinoma of stomach (3 cases), 4) signet ring carcinoma of stomach (14 cases) and 5) colorectal mucinous carcinoma (15 cases).

Mucinous tumors of ovary

Benign mucinous tumors constituted 76.56% (n=49) of total mucinous tumors of ovary. Mean age of presentation is 45±1years, size of tumor is 15cm±5cm, unilateral, left sided tumor in 36 (73.47%) cases, right sided tumor in 13 (26.53) cases. All tumors are cystic on gross examination.

Atypically proliferating mucinous tumors are 2 cases (3.12%), with mean age of 35±1 years, size of tumor 20±2 cm, unilateral on right side, purely cystic on gross examination.

Mucinous carcinoma of ovary constituted 20.32% (n=13), with mean age of 50±1 years, size of tumor: 20±5cm, left sided tumor (6 cases), right sided tumor (2 cases) and bilateral tumor (5 cases); on gross examination solid cystic tumors in 10 cases, cystic tumor in one case and solid tumor in 2 cases (Table 1).

Table 1: Distribution of mucinous tumors of ovary (n=64).

Lesions	N	%
Benign mucinous cystadenoma	49	76.56
Atypically proliferating mucinous tumor	2	3.12
Mucinous carcinoma	13	20.32
Primary mucinous cyst adenocarcinoma of ovary	8	61.54
Secondary mucinous carcinoma of ovary (Krukenberg tumor)	5	38.46

Comparison of mean age in benign and malignant mucinous tumors of ovary are p value is highly significant 0.0001 (<0.05). Comparison of mean size of tumor in benign and malignant mucinous tumors of ovary are p value is highly significant 0.0022 (<0.05).

Mean age of presentation of primary mucinous carcinoma of ovary is 50±1 and secondary mucinous carcinoma of ovary (Krukenberg tumor) is 35±1.

Comparison of mean age in primary and secondary mucinous carcinoma of ovary are p value is highly significant 0.0001 (<0.05).

Clinical history in these patients are all with multiparous with 2 children or more, age at marriage being 20-24 years. Neither history of abortions nor history of intake of oral contraceptive pills, hormones or treatment for infertility present. Breast feeding is given for more than 12 months. History of smoking is present in 23.08% of cases. There is no history of alcohol intake. There is no family history of malignancy.

In primary mucinous cystadenocarcinoma of ovary the mean tumor size is 20±5 cm, unilateral in all cases and the tumor is solid cystic in 87.5% of cases. Six cases are in stage IA and two cases in stage IC2

In secondary mucinous carcinoma of ovary the mean tumor size is 13±2 cm, solid cystic tumor in 60% of cases and all are bilateral tumors.

Comparison of mean tumor size in primary and secondary mucinous carcinoma of ovary: P value is significant 0.01 (<0.05).

Primary mucinous carcinoma of ovary with stage IA shows CK7+ve /CK20+ve expression in 83.33% of cases and in 1 case the expression is CK7-ve /CK20-ve. The stage IC2 shows, CK7+ve /CK20+ve expression in 50% of cases and in 1 case the expression is CK7-ve /CK20-ve.As the stage of the tumor increased there is variable expression of CK7 and CK20 (Table 2).

Metastatic gastric carcinoma in one case shows CK7 focal +ve /CK20 -ve expression and in one case CK 7 diffuse positive /CK 20 focal positive expression.

One case of metastatic colorectal carcinoma shows CK7-ve /CK20+ve expression in which we also received resected specimen of colon with colorectal carcinoma. The age of the patient is 39 years (Figure 1 (A-D)).

Two other cases of metastatic colorectal carcinoma show CK 7 -ve /CK 20 focal +ve expression (Table 3).

Table 2: CK7 and CK20 expression in primary mucinous carcinoma of ovary (n=8).

Stage of tumor	Number of cases	Mean tumor size	Mean age years	CK7 Positive	CK7 Negative	CK20 Positive	CK20 Negative
Stage IA	6	19±4 cm	45±5	5 (focal)	1	5 (focal)	1
Stage IC2	2	23±2	54±8	1	1	1	1

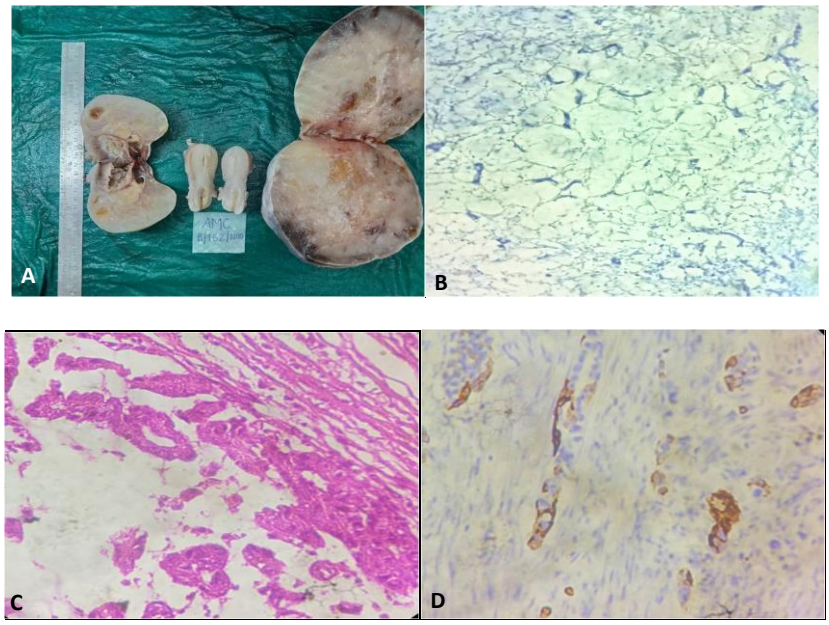

Figure 1: (A) Bilateral Krukenberg tumor of ovary from colorectal carcinoma: Gross specimen with both ovarian tumors and hysterectomy specimen. (B) Bilateral Krukenberg tumor of ovary from colorectal carcinoma HPE (H&E,400X). (C) Bilateral Krukenberg tumor of ovary from colorectal carcinoma CK 20 positive. (D) Bilateral Krukenberg tumor of ovary with colorectal carcinoma CK 7 negative.

Table 3: CK7 and CK20 expression in secondary mucinous carcinoma of ovary (Krukenberg tumor) (n=5).

Krukenberg tumor	Number of cases	Mean tumor size (cm)	Mean age (years)	CK7 Positive	CK7 Negative	CK20 Positive	CK20 Negative
Metastatic gastric carcinoma	1	11	38	1 (focal)	-	-	1
Metastatic gastric carcinoma	1	11	50	1 (diffuse)	-	1 (focal)	-
Metastatic colorectal carcinoma	3	15±2	40±3	-	3	3 (focal)	-

Mucinous tumors of gastrointestinal tract

Mucocele of appendix is seen in 5.88% of cases. Mucinous carcinoma of stomach constituted 8.82% of cases. Signet ring cell carcinoma of stomach is seen in 41.18% of cases and colorectal mucinous carcinoma constituted 44.12% of cases. Male:female ratio in mucinous carcinoma of gastrointestinal tract was 1.67:1

The clinical history in cases of mucinous tumors of gastrointestinal tract are consumption of dry fish and eating pickles is present in all the cases. History of smoking is present in 81.25% of cases. Variable amounts of alcohol are consumed by all of them. The blood group of the subjects are O+ve in 78.13% of cases and B+ve in 21.87% of cases. Type 2 diabetes is seen in 34.38% of cases. Night shift working is present in 84.38% of cases. History of gastritis is present in 90.63% of cases. There is no family history of malignancy.

In mucinous carcinoma of stomach the commonest location of tumor is in lesser curvature of stomach. Mean tumor size is 5±1cm and presented as ulcerative growth. All the cases presented with stage IV disease.

In signet ring cell carcinoma the commonest location of tumor is in the body and pylorus. Mean tumor size is 6±2 cm and ulcerative lesions are seen in 11 cases (78.57%). Six cases presented in Stage 1B and eight cases in Stage II.

In colorectal mucinous carcinoma the commonest location of tumor is in the ascending colon and rectum. Mean tumor size is 5±2 cm and ulceroproliferative lesions are seen in 11 cases (73.33%). Seven cases presented in Stage I and eight cases in Stage IIA.

Mucinous carcinoma of stomach had CK7+ve /CK20+ve expression in all the three cases with focal positivity. In cases of signet ring cell carcinoma of stomach in Stage IB disease the expression of CK7 is focally positive in 37.5% of cases and diffusely positive 62.5% of cases. In Stage II disease the expression of CK7 is focally positive in 50% of cases and diffusely positive in 50% of cases. In both the stages all the cases are CK 20 focally positive (Table 5).

In colorectal mucinous carcinoma the expression of CK7-ve/CK20+ve is seen in 86.67% of cases and CK7-ve/CK20-ve in 13.33% of cases (Table 6).

Table 4: Distribution of mucinous tumors of gastrointestinal tract.

Lesions	Number of lesions	Percentage
Mucocele of appendix	2	5.88
Mucinous carcinoma of stomach	3	8.82
Signet ring cell carcinoma of stomach	14	41.18
Colorectal mucinous carcinoma	15	44.12
Total	34	100

Table 5: CK7 and CK20 expression in mucinous carcinoma of stomach (n=15).

Stage of tumor	Number of cases	CK7+ve		CK20+ve	
		Focal (%)	Diffuse (%)	Focal (%)	Diffuse (%)
Signet ring cell carcinoma					
Stage IB	8	3 (37.5)	5 (62.5)	8 (100)	-
Stage II	6	3 (50)	3 (50)	6 (100)	-
Mucinous carcinoma					
Stage IV	3	3 (100)	-	3 (100)	-

Table 6: CK7 and CK20 expression in colorectal mucinous carcinoma (n=5).

Stage of tumor	Number of cases	CK7-ve	CK20+ve		CK 20-ve
			Focal	Diffuse	
Stage I	7	7 (100%)	4 (57.14%)	3 (42.86%)	-
Stage II A	8	8 (100%)	4 (50%)	2 (25%)	2 (25%)

DISCUSSION

Ovarian malignant tumors have varied clinical behaviour. Mucinous invasive adenocarcinoma has very low response to chemotherapy, hence wide cytoreductive surgery provides effective therapy and improves prognosis in advanced stage of disease. IHC is often useful to differentiate between primary ovarian adenocarcinoma and metastatic adenocarcinomas especially in the absence of a known primary elsewhere. Studies in English literature document incidence of mucinous cystadenocarcinoma of the ovary accounting for 5-10% of all ovarian mucinous tumors (Table 7).

Table 7: Prevalence of mucinous carcinoma of ovary compared with other studies.

Studies in literature	Prevalence of Primary Mucinous carcinoma of ovary (%)
Jindal et al[4]	7.1
Schiavone et al[5]	11.9
Shimada et al[6]	33.9
Kriplani et al[7]	10.81
Puri et al[8]	5.9
Saina et al[9]	10.42
Mondal et al[10]	7.61
Present study	12.5

Prevalence of secondary mucinous tumors of ovary in the study by Muneaki Shimada et al is 6.87% and 10.81% in the study by Divya Kriplani et al.[6,7] In the present study the prevalence of secondary mucinous tumor is 7.81%.

In the study by Divya Kriplani et al the patterns of CK7 and CK20 in mucinous carcinoma of ovary are positivity for CK7 was diffuse, whereas that for CK20 was focal.[7]

Primary mucinous adenocarcinoma of ovary out of 5 cases show: 1) CK7+ve/CK20-ve:1/5(20%), 2) CK7+ve/ CK20+ve:3/5(60%), 3) CK7-ve/CK20+ve:1/5(20%).

Antibody CK7 is the most helpful marker in distinguishing between primary ovarian carcinomas and colorectal adenocarcinoma metastatic to the ovary. Metastatic tumors, metastatic colorectal carcinomas are mostly negative for CK7 but in 20-30% they are CK 7 positive. CK20 positivity in mucinous ovarian neoplasms ranges from 40% to 83% and in colorectal adenocarcinomas is 80-100%.

Russell Vang et al analysed 179 mucinous tumors in the ovary, the observations of CK7 and CK20 IHC expression of malignant mucinous tumors was: 1) CK7+ve/CK20+ve: expression in Primary ovarian tumors was (74%), metastatic upper gastrointestinal tract tumors (78%) and colorectal (11%).[11] 2) CK7-ve/CK20+ve: expression in metastatic lower intestinal tract tumors (79%) and was uncommon in upper gastrointestinal tract tumors (9%), rarely seen in primary ovarian tumors (4%) and 3) CK7+ve/CK20-ve: expression in primary ovarian was (23%), metastatic upper gastrointestinal tract (13%), but not in lower intestinal tract tumors.

For CK20 positive tumors, staining pattern was variable, often focal in primary ovarian tumors and metastatic upper intestinal tract tumors; whereas the pattern was diffuse in metastatic lower intestinal tract tumors.

Bassiouny et al analysed, thirty-six patients with primary ovarian mucinous carcinoma. CK7 was diffuse positive in 86.1% cases; CK20 was diffuse positive in 47.2% cases and focal positive in 11.1% cases.[12]

In the present study primary mucinous carcinoma of ovary with stage IA shows CK7+ve /CK20+ve expression in 83.33% of cases and in 1 case the expression is CK7-ve /CK20-ve;In stage IC2 shows, CK7+ve /CK20+ve expression in 50% of cases and in 1 case the expression is CK7-ve /CK20-ve.As the stage of the tumor increased there is variable expression of CK7 and CK20.

Metastatic gastric carcinoma to ovary showed CK7 focal +ve /CK20 -ve expression in 50% of cases and CK7 diffuse +ve /CK20 focal +ve expression in 50% of cases. Metastatic colorectal carcinoma showed CK7-ve /CK20+ve expression in all the cases.

Zhang et al reviewed 1,278 cases of gastric carcinoma who were resected surgically from 1993 to 2003.[13] The prevalence of mucinous gastric carcinoma was 3.8%. Yuan et al analysed 996 patients with primary gastric carcinoma from June 1994 to December 2006 of which mucinous gastric carcinoma constituted 6.8% of cases.

Zhaode Bu et al studied 181 patients of mucinous gastric carcinoma with male:female ratio of 2.1:1 with mean age of 58 years of which mucinous gastric carcinoma constituted 40.88% cases and 59.11% of cases with signet ring cell carcinoma.[14] Mucinous gastric carcinoma when compared with signet ring cell carcinoma was more common in older patients, stage III and IV, upper third

stomach (36.5% vs. 12.1%), large tumor size (66.2% vs. 45.8%), positive lymph node metastasis (83.8% vs. 60.7%), and positive lymphatic vascular invasion (51.4% vs. 29.0%).

Jonathan et al analysed 579 of colorectal tumors, 53.5% were males and 46.5% females with median age of 58 years. Right colon cancers were 29.4%, left colon 22.1% and rectum 48.5%.[15] Mucinous carcinoma constituted 14.8% of cases. Mucinous cancers were predominantly in the right colon.

Ulrich Nitsche et al analysed 3881 cases of colorectal cancer between 1982 and 2012, 11% of cases were mucinous adenocarcinoma and median age was 65 years.[16] There were more men (51.94%) than women (37.69%). Intestinal tumor obstruction was seen in (4.3%) of tumors. The tumor was located within the right hemicolon in (30%), within the left hemicolon in (28%), and in the rectum in (39%) of cases. Studies in literature have documented occurrence of colororectal carcinoma with predilection to right hemicolon.

Tadashi Terada in their study documented the expression of cytokeratin (CK) in primary signet-ring cell carcinoma (SRCC) of the stomach.[17] The observations of CK7 and CK20 in 30 cases of primary signet ring cell carcinoma of stomach were: CK7 +ve (89%) and CK20 +ve (10%).

In the study by Takami et al four patterns of CK7 and CK 20 expression were observed in mucinous gastric carcinoma, they are: 17% of CK7+ve/CK20+ve, 57% of CK7+ve/CK20-ve, 9% of CK7-ve/CK20+ve and 17% of CK7-ve/CK20-ve.[18]

Park et al studied the expressions of cytokeratin (CK)7 and 20 in primary and metastatic carcinomas.[19] Little is known about the factors that determine variations in their expression patterns in primary gastric and colorectal carcinomas. It was found that 71% of the gastric carcinomas stained positively for CK7, whereas only 9% of the colorectal carcinomas proved to be CK7 positive. CK20 were positive in 41% of the gastric carcinomas and 73% of the colorectal carcinomas. The proportion of CK7+ve/CK20-ve was highest in the gastric carcinomas at 46% and was independent of the histologic classification of Lauren. CK7-ve/CK20+ve expression in colorectal carcinoma was seen in 68% of cases and varied with the histologic grade and location of the tumor.

In the present study mucocele of appendix is seen in 5.88% of cases, mucinous carcinoma of stomach seen in 8.82% of cases, signet ring cell carcinoma of stomach is seen in 41.18% of cases and colorectal mucinous carcinoma in 44.12% of cases.

History of smoking is present in 81.25% of cases. Variable amounts of alcohol is consumed by all of them. The blood group of the subjects are O+ve in 78.13% of cases and B+ve in 21.87% of cases. Type 2 Diabetes is seen in 34.38% of cases. History of gastritis in 90.63% of cases. There is no family history of malignancy.

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In colorectal mucinous carcinoma the expression of CK7-ve /CK20+ve in 86.67% of cases. CK7-ve /CK20-ve in 13.33% of cases.The main limitation of the study that it is costly.

CONCLUSION

CK7 and CK20 show variable expression basing on the stage of the tumor as documented in literature. In the present study primary mucinous carcinoma of the ovary showed CK7 positive expression in stage I tumors (83.33%) of cases. As the grade of tumor increased there was negative expression. CK7 and CK20 expression plays a significant role in distinguishing primary ovarian mucinous carcinoma and metastatic lower intestinal tract mucinous tumors when compared to metastasis from upper gastrointestinal mucinous tumors. In signet ring cell carcinoma of stomach CK7 is diffusely positive in 62.5% of cases with focal positivity in CK20 at stage I disease. As the stage of disease increased the expression of CK7 decreased to focal positivity in 50% of cases. In colorectal mucinous carcinoma CK20 positive expression was seen in 86.67% of cases and the expression became negative as the stage of the disease increased. Hence the interpretation of CK7 and CK20 should be done in the background of clinico-histopathological features.

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