A Study of β-Catenin and PTEN Expression in Ovarian Surface Epithelial Neoplasms and their Correlation with Grade and Stage in Malignant Cases

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ABSTRACT

Introduction: Ovarian carcinoma is most common ovarian malignancy which accounts for vast majority (90%) of ovarian tumors. It is invariably accompanied by changes in signal transduction pathways. The aim of the study was to evaluate the expression of β– catenin and PTEN in diagnosed cases of ovarian surface epithelial neoplasm and correlate them to histological grade and stage of ovarian carcinoma. Study design: This was a cross-sectional observational study.

Material and methods: The study was conducted over a period of one year (February 2017 to July 2018). β– catenin and PTEN expression was evaluated in 50 histologically diagnosed cases of ovarian epithelial neoplasm by immunohistochemistry (IHC) using a scoring system. Statistical analysis Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2. A *p*-value <0.05 was considered statistically significant.

Results: Membranous, Cytoplasmic and Nuclear β-catenin expression was significantly higher for high grade tumors than that of low grade tumors. No significant association between β-catenin expression and stage was found. A significant association of PTEN expression with tumor grade (p=0.0367) and histological subtype (p=0.03) has been found. Significant association of loss of PTEN expression with stage of the tumor was also found (p=0.023). No significant correlation between nuclear score of β-catenin and PTEN score was found.

Conclusion: Considering the observations of the present study, it can be concluded that β-catenin and PTEN may play an active role in the pathogenesis of ovarian carcinoma subtypes and they have a positive correlation with grade and stage of tumours. So, these biomarkers may be considered as prognostic parameters and critical evaluator of targeted therapy.

Keywords: Ovarian Carcinoma, β-catenin, PTEN

INTRODUCTION

Among all gynaecological malignancies, ovarian carcinoma still remains one of the leading causes of death.[1] Early detection is difficult because of vague symptoms. As a result, more than half of the patients are diagnosed in advanced stage of disease with extensive peritoneal metastasis. This causes a significant obstacle to efficacious treatment, often leading to chemo-resistance.[2] As combined surgery and chemotherapy is the only available treatment, there is an urgent need to develop a more effective therapy. Here comes the importance of signal transduction pathways.

Ovarian carcinoma is one of those cancers which are invariably accompanied by changes in signal transduction pathways. WNT(Wingless)/β-catenin signalling pathway and the tumour suppressor PTEN (phosphatase and tensin homolog on chromosome 10), are two such important entities. WNT/β-catenin signalling pathway plays an active role in development of cancer stem cells and carcinogenesis of all ovarian carcinoma subtypes.[3] The tumour suppressor PTEN plays an essential role in regulating signalling pathways involved in cell growth and apoptosis and is inactivated in ovarian carcinoma.[4] So, PTEN and WNT/ β-catenin signalling pathway may represent as potential targets in the development of new drugs for ovarian carcinoma as a single therapeutic agent and in combination with chemotherapy or other targeted agents.[5]

The WNT /β-catenin pathway is initiated and triggered by WNT ligand, while β-catenin remains in the centre of the pathway. β-catenin activates expression of many important proteins which are responsible for cell cycle, proliferation and survival e.g. cyclinD1, cMyc.[6] Deregulation of WNT/β-catenin pathway causes transportation of unphosphorylated β-catenin to the nucleus, where it binds T-cell factor/ lymphoid enhancer factor (TCF/LEF)[7] and activates gene expression of proteins responsible for cell cycle, proliferation and survival.[8] The most possible mechanisms of WNT/β-catenin pathway alteration is mutations of β-catenin gene (CTNNB1), which has been noted in endometroid subtype of ovarian carcinoma.[9]

PTEN is a tumour suppressor gene.[10] A loss of PTEN function leads to increased phosphatidylinositol 3-kinase and protein kinase B (P13K/AKT) activity that leads to subsequent increased cell proliferation, altered cell migration as well as inactivation of cell death proteins such as BAD14

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and caspase-9.[11] PTEN mutations or deletions have been identified in a wide variety of primary malignant tumours. Ovarian carcinoma is one of them.

Thus, the current study intended to assess β-catenin and PTEN expression in different subtypes of ovarian surface epithelial neoplasms and document the correlation of β-catenin and PTEN expression with histological grade and stage in malignant cases.

MATERIAL AND METHODS

Specimens and general information

A total of 50 specimens of ovarian epithelial neoplasms were studied which were collected in the department of General Surgery of a tertiary care institute in eastern India from February 2017 to July 2018. Relevant information like age of the patient, parity, CA-125 level and laterality of the tumours were noted. Diagnosed cases of ovarian epithelial neoplasms were included in the samples and non-epithelial ovarian tumours, inflammatory conditions of the ovary and neoadjuvant chemotherapy treated cases were excluded from the study.

Histopathological examination

Grossing and reporting of ovarian epithelial neoplasms were done according to CAP (College of American Pathologists) protocol which is based on AJCC/UICC TNM, 8th edition.[12] Specimens were fixed in 10% neutral buffered formalin. Representative areas were sampled and histopathological examination was done following proper tissue processing, paraffin embedding and staining with haematoxylin-eosin (H&E) respectively. Specific histologic subtype was assigned according to WHO 2014 classification of tumours of female reproductive organs.[13]

Immunohistochemistry (IHC)

Immunohistochemical staining for β-catenin and PTEN was done in the sections (2-3 micron), prepared from the same block following a standard streptavidin-biotin-peroxidase technique. Mouse monoclonal antibody for β-catenin and PTEN was used. Primary antibodies which were used for detection of β-catenin and PTEN are as follows- **β-catenin:** Mouse monoclonal Anti-Human antibody β-catenin (14), Cell Marque; **PTEN:** Monoclonal Mouse Anti-Human, 6H2.1 Mastac Diagnostica. Di-amino benzidine (DAB) was used as chromogen. Positive controls which were used are as follows- (1) normal colonic tissue for β-catenin, (2) normal endometrial tissue for PTEN. Negative control was achieved by omitting primary antibody.

Evaluation of IHC staining

β-catenin scoring

Positive β-catenin staining was observed as brown, granular cytoplasmic, nuclear and membranous staining. For analysis of β-catenin staining, the most positive area of the tumour was selected avoiding foci of inflammation. Firstly, the localisation of β-catenin staining was ascertained (membranous/ cytoplasmic/nucleus). Then, the number of tumour cells staining positively for β-catenin in the cytoplasm, membrane and nucleus was counted in 1000 cells in a high-power field (400X magnification). The staining intensity was scored as follows:

- 0: no expression
- 1 +: weak expression
- 2 +: moderate expression
- 3+: strong expression.

Then, the staining intensity score was multiplied by the percentage of positive cells adopting a scoring protocol followed by Wong et al[14] with slight modification. The average score of the four fields was expressed as the final score.

PTEN scoring

Positive staining for PTEN was observed as light yellow to brown granular cytoplasmic staining in the tumour cells. The staining intensity was scored as follows:

- 0: no colour,
- 1: light yellow,
- 2: brownish yellow
- 3: brown.

The score for the percentage of the positive cells are as follows:

- <5%:0,
- 5-25%:1,
- 26-50%:2,
- 51-75%:3
- >75%:4

The final result was calculated as mean of the product of intensity score and the score of the tumour cells showing positivity in five high power fields according to Lili Wang et al.[15] The results were interpreted as follows: ≤ 2=negative, 3-4=weakly positive, 5-8=moderately positive and 9-12=strongly positive.

STATISTICAL ANALYSIS

Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2. EPI INFO is a trademark of the Centre for Disease Control and Prevention (CDC). Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (S.D.). Chi-square (χ^2) test was performed to find the associations. One Way Analysis of variance (ANOVA) followed by post hoc Tukey's Test was performed with the help of Critical Difference (CD) or Least Significant Difference (LSD) at 5% and 1% level of significance to compare the mean values; p value <0.05 was considered to be statistically significant.

RESULTS

Among total 50 cases, there were 11 benign, 4 borderline and 35 malignant cases respectively. 4 cases of serous cystadenoma, 5 cases of mucinous cystadenoma and 2 cases of serous cystadenofibroma were included in the benign cases, whereas there were 2 borderline serous tumours and 2 borderline mucinous tumours. Among the malignant cases there were 15 serous papillary cystadenocarcinomas, 12 mucinous cystadenocarcinomas, 6 endometrioid and 2 clear cell carcinomas respectively (*Figure-1*).

The average age of the patients at the time of diagnosis was

Subtypes	Membranous score	Cytoplasmic score	Nuclear score
Clear cell carcinoma			
Mean±sd	30.00±2.83	90.00±2.83	23.00±2.83
Median	30	90	23
Range	28 - 32	88 - 92	21 - 25
Endometrioid carcinoma			
Mean±sd	27.33±6.53	260.00±8.94	124.17±18.66
Median	26	262.5	120
Range	20 - 37	245 - 270	106 - 147
Mucinous cystadenocarcinoma			
Mean±sd	37.25±11.13	168.17±43.67	20±0.00
Median	35.5	171.5	20
Range	22 - 58	90 - 225	20 - 20
Serous papillary cystadenocarcinoma			
Mean±sd	35.80±12.07	198.07±45.58	42.60±13.89
Median	33	192	41.2
Range	22 - 68	136 - 270	8 - 43
p-value	0.284	<0.0001	<0.0001

Table-1: Comparison of β-catenin scores in different subtypes of ovarian carcinoma

Parameters	Membranous score	Cytoplasmic score	Nuclear score
Grade			
High grade (n=16)			
Mean±s.d.	56.08±17.14	174.68±53.12	108.90±46.64
Median	33.00	165	96
Range	12 - 82	88 - 270	52 - 190
Low grade(n=7)			
Mean±s.d.	36.42±23.11	138.57±27.34	56.00±5.65
Median	68.00	135	56
Range	27 - 82	105 - 180	52 - 60
p- value	0.012	0.0005	0.003
Stage			
Stage I(n=6)			
Mean±s.d.	32.33±5.03	253.33±7.63	58.00±2.00
Median	33	255	54
Range	27 - 37	245 - 260	46 - 110
Stage II(n=2)			
Mean±s.d.	34.00±8.48	125.50±53.03	10.50±14.84
Median	34	125.5	10.5
Range	28 - 40	88 -108	0 - 21
Stage III(n=20)			
Mean±s.d	30.60±7.69	188.75±52.01	66.45±50.60
Median	30.5	182.5	56
Range	20 - 45	90 - 270	0.00 - 147
Stage IV(n=7)			
Mean±s.d.	38.28±12.37	179.42±63.42	44.14±9.92
Median	35	155	43.4
Range	25 - 58	96 - 270	0 -82
p-value	0.056	0.040	0.332

Table-2: Correlation of β-catenin expression with grade and stage of ovarian carcinoma

45.96±13.97 years with a range of 17-72 years. Majority of cases were found between 40-59 years. 52.0% of the patients had parity≥3.Symptoms like pelvic and abdominal pain, elevated CA-125 level as well as cystic and solid cystic gross findings of the tumours were significantly associated with the malignant tumours (p<0.0001). Among the histopathological types, malignant tumours were significantly higher (p<0.002) whereas among the histopathological sub-types serous papillary cystadenocarcinoma was significantly higher followed by mucinous cystadenocarcinoma (p<0.0001).

EVALUATION OF B-CATENIN EXPRESSION

β-catenin expression in benign, borderline and malignant tumours

All cases of benign and borderline tumours showed only

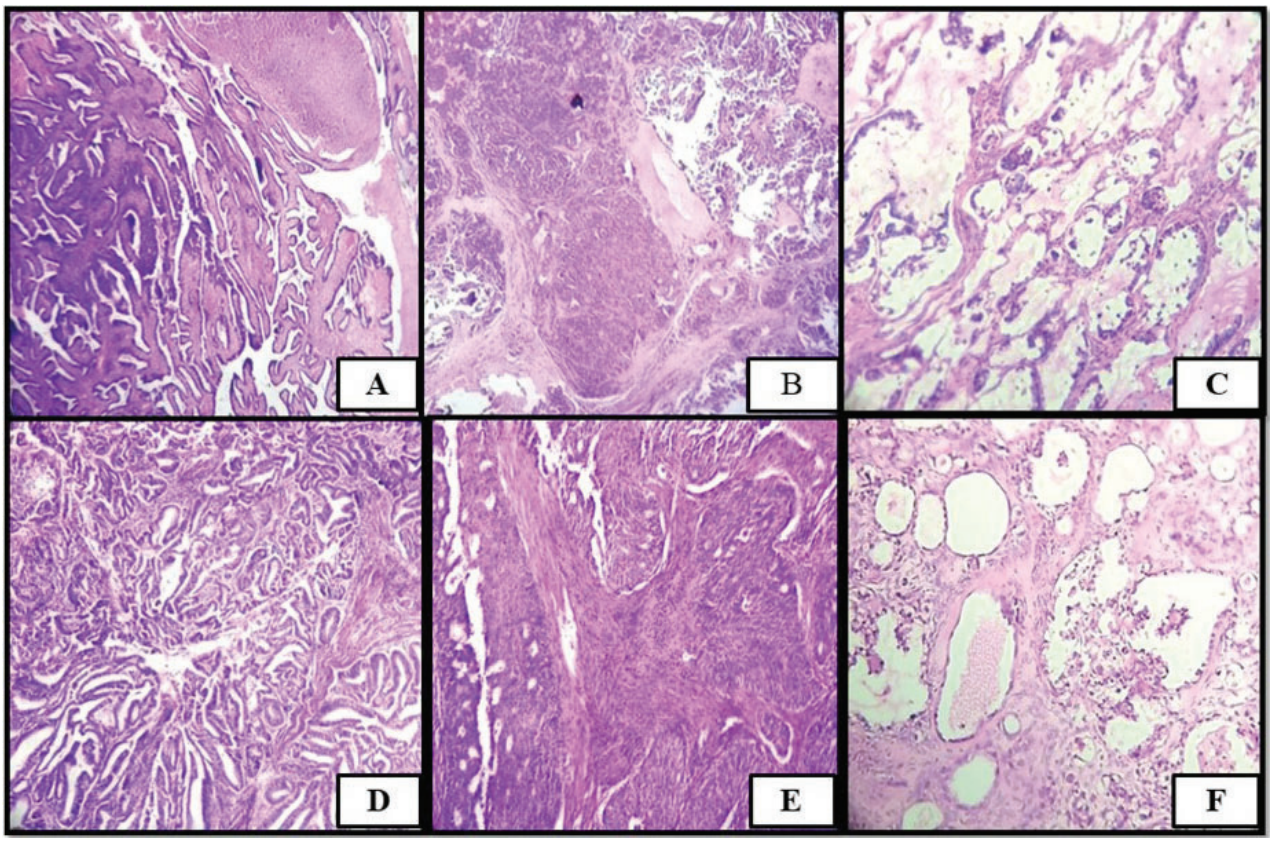

Figure-1: H&E stained sections of different ovarian carcinomas at 100X magnification: (A) Low grade serous papillary carcinoma, (B) High grade serous papillary carcinoma, (C) Mucinous carcinoma, (D) Low grade endometrioid carcinoma, (E) High grade endometrioid carcinoma, (F)Clear cell carcinoma

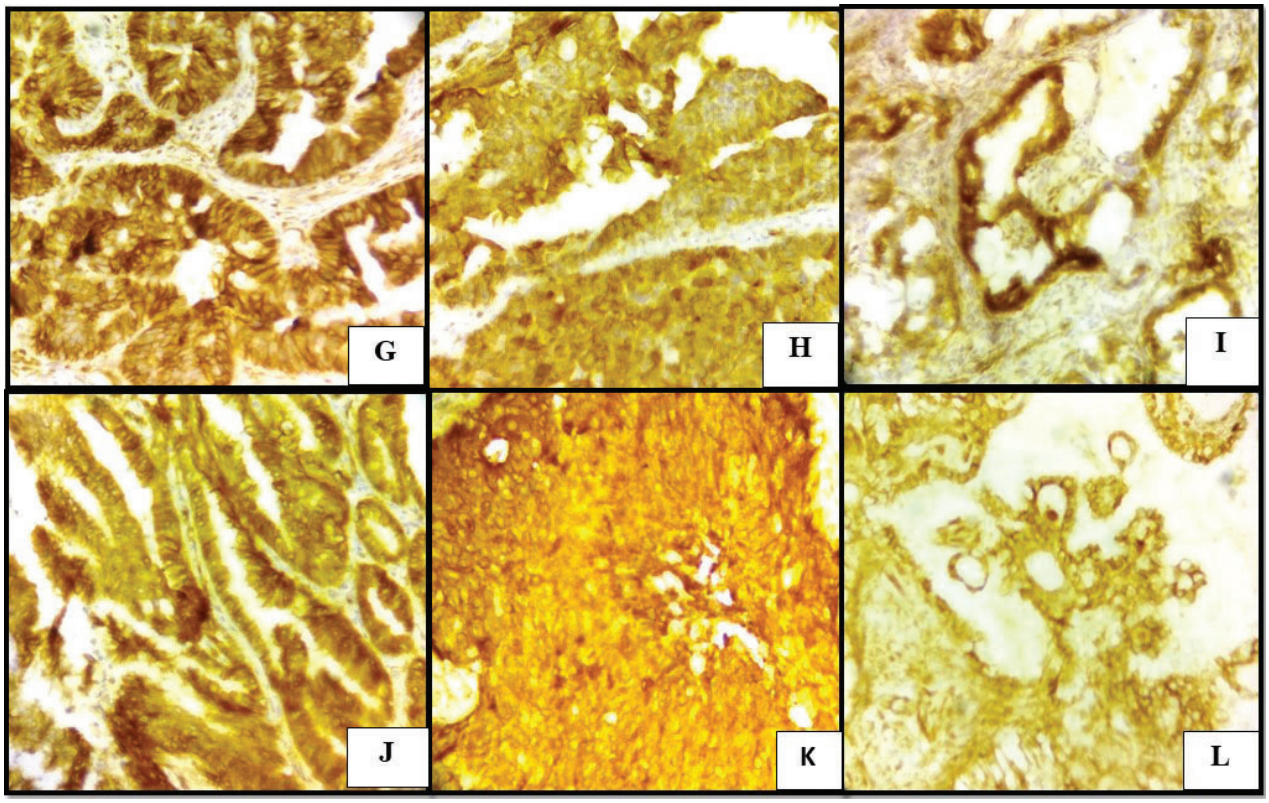

Figure-2: β-catenin expression in different subtypes of ovarian carcinoma at 400X magnification: (G) strong cytoplasmic and weak nuclear expression in low grade serous papillary carcinoma (H) moderate cytoplasmic and strong nuclear expression in high grade serous papillary carcinoma, (I) strong cytoplasmic positivity in mucinous carcinoma, (J) strong cytoplasmic and moderate nuclear expression in low grade endometrioid carcinoma, (K) strong cytoplasmic and strong nuclear positivity in high grade endometrioid carcinoma, (L) moderate cytoplasmic and strong nuclear expression in clear cell carcinoma

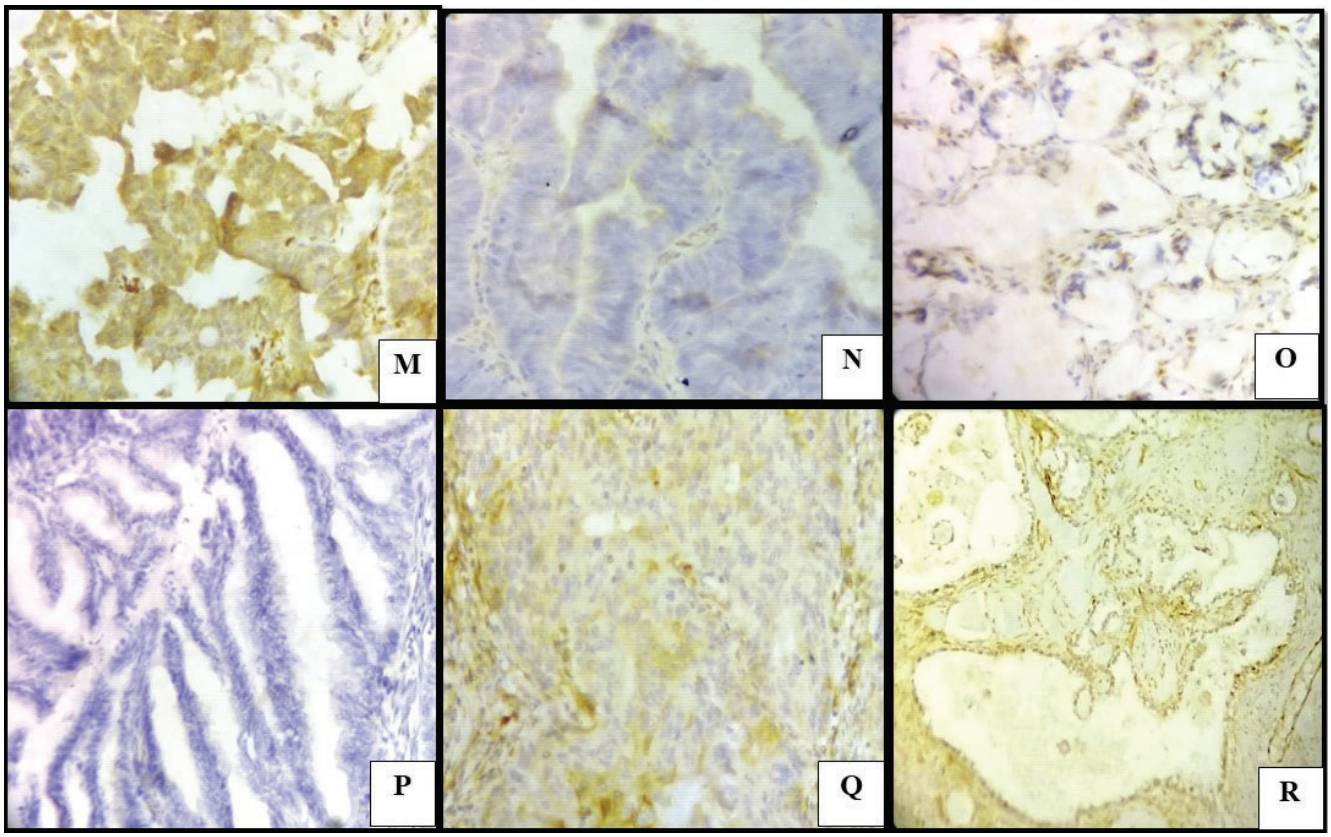

Figure-3: PTEN expression in different subtypes of ovarian carcinoma at 400X magnification:(M) Moderately positive PTEN expression in low grade serous papillary carcinoma, (N) Negative PTEN expression in high grade serous papillary carcinoma, (O) Negative PTEN expression in mucinous carcinoma, (P)Negative PTEN expression in low grade endometrioid carcinoma, (Q)Weak positivity of PTEN in high grade endometrioid carcinoma (R)Weak PTEN expression in clear cell carcinoma

Parameters	Negative	Weakly positive	Moderately positive	Total	p value
Grade					
High grade	14(87.5%)	2(12.5%)	0(0.0%)	16(100.0%)	0.036
Low grade	3(42.9%)	2(28.6%)	2(28.6%)	7(100.0%)	
Stage					
Stage I	3(50.0%)	2(33.3%)	1(16.7%)	6(100.0%)	0.023
Stage II	1(50.0%)	0(0.0%)	1(50.0%)	2(100.0%)	
Stage III	18(90.0%)	2(10.0%)	0(0.0%)	20(100.0%)	
Stage IV	7(100.0%)	0(0.0%)	0(0.0%)	7(100.0%)	

Table-3: Correlation of PTEN expression with grade and stage of ovarian carcinoma

	Pearson Correlation and p-value	Membranous Score	Cytoplasmic Score	Nuclear Score
PTEN Score	Pearson Correlation	0.888	-0.719	0.529
	p-value	<0.0001	<0.0001	0.094

Table-4: Correlation of membranous, cytoplasmic and nuclear β-catenin expression with PTEN expression

membranous and cytoplasmic β – catenin expression, whereas malignant cases showed membranous, cytoplasmic as well as nuclear expression.

β-catenin expression in different subtypes of malignant tumours

Among the malignant tumours, out of 15 serous papillary cystadenocarcinomas, 10 showed membranous and cytoplasmic expression and 5 showed membranous, cytoplasmic and nuclear expression. Out of 12 cases of mucinous cystadenocarcinoma, 11 showed membranous and cytoplasmic β-catenin expression and 1 showed membranous, cytoplasmic and nuclear β-catenin expression. All cases of endometrioid carcinomas and clear cell carcinomas showed membranous, cytoplasmic and nuclear β-catenin expression.

Comparison of β-catenin scores in different subtypes of malignant tumours

Membranous score was more or less same in different subtypes but cytoplasmic score was highest in endometrioid carcinoma (260.00±8.94) followed by serous papillary cystadenocarcinoma (198.07±45.58) and mucinous cystadenocarcinoma (168.17±43.67). Nuclear score was also highest in endometrioid carcinoma (124.17±18.66).

(*Table-1*)

Comparison of β-catenin scores according to the grade and stage of the tumours

All cases of high-grade carcinomas showed higher membranous (p=0.012), cytoplasmic (p=0.0005) and nuclear score (p=0.003) than that of low-grade carcinomas (*Figure-2*). Membranous score (p=0.056) and cytoplasmic score (p=0.040) of β-catenin showed significant association with the stage of the tumour, whereas nuclear score didn't show any significant association (p=0.332). (*Table-2*)

EVALUATION OF PTEN EXPRESSION

PTEN expression in benign, borderline and malignant tumours

Out of 11 benign tumours, 7 cases showed strong positive PTEN expression, 4 showed moderately positive PTEN expression. Out of 4 borderline tumours, 2 tumours showed moderate PTEN positivity, 1 showed weak positivity and only 1 showed strong positive PTEN expression. Out of 35 malignant tumours, 29 tumours didn't show PTEN expression while 4 showed weak positivity and only 2 showed moderate positivity.

PTEN expression in different subtypes of malignant tumours

Among the benign tumours, out of 4 serous cystadenomas, 2 showed strong positivity and rest 2 showed moderate PTEN expression; 3 out of 5 mucinous cystadenomas showed strong positivity for PTEN expression and the rest 2 showed moderate expression. Remaining 2 cases of serous cystadenofibromas showed strong positive PTEN expression. Out of 2 borderline serous papillary tumours, one showed strong positivity while the other showed weak expression. All 2 cases of mucinous borderline tumours showed moderate expression. Out of 15 serous papillary cystadenocarcinomas, 10 showed negative PTEN expression, 3 showed weak positivity and 2 showed moderate PTEN expression. Out of 6 endometrioid carcinomas, 5 showed negative PTEN expression and 1 showed weak positivity. Out of 2 clear cell carcinomas 1 showed negative PTEN expression and other 1 showed weak positivity. All mucinous cystadenocarcinomas typically had negative PTEN expression.

PTEN expression according to the grade and stage of the tumour

Out of 11 high grade serous papillary cystadenocarcinomas, 10 showed negative PTEN expression, 1 showed weak positivity. Out of 3 high grade endometrioid carcinomas, 2 showed negative and 1 showed weakly positive PTEN expression. Whereas all clear cell carcinomas showed negative PTEN expression. Out of 4 low grade serous papillary cystadenocarcinomas, 2 showed weak positivity and rest 2 showed moderate PTEN expression. All 3 low-grade endometrioid carcinoma showed typically negative PTEN expression. (*Figure-3*)

Out of 6 stage I tumours, 3 showed negative PTEN expression, 2 showed weak positivity and 1 showed moderate PTEN expression. Out of 2 stage II tumours, 1 showed moderate positivity and the other one showed negative PTEN expression. Out of 20 stage III tumours 18 showed negative expression and the rest 2 showed weak positivity. All 7 stage IV tumours showed negative PTEN expression. (*Table-3*)

Correlation between β-catenin and PTEN expression

As per Pearson correlation co-efficient, positive correlation was found between PTEN expression and membranous score of β-catenin (p<0.0001) but there was no significant association with the nuclear β-catenin score (p=0.094). However, significant negative correlation was found between cytoplasmic score of β-catenin and PTEN score (p<0.0001). (*Table-4*)

DISCUSSION

The most important prognostic factors for epithelial ovarian cancer are age, histological type, tumour grade and International Federation of Gynaecology and Obstetrics (FIGO) stage.[16,17] However these parameters are still insufficient to identify high–risk patients. Therefore, specific prognostic markers for evaluating the progression of ovarian carcinoma are still warranted. So, recently more attention has been focused on the molecular markers of the P13K/AKT pathway and WNT /β-catenin pathway, which are being widely studied in ovarian carcinoma.[18,19] In this scenario, an institutional based cross-sectional observational study was done among the different types of ovarian carcinoma cases with a purpose to assess the β–catenin and PTEN expression and study their correlation with histological grade and stage of ovarian carcinoma by immunohistochemistry.

Expression of β-catenin

In our study we found that all the patients with benign and borderline tumours had membranous and cytoplasmic β–catenin expression. For malignant cases, 60% of cases showed membranous and cytoplasmic expression which was significantly higher than that of combined membranous, cytoplasmic and nuclear expression (40.0%). This significant increase in membranous and cytoplasmic expression in borderline and malignant tumours than benign tumours is concordant with the study of Rask K et al.[20] This data shows that localization of β-catenin changes along with the tumour types.

We also noted that there was significant association between localization of β–catenin and different histological subtypes of the malignant tumours (p=0.0003). Among the malignant tumours, 66% serous papillary cystadenocarcinomas showed membranous and cytoplasmic expression and 33% showed combined membranous, cytoplasmic and nuclear expression. Most of the mucinous cystadenocarcinoma (91%) showed membranous and cytoplasmic β- catenin expression. All cases of endometrioid carcinomas and clear cell carcinomas showed combined membranous, cytoplasmic and nuclear β-catenin expression. Kildal W et al[21] found significant association between cytoplasmic and nuclear beta-catenin expression and histological subtypes which was similar to our study although no such significant association between membranous beta-catenin expression and different subtypes

was found. In our study, nuclear β-catenin staining was noted in all 6 cases of endometroid carcinoma (100%), whereas Kildal W et al[21] documented nuclear β-catenin staining in 53% of such tumours. However, Wang H et al[18] showed in their study that predominantly positive immunostaining was localized in both membrane and cytoplasm in case of serous papillary cystadenocarcinoma. Lee CM et al[22] found that 13 of 105 serous carcinomas (12.3%) demonstrated nuclear staining of β-catenin whereas we found combined membranous, cytoplasmic and nuclear beta-catenin staining in 33.3% of serous carcinomas. These differences among the studies may be attributed to the diversity in detection techniques and sample size.

Membranous, cytoplasmic and nuclear β-catenin expression was significantly higher for high grade malignant tumours than that of low-grade malignant tumours which was consistent with the study of Guo H et al[23] but Aslani FS et al[24] had found that in general, diminished expression of β-catenin was associated with higher tumour grade.

Furthermore, we found a significant association between cytoplasmic and membranous β-catenin expression and stage of the tumour although no significant association with nuclear β-catenin expression was noted. Similar findings were observed in the study of Guo H et al[23] where the positive expression of β-catenin in stage III-IV tumours was significantly higher than stage I-II tumours (P<0.05). However, Kildal W et al[21] and Aslani FS et al[24] observed no association between β-catenin expression patterns and FIGO staging.

Expression of pten

PTEN expression was reduced from benign to malignant ovarian surface epithelial neoplasms (p<0.000001) which was concordant with the study of Sui L et al.[25] In our study, we noted that PTEN expression gradually diminished from benign to borderline to malignant tumours (p=0.0003). These findings suggested that down-regulated PTEN expression might be closely associated with malignant transformation of ovarian surface epithelial neoplasms.

Among the low-grade carcinomas, all 3 cases of low grade endometrioid carcinoma showed lack of PTEN expression. Similar findings were found in the studies of Gomes CP et al[26] and Aslani FS et al.[24]

Sui L et al[25] also found that PTEN expression was significantly lower in the endometrioid histological subtype than other subtypes but in our study, all mucinous cystadenocarcinoma lacked PTEN expression. Whereas Obata et al[27], documented that lack of PTEN expression was frequently observed in endometrioid but not in serous ovarian carcinomas. Similar findings were observed in our study where low-grade serous carcinomas showed variable expression and most of the high-grade serous carcinomas lacked PTEN expression. Sui L et al[25] had also found that loss of PTEN expression was significantly associated with different histological subtypes of ovarian carcinomas (p=0.037). Similar results were also noted in our study (p=0.0001).

A significant association of PTEN expression with tumour grade (p=0.0367) has been found in our study which corroborated with findings of Sui L et al.[25]

In our study loss of PTEN expression was observed with increasing stage of tumours (p=0.023). Similar findings were observed in the study of Hao T et al[28] where he found significant loss of PTEN expression in higher stage of endometrioid, mucinous and clear cell carcinomas. However, the studies of Gomes CP[26] and Aslani FS et al[24] failed to show such association.

Correlation between β-catenin and PTEN

A significant positive association was found between membranous expression of β-catenin and PTEN. However, a significant negative association was found between cytoplasmic expression β-catenin and PTEN. However, we did not find any significant association between nuclear expression of β-catenin and PTEN. Aslani FS et al[24] also failed to show any significant association between β-catenin expression and PTEN.

CONCLUSION

Considering the observations of our study, we can conclude that β-catenin and PTEN may play a crucial role in the pathogenesis of ovarian carcinoma. Recent studies support the need for further evaluation of WNT/β-catenin and PTEN signalling as a potential therapeutic target. However, their role has not been exclusively evaluated in ovarian carcinoma. One of the known mechanisms of drug resistance is cell adhesion mediated drug resistance. So β-catenin, a protein involved in cell adhesion, may be evaluated as a potential predictor of response to chemotherapy in ovarian carcinoma. As activation of β-catenin and PTEN pathway is found to correlate with poor prognosis and drug resistance, they might be considered as a promising target for therapy with agents like Curcumin, Rapamycin and its related mTOR (mammalian target of rapamycin) inhibitors. As our study was restricted to a small number of samples and lacked long term follow up of the cases, further studies are needed to validate our results and merit the role of β-catenin and PTEN as potential therapeutic agents.

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