Section: Pathology

Original Research Article

CLINICOPATHOLOGICAL STUDY OF OVARIAN NEOPLASMS WITH SPECIAL REFERENCE TO P53 OVEREXPRESSION IN EPITHELIAL OVARIAN NEOPLASMS– A HOSPITAL BASED CROSS-SECTIONAL STUDY

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Abstract

Background: Ovarian cancer is one of the most common gynaecologic malignancies of present era. Age-adjusted incidence rate of ovarian cancer varies between 5.4 and 8.0 per 1 lakh population in different parts of our country. **Objectives:** To study the clinicopathological features of Ovarian Neoplasms and p53 positivity in Epithelial Ovarian Neoplasms. **Materials and Methods:** It was a hospital based cross sectional study conducted for a period of 1 year at a tertiary care centre of North east India. One hundred cases of ovarian tumours were included in this study. The clinical history and relevant examinations were done and the H&E-stained biopsy slides were studied under light microscope. P53 staining was done on the epithelial tumours and their positivity was noted. Mean age and p value were calculated. **Result:** Out of the 100 cases, 54 cases (54%) were benign, 11 cases borderline (11%) and 35 cases (35%) were found to be malignant. Among the benign tumours, mature teratoma was the commonest (26 cases, 26%) and among the malignant tumours, high grade serous carcinoma had the maximum incidence (9 cases, 9%). P53 immunostaining was performed and was found to be positive in most of the malignant epithelial ovarian tumours. **Conclusion:** As P53 is overexpressed in high grade serous tumours, it is found to have a prognostic role. P53 mutation is present in most of the human cancers and a targeted therapy will usher a new era in cancer treatment.

INTRODUCTION

Ovarian cancer is the fifth most common malignant cancer and is the most lethal gynaecologic malignancy with a five-year survival rate of only 35% after diagnosis.[1] Among women, ovary is the third most common site of cancer after cervix and breast. Age-adjusted incidence rate of ovarian cancer varies between 5.4 and 8.0 per 1 lakh populations in different parts of our country.[2]

Ovarian tumours mostly occur in adult females. Carcinomas are more common in perimenopausal and postmenopausal woman. The symptoms of ovarian cancer are vague and as a result almost 70% of the women have extensive extraovarian tumour spread at the time of diagnosis. Patients often present as pelvic pain or discomfort, abdominal fullness, gastrointestinal disturbances, urinary frequency, menstrual abnormalities and ascities (if the tumour size is more than 15 cm).[3] Aggressive debulking surgery and platinum based chemotherapy may provide remission but about 80% of the patients relapse and succumb to the disease.[4]

Germline mutations of p53, BRCA1 and 2 mutations, KRAS, BRAF or ERBB2 oncogenes are associated with ovarian neoplasms. High grade ovarian cancers are associated with high frequency of TP53 mutation.[3] P53 gene is found to be mutated in 30-80% of ovarian cancer and is strongly associated with high grade serous carcinomas.[5]

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There was dearth of p53 study in this part of Assam. Considering the importance of this tumour suppressor gene in human carcinogenesis, especially in epithelial ovarian cancer, this study has been undertaken in a tertiary care centre of North-East India.

The Aims and Objectives of this study were to study the clinicopathological features of Ovarian Neoplasms and to study p53 positivity in Epithelial Ovarian Neoplasms.

MATERIALS AND METHODS

The study was done in the Department of Pathology of a tertiary care centre of North East India. It was a hospital based cross sectional study for a period of one year. Ethical clearance was taken before starting the study. Total 100 cases of ovarian neoplasms were diagnosed during the study period.

Inclusion Criteria

All specimens of ovarian tumours received in the histopathology section of the department of Pathology were included in the study.

Exclusion Criteria

Incomplete specimen, poorly preserved specimen and non-compliant patients were excluded. Tumour like lesions of the ovary like oophoritis, ovarian tuberculosis, pregnancy luteoma, polycystic ovarian syndrome etc was excluded.

The specimens were collected in 10% buffered formalin and in case of the larger specimens, bread loafing was done and then fixed in 10% buffered formalin. Thorough grossing of the specimen was done, and sections were taken per 1cm of the tumour in greatest dimension followed by routine tissue processing and staining with Harris haematoxylin and eosin (Hi media). Slides were examined under Light Microscope. P53 immunostaining was done on all epithelial ovarian tumours where microwave oven was used for antigen retrieval. The method of generating heat in microwave technique enhances the rate of diffusion of fluids both inside as well as outside of the tissue sections more effectively than the conventional heating techniques.[6] Avidin-biotin technique was used in immunohistochemical staining with peroxidase as the enzyme label. We have taken sections from carcinoma colon as positive control and normal breast tissue as negative control.

P53 Reporting

The distribution of p53 immunoreactivity in surface epithelial tumours of ovary can be quantitatively assessed as –ve (less than 10% are negative cells) and +ve (equal or more than 10% positive cells) and the positive cases were graded as + (10-30%); ++ (30-50%); and +++ (more than 50%) positive cells. Positive cells were determined by counting 1000 cells in at least 10HPF (x40) for each case.[7] Positive immunostaining was observed as brown, granular nuclear staining.

Statistical Analysis

The data were plotted in Microsoft excel sheet. This data was shown in tables and results were expressed in terms of number and percentage. Mean age and p value were calculated and p value <0.05 was considered as significant.

RESULTS

In this study on 100 cases of ovarian tumours, it was found that the highest number of ovarian tumour cases present with abdominal pain [Table1] and they occur in the age group of 31-40 years with number of cases being 30 (30%) [Table 2]. 54 (54%) were found to be benign, 11 (11%) were borderline and 35 (35%) were malignant [Table 3]. The highest frequency of benign tumours was in the age group of 21-30 years with 20 cases (20%), while in case of the malignant tumours, the highest frequency of cases was seen in the age group of 41-50 years with 12 cases (12%). The highest frequency of borderline tumours was in age group of 31-40 years with 4 cases (4%) [Table 2]. Most of the ovarian tumours presented as purely cystic masses in about 32 cases (32%) of ovarian tumours. It was seen that most of the malignant tumours usually had entirely solid morphology whereas benign tumours predominantly were purely cystic.

In this study, 55 (55%) cases were epithelial tumours, 6 (6%) cases were sex cord-stromal tumours, 37 (37%) cases were germ cell tumours, and two (2%) cases were metastatic tumours [Table 4]. Among the benign tumours, mature teratoma was found to be the commonest accounting for 26 cases (26%) followed by serous cystadenoma accounting for 21(21%) cases. In case of malignant cases, high grade serous carcinoma was found to be the commonest accounting for 9 (9%) cases.

P53 was found to be positive in 8 cases of high-grade serous carcinomas whereas one case showed P53 negative staining. P53 staining was negative in all the benign and borderline tumours. P53 staining was also found to be positive in 3 cases of mucinous carcinoma and one case of poorly differentiated endometrioid carcinoma. P53 positivity was given based on the nuclear staining. P value was calculated, and it came out to be 0.0004 which is highly significant [Table 5].

P53 was seen to show strong nuclear staining in 6 cases (88.9%) of high-grade serous carcinomas (score 3+) and moderate nuclear staining (score 2+) in 2 cases (22.2%) and negative staining in 1 case (11.1%). One case each of malignant mucinous tumours showed negative, weak, moderate, and strong positive (25%) while endometrioid carcinoma showed strong nuclear staining (score 3+, 100%). P value was calculated and came out to be 0.62 which suggest that the test was not significant.

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Table 1: Clinical Presentation of the Patients with Ovarian Tumours

Clinical Features	No Of Cases	Percentage (%)
Abdominal Lump	22	22
Pain Abdomen	80	80
Gi Disturbances	9	9
Loss of Weight/Loss of Appetite	7	7
Ascites	3	3
Menstrual Abnormality/Bleeding Per Vagina	46	46
Infertility	2	2
Asymptomatic	1	1

Table 2: Distribution of Ovarian Tumours in Different Age Groups

Age Group (Years)	No. of Cases (N=100)	Percentage (%)
≤10	0	0
11-20	14	14
21-30	22	22
31-40	30	30
41-50	22	22
51-60	10	10
61-70	2	2
>70	0	0

Table 3: Frequency of Ovarian Neoplasm

Type of Neoplasm	No of Cases (n=100)	Percentage (%)
Benign	54	54
Borderline	11	11
Malignant	35	35

Table 4: Major Histological Groups According to the Who Classification

Groups	No of Cases (N=100)	Percentage (%)
Epithelial Tumours	55	55
Sex Cord-Stromal Tumours	6	6
Germ Cell Tumours	37	37
Metastatic Tumours	2	2

Table 5: P53 Expression across Epithelial Tumours

Histological Subtypes		P53 Positive	P53 Negative	Total
Serous Epithelial Tumours	Benign	0	26	26
	Borderline	0	0	0
	Malignant	8	1	9
Mucinous Epithelial Tumours	Benign	0	5	5
	Borderline	0	8	8
	Malignant	3	1	4
Endometrioid Adenocarcinoma		1	0	1
Brenner Tumour		0	2	2
P Value = 0.0004 (<0.05)				

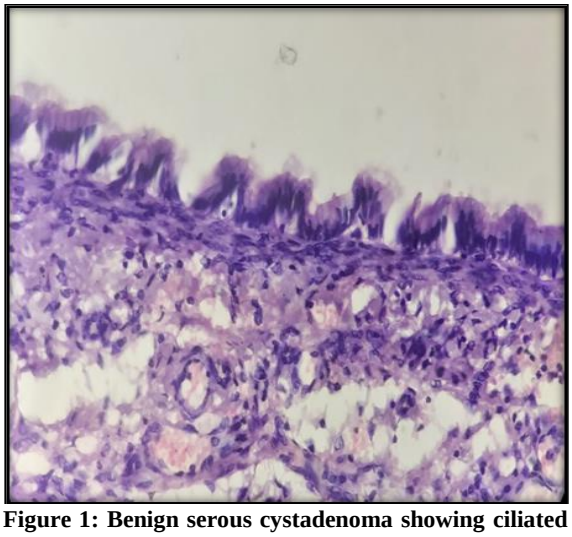

Figure 1: Benign serous cystadenoma showing ciliated columnar lining epithelium (40x)

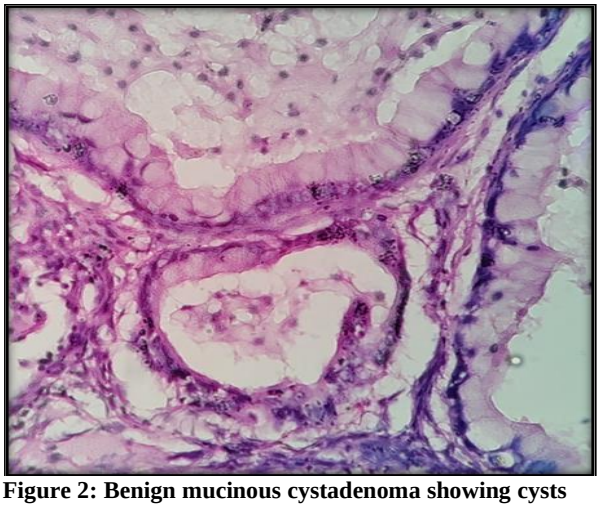

Figure 2: Benign mucinous cystadenoma showing cysts lined by single layer of endocervical type of epithelium containing mucin (40x)

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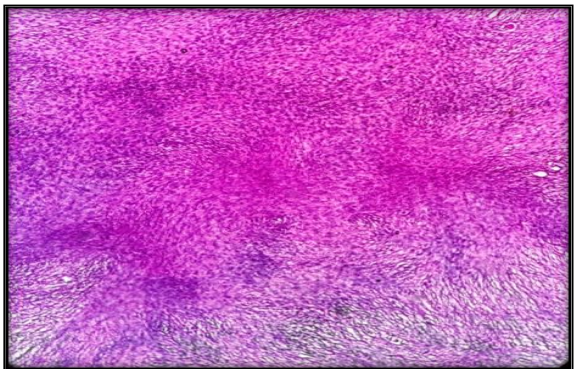

Figure 3: Cellular fibroma showing thin spindle cells growing in fascicles (10x)

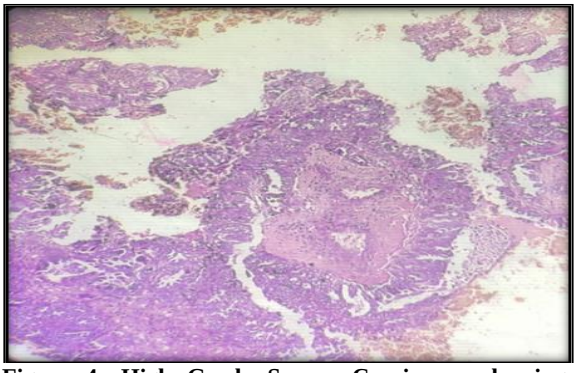

Figure 4: High Grade Serous Carcinoma showing papillary structures lined by cells with markedly pleomorphic nuclei(40x)

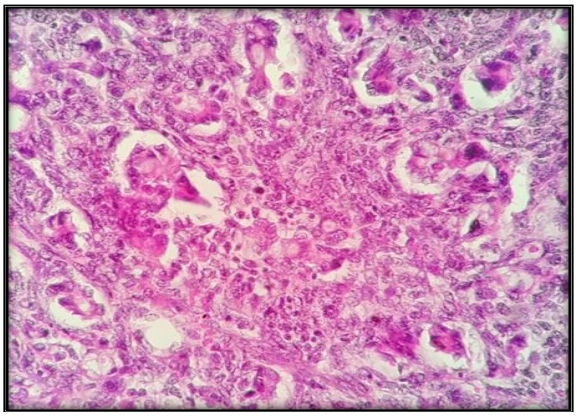

Figure 5: Yolk Sac Tumour showing Schiller duval bodies (arrow) (40x)

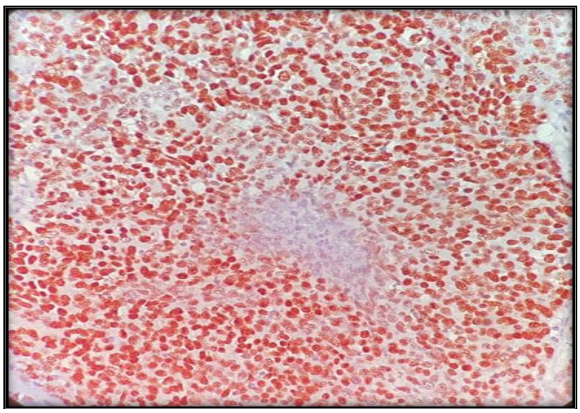

Figure 6: High grade serous carcinoma showing p53 nuclear positivity (3+) (40x)

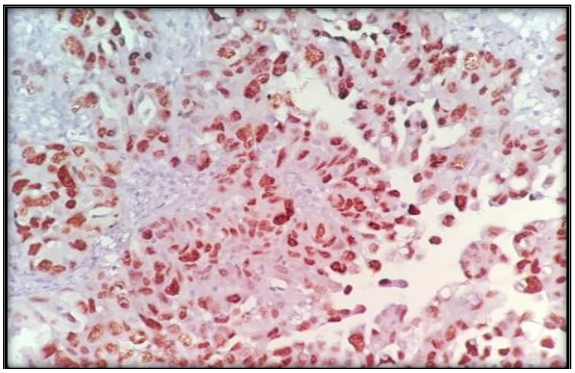

Figure 7: High grade papillary serous carcinoma showing p53 nuclear positivity (3+) (40x)

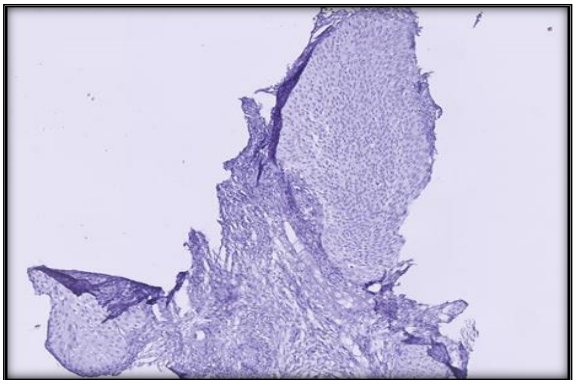

Figure 8: Benign Brenner tumour showing negative immunostaining for p53 (10x)

DISCUSSION

Of the 100 cases of ovarian tumours studied, it was seen that the ovarian tumour cases were highest in the age group of 31-40 years with 30 cases (30%) which is correlating with the study done by P. Vasanthamani et al.[8] In the present study, most of the ovarian tumour cases came with pain abdomen (80 cases, 80%) followed by menstrual abnormality or bleeding per vagina (46 cases, 46%). Studies done by P. Vasanthamani et al,[8] Chandekar Sushama A et al [9], Mankar DV et al,[10] and Phukan Angela et al,[11] also found abdominal pain to be the commonest presenting symptom. The benign tumours were found to be the commonest with 54 cases (54%) followed by malignant tumours with 35 cases (35%). Swarnalatha P et al,[12] Mankar DV et al,[10] and Phukan Angela et al,[11] in their studies have also found that the benign tumours were commonest followed by malignant tumours.

In the studies done by Phukan Angela et al,[11] and Chandekar Sushama A et al,[9] the ovarian tumours predominantly showed purely cystic consistency on gross examination which is correlating with the present study.

The frequency of surface Epithelial Ovarian Tumour (EOT), Germ Cell Tumour (GCT), Sex Cord Stromal Tumour (SCST) and metastatic tumour in our study varies from that of the studies done by Phukan Angela et al,[11] Swarnalatha P et al,[12] Chandekar Sushama A et al,[9] and P. Vasanthamani et al.[8]

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However, all the mentioned studies including the present study found epithelial ovarian tumours to be the most common histological group of ovarian tumours.

In the present study, p53 immunostaining was done on 55 cases of epithelial ovarian tumours out of which p53 expression was shown by 21.8% of the cases (12/55) which is correlating with that of the studies done by Razak Amanullah NA et al,[13] and Naik PS et al,[2] whereas the studies done by Singh A et al,[14] Hamdi Elaf et al,[15] and Choudhury M et al,[16] has shown a higher frequency of positive cases in comparison to the present study. P53 shows the highest expression in malignant epithelial ovarian tumours (out of 14 cases of malignant Epethalial ovarian tumour, 12 were p53 positive, 85.7%) whereas p53 expression was found to be negative in benign and borderline tumours. Similar results of p53 expression in malignant epithelial tumours were obtained by Naik PS et al.[2] Razak Amanullah NA et al,[13] has obtained the lowest frequency of p53 expression in malignant ovarian tumours (65.2%) whereas Qasim YA et al,[17] obtained the highest frequency of p53 overexpression (90%).

In this study, it was reported the highest frequency of p53 positivity in High Grade serous cystadenocarcinomas. Similar results were also reported by Milner BJ et al,[18] and Gottlieb WH, Berek JS.[19] Mohapatra I et al,[7] found that the highest p53 immunoreactivity was seen in malignant tumours (89.5%) compared with borderline (75%) and benign tumours (14.3%). This association of p53 over expression with biological tumour behaviour was found to be statistically significant ($p<0.05$). However, in their study, no significant relationship between histopathological subtype of epithelial tumours and p53 over expression could be found (p value>0.05). This is correlating with the present study which also showed statistically significant relationship of p53 (p value 0.0004 which is <0.05) in malignant epithelial tumours (85.7%) compared to borderline (0%) and benign (0%) tumours. However, no significant relation is seen in this study between the histological subtype of epithelial tumours and p53 over expression (p value 0.62 which is >0.05).

The study has limitation due to lesser no of cases and short study period. The study was also limited by inability to follow-up the patients.

CONCLUSION

In this study, it was found that 31-40 years of age group has the highest incidence with abdominal pain being the commonest symptom. Most of the tumours were found to be benign with mature cystic teratoma being the commonest followed by serous cystadenoma. Among the malignant tumours, high grade serous carcinomas were the commonest. Overall epithelial tumours have the highest incidence.

It has also observed that most of the high grade malignant epithelial ovarian tumours have shown p53 positivity. Thus it was found to have a prognostic role in being only expressed highly in high grade epithelial tumours and if could be channelized the efforts in targeting the p53 mutation, it will go a long way in increasing the survival of the patients.

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