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Research Article

Clinico-Immunohistochemical Analysis of Ovarian Tumors in a South Indian Population: A Single-Center Study

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ABSTRACT

Background and objectives: In India, ovarian tumors are the fifth leading cause of death in women. They account for 6% of all cancers in women. The present study aimed to provide support for a new theory of ovarian carcinogenesis by investigating the frequency of ovarian tumors and determining whether the Ki-67 labeling index and p53 overexpression help in differentiating borderline and malignant surface epithelial tumors.

Methods: The study included all ovarian tumor specimens sent for histopathological examination to the Department of Pathology of Narayana Medical College between June 2017 and October 2019.

Results: The frequency of benign epithelial and malignant tumors was 85.47% and 11.97%, respectively. Surface epithelial tumors (81.96%) and germ cell tumors (8.54%) were the most common ovarian tumors. In immunohistochemistry, p53 overexpression in surface epithelial neoplasms showed moderate positivity in all 2 cases of serous carcinomas, while 2 out of 6 mucinous carcinomas cases showed weak positivity. All six cases of mucinous carcinomas showed a Ki-67 labeling index of 26-50%. Serous carcinomas showed a high index of 51%, while mucinous carcinomas had a mean index of 37%. Overexpression of Ki-67 was significantly more common in malignant surface epithelial neoplasms (41.83%) when compared with borderline epithelial neoplasms (27%) ($p<0.001$)

Conclusion: In comparison to borderline serous and mucinous tumors, Ki-67 overexpression is significantly more common in malignant surface epithelial tumors. Moreover, p53 overexpression is significantly more common in serous carcinoma when compared with borderline serous tumors but not mucinous tumors. Overall, these markers could be beneficial for diagnosing difficult cases and predicting prognosis.

Keywords: Ki-67, p53, ovarian carcinoma, Immunohistochemistry

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Introduction

In India, ovarian tumors are the fifth leading cause of death in women. They account for 6% of all cancers in women (1). The annual incidence rate in India has been estimated to be 9 per 100,000 people. Ovarian tumors are most common in the upper socioeconomic group and Caucasians, while black women are at lower risk (2). Most of the tumors are seen between the age group of 25-45 years and in those with risk factors including positive family history, genetic mutations, and hormonal imbalance (3). Different tumors tend to involve different age groups. Cyclical changes in the ovary from the stage of puberty to menopause give rise to several cell types, each of which is capable of giving rise to tumors.

Tumorigenesis of the ovary is due to monthly endocrine and traumatic insults during regular ovulatory cycles. Theoretically, malignant genetic mutations are due to repeated ovulatory rupture and repair.

This explains the protective effects of oral contraceptive pills, late menarche, early menopause, multiparty, and breastfeeding in reducing the occurrence of ovulation (4). Ultrasonography and cancer antigen 125 studies were considered as screening methods for early diagnosis. However, fine needle aspiration cytology is the primary diagnosis and prognosis test with an accuracy of 90-95%, capable of differentiating benign from malignant tumors (5). Preventive measures for ovarian tumors are modification of lifestyle and eating habits, avoiding smoking or tobacco use, and prophylactic oophorectomy in high-risk cases (6).

Despite new diagnostic and therapeutic strategies, the increased mortality rate in ovarian tumors is due to an advanced stage of presentation in patients, reducing the 5-year survival rate to less than 20% (7). Persistent ovarian enlargement is an immediate indication for surgical assessment with diagnosis dependent on histopathological examination. Based on the World Health Organization (WHO) classification, ovarian surface epithelial tumors are classified into benign, borderline, and malignant tumors. Variations in histopathological patterns of both primary and secondary tumors of the ovary are relatively frequent (8).

The present study aimed to provide support for a new theory of ovarian carcinogenesis by investigating the frequency of ovarian tumors and determining whether the Ki-67 labeling index and p53 overexpression help in differentiating borderline and malignant surface epithelial tumors.

Materials And Methods

This study was conducted at the Department of Pathology, Narayana Medical College in Nellore, India. The study included all ovarian tumor specimens sent for histopathological examination to the Department of Pathology of Narayana Medical College between June 2017 and October 2019. The study protocol was approved by the Ethics Committee of Narayana Medical College (approval code: NMC/IEC/Path/2017).

Female patients aged above 20 years admitted to the gynecology ward of Narayana General Hospital with clinical features and radiological findings favoring ovarian tumors were included. Hysterectomy specimens with incidental ovarian tumors were also included. Autolyzed samples and non-neoplastic ovarian lesions such as simple ovarian cysts, tubo-ovarian abscess, and polycystic ovaries were excluded.

Serial sections of the tumors with 1 cm thickness were prepared and fixed in 10% formalin for 24-48 hours. Next, sections with a thickness of 4-5 microns were cut and stained with hematoxylin and eosin. Slides and blocks were retrieved for these cases. All histopathology slides were studied in detail. Histopathology reports for each tumor were also retrieved from the Department of Pathology. Immunohistochemistry was performed on all cases of benign, borderline, and malignant serous and mucinous tumors. All details of the specimens consisting of gross features, microscopic features, and final diagnosis were studied. Tumors were classified according to the WHO classification (2014). Immunohistochemistry markers p53 and Ki-67 were purchased from Agilent (US) Company and subjected to the poly-horseradish peroxidase (HRP) technique. First, the sections were deparaffinized and transferred to positively-charged slides, followed by microwave antigen retrieval. Endogenous peroxidase blocking was done by using H2O2 (3% in methanol) for 10 minutes. The sections were incubated with primary antibody for 1 hour, super-enhancer for 30 minutes, poly-HRP for 30 minutes, and 3,3'-diaminobenzidine for 8 minutes. In between the above steps, the sections were rinsed with a buffer. Lastly, counterstaining with hematoxylin was done for 30 seconds. The sections were dried with alcohol, cleared in xylene, and mounted with DPX. The development of brown color intense nuclear staining was considered as positivity, and scoring was interpreted by using a quick score method. Blinded scoring was done by a pathologist.

The frequency of various ovarian tumors, age of presentation, gross features, and histopathology patterns of individual tumor types were also

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determined. The frequency of benign versus malignant tumors was also studied. This was a prospective study and analysis of data was done using the chi-square test. P-values less than 0.05 were considered statistically significant. All statistical analysis was done by using SPSS software version 22.0 (IBM, Armonk, NY, USA).

Results

Of 117 cases studied in the study period, 100 (85.47%) were benign, while 14(11.97%) and 3(2.56%) were malignant and borderline tumors, respectively. In addition, 109 tumors were found in subjects aged 21-60 years. The majority of malignant tumors (12 cases) were seen in those aged >40 years. The frequency of malignancy increased significantly with age (p=0.001). Most subjects (81.19%) attained menarche after the age of 12 years. The remaining subjects (18.80%) attained menarche before the age of 12 years. The premenopausal age group was more common than the postmenopausal one, contributing to 77.78% of the tumors. Malignant tumors were more common in the postmenopausal age group.

Abdominal pain, followed by abdominal mass, were the most common presentations of malignant tumors. Ovarian tumors were rarely asymptomatic. Moreover, most tumors were unilateral (89.75%) and less than 20 cm in the largest dimension. The largest tumor was 30×25×15 cm in size, which was a unilateral benign papillary serous cystadenofibroma, affecting a 40-year-old female. Unilateral granulosa cell tumor was the smallest tumor in this study (3×3×3 cm), presenting in a 45-year-old female.

The commonest gross morphology was the cystic nature of tumors (68.38%), which were benign tumors, especially of the surface epithelial category. Most tumors with solid or complex morphology were malignant.

The most common histopathological patterns encountered in the present study were surface epithelial tumors (81.96%), followed by germ cell tumors (8.54%), sex cord-stromal tumors (6.83%), and mixed tumors (3.41%). Benign serous cystadenoma (41.88%) and benign mucinous cystadenoma (26.5%) were the most common histopathological patterns. Only one case of mixed germ cell tumor was observed. Germ cell tumors were most common in subjects aged 21-40 years. After the age of 40 years, surface epithelial tumors were the predominating category, but germ cell tumors were rare. Our study showed that 8.54% of the surface epithelial tumors and 1.7% of the germ cell tumors were bilateral, whereas none of the sex-cord stromal tumors were bilateral. Among the benign tumors,

mature teratoma and serous cystadenoma were mostly presented bilaterally. Both cases of serous cystadenocarcinoma were also presented as bilateral. Half of the mucinous cystadenocarcinoma cases were presented bilaterally (Table 1).

Table 1. Variables related to the risk of malignancy in ovarian tumors

Variable	Benign	Borderline	Malignant	Total	% of Malignancy	*p*-value
Age						
<50 years	82	3	6	91	6.59%	0.001
>50 years	18	-	8	26	30.77%	
Age of menarche						
<12 years	15	3	4	22	18.18%	0.319
>12 years	85	-	10	95	10.57%	
Laterality						
Unilateral	93	3	9	105	7%	0.001
Bilateral	7	-	5	12	35.71%	
Size of tumor						
<10 cm	48	1	4	53	7.58%	0.18
>10 cm	52	2	10	64	17.18%	
Tumor morphology						
Cystic	75	3	2	80	2.5%	0.0001
Solid	14	-	8	22	36.36%	
Cystic and solid	11	-	4	15	26.67%	
Menopausal status						
Premenopausal	84	2	5	91	5.49%	0.0001
Postmenopausal	16	1	9	26	34.62%	

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Increasing age, postmenopausal status, bilaterality, and complex or solid tumor morphologyconferred a higher risk of malignancy. Early menarche and the size of the tumor did not correlate with an increased risk of malignancy.

Ki-67 labeling index was done for all 6 cases of borderline tumors and 8 cases of malignant tumors of epithelial origin. Diffuse intense nuclear staining was considered positive, adweak cytoplasmic staining was considered negative (Table 2).

Table 2. Ki-67 expression in serous carcinomas and mucinous tumors

Histopathological diagnosis	0-25%	26-50%	51-75%	76-100%	Total
Borderline serous tumor	2	1	-	-	3
Serous malignant tumor	-	1	1	-	2
Borderline mucinous tumor	1	2	-	-	3
Mucinous carcinoma	-	6	-	-	6

There were two cases of high-grade serous carcinomas out of which one case shows a Ki-67 labeling index of 26-50% and the other case showed a Ki-67 labeling index of above 50%. The highest Ki-67 labeling index was found to be 51%.

The immunostaining pattern was heterogeneous throughout the tumors, and evaluation was done in most positively stained areas. The mean Ki-67 labeling index in borderline tumors was 27%. The mean Ki-67 labeling index in malignant tumors was 41.83%. When compared with the borderline tumors, the Ki-67 labeling index was found to be significantly higher in malignant tumors ($p<0.001$). In the malignant group of tumors, serous carcinomas (51%), followed by mucinous carcinomas (37%) showed a high mean Ki-67 labeling index. All benign and borderline serous tumors as well as all benign and borderline mucinous tumors were negative for p53 overexpression. Malignant serous tumors showed moderate positivity for p53 overexpression, while 2 out of 6 malignant mucinous tumors show weak expression of p53 (Figure 1).

There were two cases of serous carcinomas showing p53 overexpression of 25-75%. The highest p53 overexpression was found to be 58% (Table 3).

Out of 6 cases of mucinous carcinomas, 2 cases were showing weak p53 overexpression, and the remaining 4 cases were negative for p53 overexpression (Figure 2).

Table 3. P53 overexpression in serous and mucinous tumors

P53 overexpression	Serous tumors		Mucinous tumors	
	Borderline	Malignant	Borderline	Malignant
Negative	3	-	3	4
5-25%	-	-	-	2
25-75%	-	2	-	-
>75%	-	-	-	-
Total	3	2	3	6

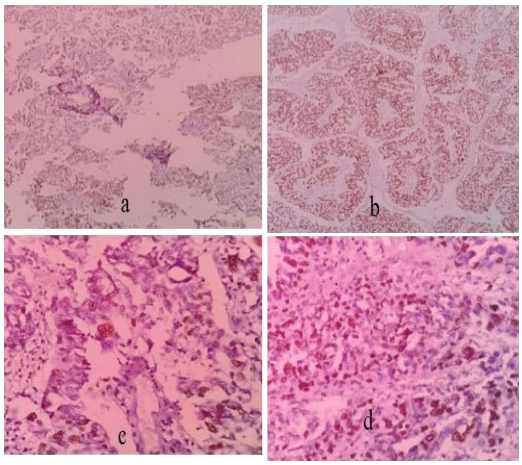

Figure 1. Overexpression of p53 in mucinous carcinoma (a) and serous carcinoma (b) as well as Ki-67 expression in borderline mucinous tumor (c) and mucinous carcinoma (d). All images were taken under 400× magnification.

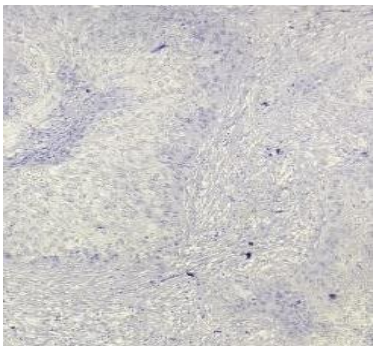

Figure 2. Negative p53 overexpression in mucinous carcinoma. The image was taken under 400× magnification.

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Discussion

Ovarian tumors are common in all age groups without exemption. The youngest patient in this study was a 21-year-old female with unilateral mature teratoma (9.5×5.5×4 cm), presented with pain abdomen, which is the most common germ cell tumor of the adolescent age group. The oldest patient was an 80-year with unilateral mucinous cystadenocarcinoma. She presented with ascites, and the tumor was 19×14×12 cm in size. These findings are in concordance with the findings of some previous studies (8,11).

Increased risk of ovarian tumors associated with early menarche has been proposed by various studies (12,13). In the present study, only 18.80% of the patients attained menarche before the age of 12. The onset of menarche is influenced by female biology as well as genetic and environmental factors, especially nutritional status.

A higher frequency of ovarian tumors is observed in the premenopausal age group. In postmenopausal patients, a comparatively higher frequency of malignant tumors was observed. Similar findings were reported in the studies by Jha and Karki (9) and Kayastha (10). Only 3 patients were asymptomatic (2.56%), with these tumors being incidentally diagnosed on an ultrasound done for other causes or as a routine workup.

In line with our findings, a study carried out by Rashid et al. (14) showed that abdominal pain (59%), followed by abdominal mass (25.42%) were the most common complaints. In the present study, most of the tumors were unilateral. Only 12 out of 117 tumors had a bilateral presentation. Among bilateral tumors, 5 cases (35.71%) were malignant. Moreover, 5 out of 14 malignant tumors (35.71%) and 7 out of 100 benign tumors (7%) were bilateral. These findings are similar to those of the study done by Jha and Karki (9). A higher frequency of bilaterality was present in a previous study which showed 26.8% bilaterality (11). All serous carcinomas and 3 out of 6 mucinous carcinomas in our study showed bilaterality. The most common benign tumor to present bilaterally was mature teratoma, which showed 25% bilaterality. Tumors in the sex-cord stromal category are almost confined to a single ovary. Out of 8 sex-cord stromal tumors, none had a bilateral presentation.

In the present study, tumors ranged in size from 3 to 30 cm. Majority of tumors (88.87%) were less than 20 cm in the largest dimension. Only 13 tumors (11.11%) had their largest dimension between 21 and 30 cm. The largest tumor was 30×25×15 cm, which was a unilateral benign papillary serous cystadenofibroma affecting a 40-year-old female. A unilateral granulosa cell tumor was the smallest tumor in this study (3×3×3 cm), which was presented in a 45-year-old female. This finding correlated with the findings of a study by Pilli et al. (15) in which the largest tumor measured 33×23×22 cm and the smallest one measured 3×2×1 cm.

Patients with solid or complex ovarian tumors are at high risk of ovarian malignancy (16).

In our study, the frequency of tumors was similar to that of previous studies (17), with benign tumors being the most common and borderline being the least common.

Benign serous cystadenoma (41.88%), followed by benign mucinous cystadenoma (26.50%) were the most prevalent tumor types. Among malignant tumors, mucinous cystadenocarcinoma and serous cystadenocarcinoma were the most common categories These findings are similar to the findings of some previous studies (9,18).

Benign serous tumors are more frequently observed compared with malignant serous tumors. The frequency of benign serous tumors in our study correlates with that in Hiremath et al. study (19). In our study, mucinous tumors with the benign variant were more frequently observed compared with the borderline variant. In line with a study by Fattaneh et al. (20), only two benign Brenner tumors (3.16%) were detected in our study. We found 10 cases of germ cell tumors, accounting for 8.55% of all ovarian tumors. Among these tumors, mature cystic teratoma and mixed germ cell tumors were the most prevalent. This is in accordance with the findings of a previous study conducted by Ulbright (21).

It is believed that Epithelial malignancies showing p53 aberrations are significantly less sensitive to cisplatin-based chemotherapy and more aggressive than those with functional p53 (20). Hence overexpression of p53 is a poor prognostic factor. In our study, 2 out of 8 epithelial carcinomas showed moderate positivity for p53 overexpression, contributing to the poor prognosis of the patients.

Our study showed that p53 is significantly overexpressed in serous cystadenocarcinomas when compared with mucinous cystadenocarcinoma. This is supported by findings of previous studies (22,23).

In the present study, the mean Ki-67 expression was 41.83% in malignant epithelial tumors and 27% in borderline tumors. This is in line with the findings of a study by Gursan et al. (24). A previous study also demonstrated a significant relationship between Ki-67 antigen expression and long-term survival and patient outcome in surface epithelial tumors (25).

According to Ayadi et al. (23) and Sylvia et al.(26), a panel of markers including p53, BCL-2, and Ki-67,

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all of which reflect the proliferative activity of the tumor, should be used to further define the biological potential of a specific tumor.

Conclusion

Benign serous cystadenoma and mucinous cystadenoma are the most common ovarian tumors in the studied population of Indian women. Malignancy in germ cell tumors is more frequent among females aged 20-40 years old. Menarche does not correlate with an increase in the risk of malignancy. Menstrual complaints are observed more commonly with tumors with functional stroma with the possible role of hormonal influence. Age of >50 years, post-menopausal age, solid and complex tumor morphology, and bilaterality of tumors may significantly increase the risk of malignancy; therefore, these factors can be used to predict the risk of malignancy in ovarian tumors. Moreover, Ki-67 expression in borderline serous and mucinous tumors was significantly higher than that in malignant surface epithelial tumors. Furthermore, p53 overexpression is significantly more common in serous carcinoma when compared to borderline serous tumors but not in mucinous tumors. Overall, these markers could be beneficial for diagnosing difficult cases and predicting prognosis.

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Declarations:

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Ethics approvals and consent to participate

The study protocol was approved by the Ethics Committee of Narayana Medical College (approval code: NMC/IEC/Path/2017).

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors' contributions

BHC, GSL, and MVL wrote the main manuscript. BHC provided resources for this research. BHC, GSL, MVL, and BKM were involved in data extraction. BHC, GSL, MVL, and BKM were involved in data analysis. BKM reviewed and edited the manuscript. BHC designed the study and contributed to the data analysis and interpretation. All authors read and approved the final manuscript

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