

CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL PROFILE OF ENDOCERVICAL ADENOCARCINOMA

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ABSTRACT

BACKGROUND

Primary adenocarcinoma of cervix constitutes 10-15% of all cases of carcinoma of cervix, which is the second most common carcinoma next to squamous cell carcinoma. Endocervical adenocarcinoma have a considerable morphological overlap with endometrial adenocarcinoma though they differ in their aetiologies, behaviour, and treatments. This makes their diagnosis very difficult particularly in biopsy or curetting specimens or when a fractional dilation and curettage specimens show adenocarcinoma in both components of it. This study was done in the aim to suggest the possible origin of the tumour with the help of immunohistochemistry.

AIMS AND OBJECTIVES

To identify the incidence, distribution, clinicopathological, histomorphological features of endocervical adenocarcinomas and to determine the immunohistochemical expression of CEA, Vimentin, ER and PR in endometrioid type of adenocarcinoma detected in endocervical biopsies, fractional dilation and curettage specimens (Both the components showing similar morphology), and in hysterectomy specimens to suggest the site of origin of tumour.

MATERIALS AND METHODS

It is a retrospective descriptive study of cervical adenocarcinomas conducted in the Institute of Obstetrics and Gynaecology, Madras Medical College, Chennai for a period of 4 years during the period between 2009 November to 2013 October. The statistical analysis was performed using statistical package for social science software version 11.5 the clinicopathological profile of the tumour were calculated using Student t-test and chi-square test.

OBSERVATION AND RESULTS

Among the total 13499 cases received during the study period, 2489 were cervical malignancies comprising 148 adenocarcinoma. It includes 101 mucinous (Endocervical) type, 44 endometrioid type, 2 serous type, and 1 clear cell type. Among the 30 cases of endometrioid type, 16 cases showed definite immunophenotype of cervical origin, 9 cases of endometrial origin and in the remaining 4 cases origin could not be made out as they showed aberrant immunophenotype. Association between CEA and tumour grade and FIGO stage was found to be statistically significant.

CONCLUSION

Identifying the expression of CEA, Vimentin, ER and PR in cervical adenocarcinoma can help to identify the origin of the tumour and plan the treatment preoperatively.

KEYWORDS

Endocervical Adenocarcinoma-Immunohistochemical Profile-CEA-VIM-ER-PR-Endometrioid Type.

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INTRODUCTION

Primary adenocarcinoma of cervix constitutes 10-15% of all cases of carcinoma of cervix. It is the second most common next to squamous cell carcinoma^{1,2} comprising a large heterogeneous group of neoplasms that exhibits a variety of histological patterns.

Endocervical adenocarcinoma and endometrial adenocarcinoma are two distinct entities with different

aetiologies, behaviour, and treatments, but there is considerable overlap in the morphological features of adenocarcinoma arising from these two different sites. This morphological overlap makes their histological differentiation, a diagnostic problem in biopsy or curetting specimens, especially in a small biopsy, or when a fractional dilation and curettage specimens show adenocarcinoma in both components of it.³

The preoperative distinction between these two is very important because the treatment for an endometrial cancer is commonly a simple hysterectomy (Sometimes, if the cervical involvement is identified before surgery, the treatment is modified radical hysterectomy), while for an endocervical adenocarcinoma primary chemotherapy is given with radical hysterectomy. Sometimes, even a combination of clinical, hysteroscopic, radiologic, and pathologic examination fails to identify the definite primary site.

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Several studies performed in the past suggested a panel of markers to differentiate these tumours. So, 30 cases of endometrioid type of adenocarcinoma were selected and subjected to a panel of 4 immunohistochemical markers, Carcinoembryonic Antigen (CEA), Vimentin (VIM), Oestrogenic Receptor (ER), and Progesteronic Receptor (PR).⁴⁻⁹ This study was done in the aim to suggest the possible origin of the tumour (Endocervix or endometrium) and to assess the clinicopathological profile of endocervical adenocarcinoma.

MATERIALS AND METHODS

This study is a retrospective descriptive study of endocervical adenocarcinomas conducted in a tertiary care hospital for a period of 4 years between 2009 November to 2013 October. Total of 13499 cases were received for histopathological examination in the Institute of Obstetrics and Gynaecology, Madras Medical College. Among 2489 cervical malignancies, 148 were adenocarcinoma, which constituted 5.94%. In these 148 cases of adenocarcinoma of cervix, 118 were detected by endocervical biopsy, 15 were detected by hysterectomy, 15 were detected by fractional dilation and curettage specimens (Which showed similar features of malignancy in both the components). All the cases of adenocarcinomas irrespective of the age, stage were included for the study. Adenocarcinoma confined to uterine corpus and other morphological types of carcinoma of cervix other than adenocarcinoma were excluded.

Detailed history of the cases regarding age, history, type of procedure, site, stage, and histological type were obtained for all the 148 cases from pathology records. Haematoxylin and Eosin-stained 4 μ thick sections of the paraffin tissue blocks of specimens were reviewed. Of the 148 cases, a total of 30 cases were selected and their representative formalin fixed paraffin embedded tissue samples were subjected to immunohistochemical analysis for a panel of 4 markers-CEA, Vimentin, ER and PR.

The immunohistochemically-stained slides were analysed for the presence of cellular localization, percentage of cells stained, and intensity of reaction. Cytoplasmic and membrane staining was noted for CEA, Typical paranuclear membrane, or lateral cell border staining was assessed for Vimentin⁶ and Nuclear staining for ER and PR.¹⁰

Negative Staining	<1% tumour cells show positive staining
Weak Positive Staining	1-10% of tumour cells show weak positive staining
Strong Positive Staining	>10% of tumour cells show positive staining

Table 1: Criteria for Immunohistochemical Analysis of Percentage of Cells⁶ Expressing the Marker

This table illustrates the criteria for immunohistochemical analysis of percentage of cells⁶ expressing the marker.

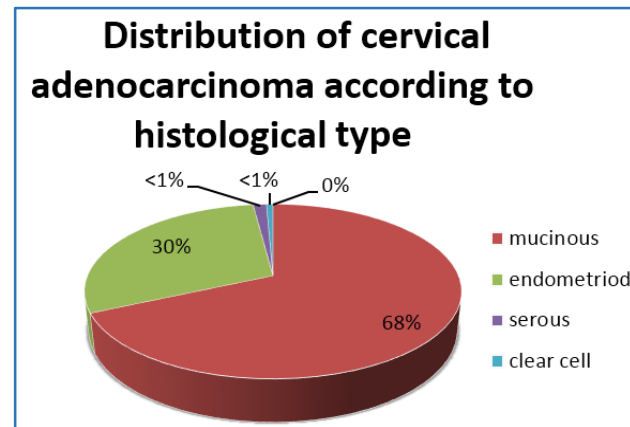
Simplified scoring results then were made as either negative or positive results (Combining weak and strong positive results), unsatisfactory/uninterpretable results were discarded from further consideration.

The statistical analysis was performed using statistical package for social science software version 11.5, which consisted computing the frequency counts and percentages for qualitative variables and mean for the quantitative variables.

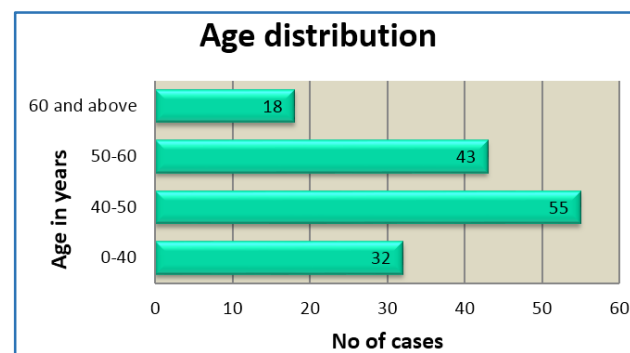
The clinicopathological profile of the tumour were calculated using Student t-test and chi-square s test.

STATISTICS AND RESULTS

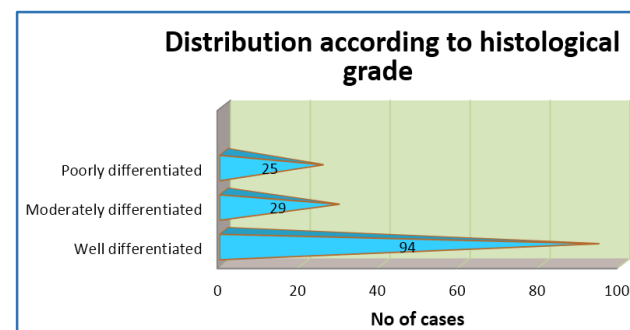
Among 2489 cervical malignancies, 148 were adenocarcinoma, which includes 101 of mucinous type, 44 of endometrioid type, 2 of serous type, and 1 clear cell type. Adenocarcinoma of cervix constituted for 5.94% of cervical malignancies received and endometrioid type constituted 29.73% of adenocarcinoma.

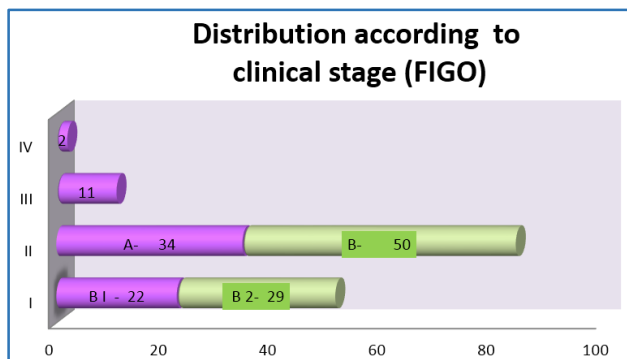


Adenocarcinoma of cervix showed a peak incidence in the age group of 40 to 50 years. The oldest age of presentation was 81 years and youngest age of presentation was 22 years. Mean age at presentation is 50.20 years.



The distribution of endocervical adenocarcinoma based on histological grading showed majority of well differentiation. (94 cases-63%) followed by moderate differentiation (29 cases-19.59%). 84 cases presented in the FIGO stage of II (56.75%), followed by stage I (51-34.45%), and stage III and IV (8.7%).





Among the 30 cases of endometrioid type, 16 cases showed definite immune phenotype of endocervical origin [i.e., a combination of CEA positivity, VIM negativity, ER negativity] and 9 cases showed definite immunophenotype of endometrial origin [i.e., a combination of CEA negativity, VIM positivity, ER positivity] and in the remaining 4 cases origin could not be made out as they showed aberrant immunophenotype.

Among the 17/30 cases, which showed CEA positivity, 16 cases show concomitant negative expression of VIM, ER suggesting endocervical origin.

Expression of CEA in Comparison with Other Markers

	VIM+	VIM-	ER+	ER-	PR+	PR-
CEA+	1	16	1	16	2	15
CEA-	10	3	9	4	6	7

Among the 11/30 cases, which showed VIM positivity, 9 cases show concomitant negative expression of CEA and positive expression of ER suggesting endometrial origin.

Expression of Vimentin in Comparison with Other Markers

	CEA+	CEA-	ER+	ER-	PR+	PR-
VIM+	1	10	10	1	6	5
VIM-	16	3	0	19	1	18

Correlation of CEA with Various Clinicopathological Factors like Age, Grade, Stage of Tumour

The mean age of patients with CEA expression was 49.29 years and that of patients without CEA expression was 53.69 years. There was no significant difference in the age at presentation between the two groups.

Among the 17 cases of CEA positivity, 11 cases showed moderate differentiation. Significant association was found between the CEA expression and tumour grade as depicted in Table 2.

Grade	Positive	Negative	Total
Well Differentiated	3	11	14
Moderately Differentiated	11	1	12
Poorly Differentiated	3	1	4
Total	17	13	30
Chi-Square Test	p value 0.001		

Table 2: Association of Tumour Grade with CEA Expression

Of the 17 CEA positive cases, 12 cases presented in stage IIB. Significant association was found between stage and CEA- Table 3.

Stage	Positive	Negative	Total
IB1	1	6	7
IB2	1	3	4
IIA	1	2	3
IIB	12	1	13
III	2	1	3
IV	0	0	0
Total	17	13	30
Chi-square test	p value 0.006		

Table 3: Association of Tumour Stage with CEA Expression

Clinicopathological Factor	No. of Cases (%)
Age	<50 Years 87 (58.7%)
	>50 Years 61 (41.2%)
Histological Type	Mucinous 101 (68.2%)
	Endometrioid 44 (29.7%)
	Serous 2 (1.35%)
	Clear Cell 1 (0.67%)
Grade	I 94 (63.5%)
	II 29 (19.5%)
	III 25 (16.8%)
	IV 2 (1.35%)
Stage	I 51 (34.4%)
	II 84 (56.7%)
	III 11 (7.4%)
	IV 2 (1.35%)
CEA	Positive 17 (56.67%)
	Negative 13 (43.34%)
VIM	Positive 11 (36.67%)
	Negative 19 (63.34%)
ER	Positive 10 (33.64%)
	Negative 20 (66.67%)
PR	Positive 7 (23.34%)
	Negative 23 (76.67%)

Table 4: Overall Clinicopathological Profile of Cervical Adenocarcinoma

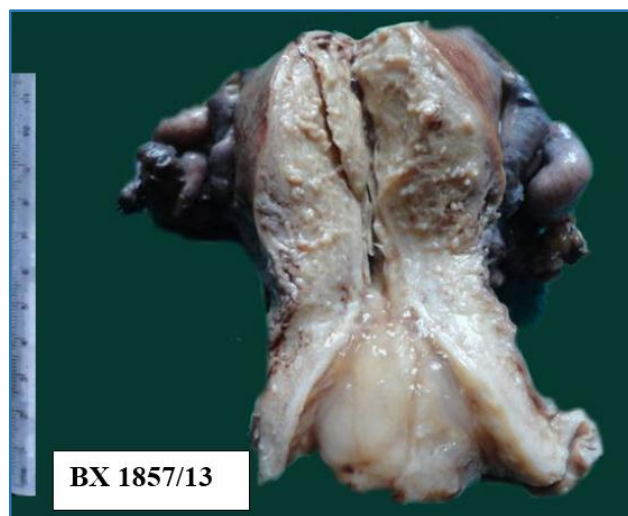


Fig. 1: Gross Picture of TAH Specimen with a Polypoidal Growth Arising from the Endocervix



Fig. 2: Gross Picture of TAH Specimen Showing a Proliferative Growth Involving the Endocervix

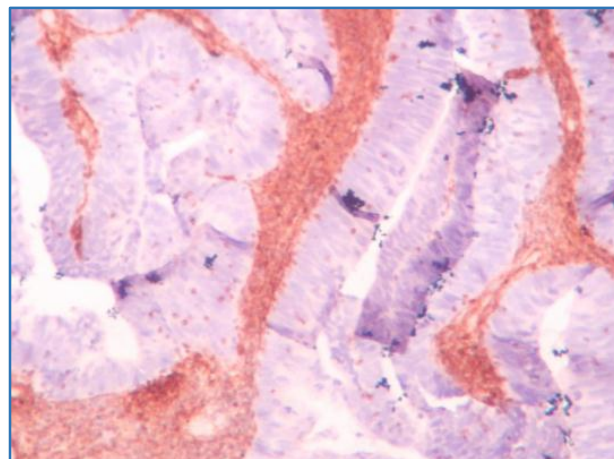


Fig. 5: VIM Staining, Malignant Glands Show Negative Staining, (Underlying Endometrial Stroma Show Positive Staining) 40 X, HPE 1171/10

Endometrioid Adenocarcinoma Arising from Endocervix

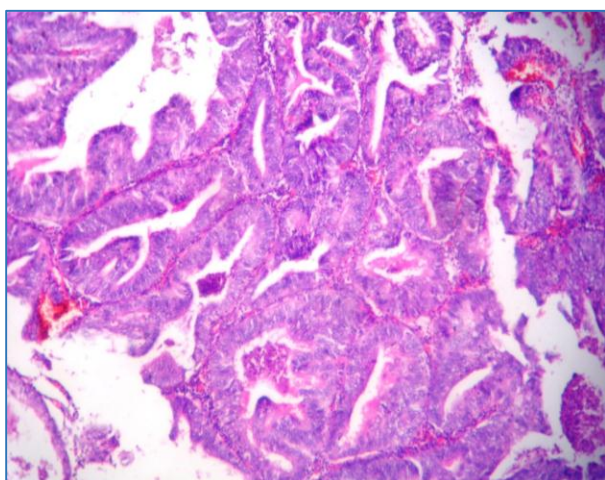


Fig. 3: Tubules and Glands of Various Sizes Arranged Back to Back, lined by Stratified Columnar Epithelium Exhibiting Mild Atypia, 10 X, HPE 1171/10

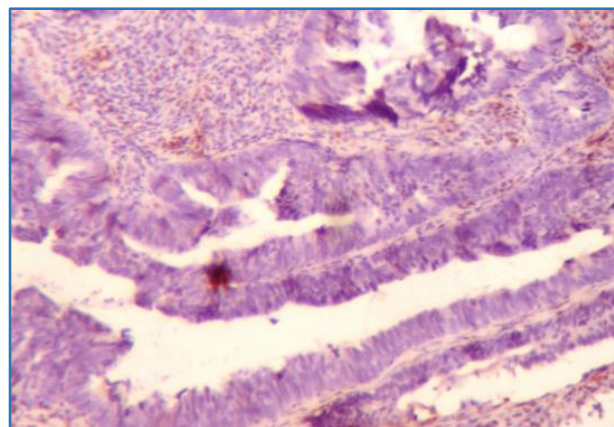


Fig. 6: ER Staining, Malignant Glands Show Negative Staining, (Underlying Endometrial Stroma Show Positive Staining) 10 X, HPE-1171/10

Immunohistochemical Analysis of Endometrioid Adenocarcinoma–Arising from Endocervix

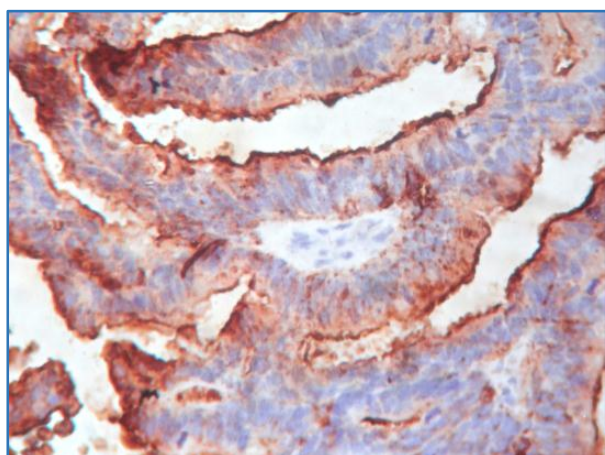


Fig. 4: CEA Staining, Malignant Glands Show Strong Cytoplasmic and Membrane Staining, 40 X, HPE 1171/10

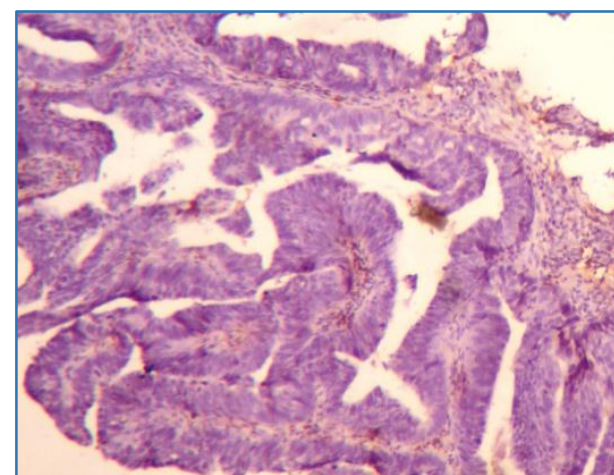


Fig. 7: PR Staining, Malignant Glands Show Negative Staining, (Underlying Endometrial Stroma Show Positive Staining) 10 X, HPE-1171/10

Endometrioid Adenocarcinoma Arising from Endometrium

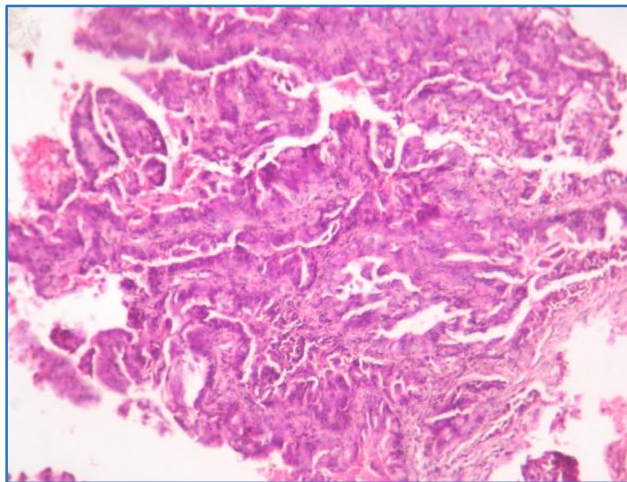


Fig. 8: Tubules and Glands Fused Together with Stromal Invasion Lined by Stratified Columnar Epithelium Exhibiting Moderate Atypia, 10 X, HPE- 7/11

Immunohistochemical Analysis of Endometrioid Adenocarcinoma - Arising from Endometrium

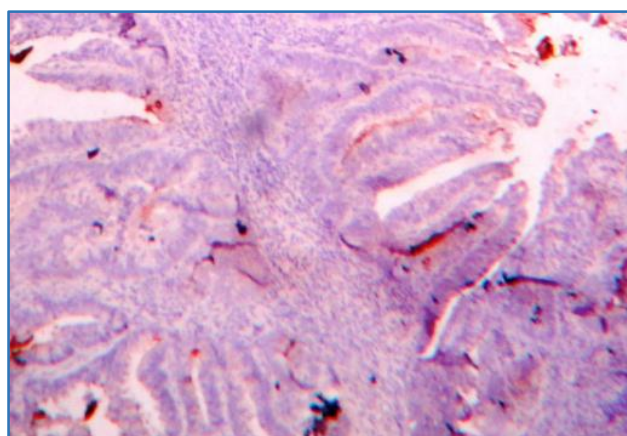


Fig. 9: CEA Staining, Malignant Glands Show Negative Staining, 10 X, HPE -7/11

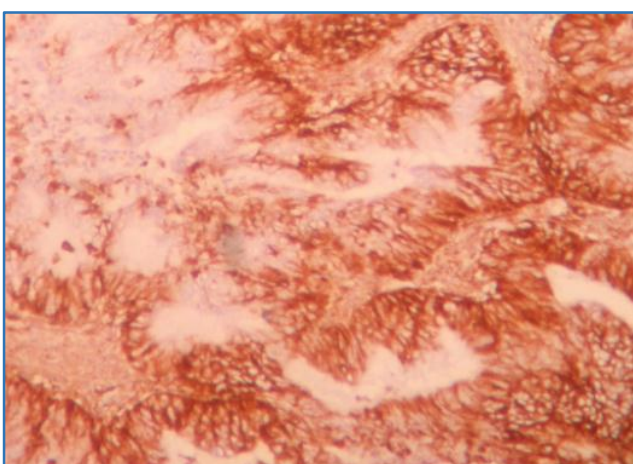


Fig. 10: VIM Staining, Malignant Glands Show Positive Cytoplasmic Staining, (Underlying Endometrial Stroma Show Positive Staining) 10 X, HPE 7/11

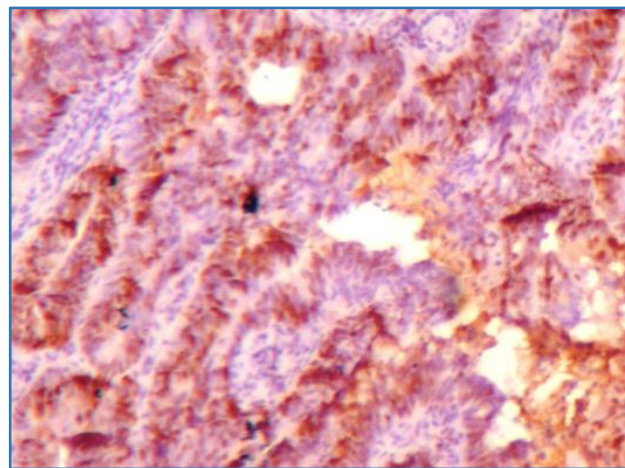


Fig. 11: ER Staining, Malignant Glands Show Strong Nuclear Staining, 10 X, HPE-7/11

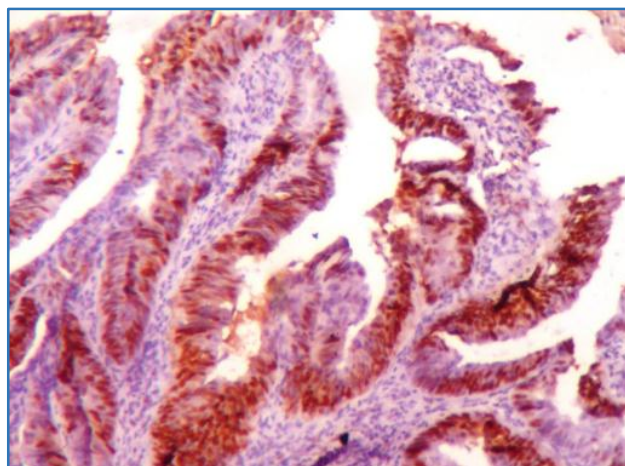


Fig. 12: PR Staining, Malignant Glands Show Strong Nuclear Staining, 10 X, HPE 7/11

DISCUSSION

Carcinoma of cervix is the third leading cause of death in females of age group 20-39. The age of diagnosis and death has come down. Recently estimated new incidence of cancer cases is 12,340 and deaths is 4,030, in United States in 2013. The probability of developing uterine cervical cancer from birth to death is 0.68 (1 in 147).¹¹

Cervical malignancy kills nearly 72,000 women every year in India, which is more than 26% of the 2,75,000 deaths happening all over the world. More than 50% of cervical cancer deaths happen altogether in India, China, Bangladesh, Nigeria, and Brazil among the worldwide countries.¹²

Endocervical adenocarcinoma and endometrial adenocarcinoma are two distinct entities. In spite of being different in their aetiologies, behaviour, and treatments, they have a considerable morphological overlap, which makes their diagnosis very difficult particularly in biopsy or curetting specimens especially in a small biopsy or when a fractional dilation and curettage specimens show adenocarcinoma in both components of it.

Adenocarcinoma of cervix showed a peak incidence in the age group of 40 to 50 years. Mean age at presentation is 50.20 years. This is in concurrence with the study conducted by Klaus Bodner et al (2010)¹³ who observed the median age of 51 years with the range of 24-60 years and the study conducted by Farveen Marican Abu Backer et al¹⁴ who

observed the median age to be 48.5 years in the patients of cervical adenocarcinoma.

The common tumour subtype among adenocarcinoma detected in cervix in this study is mucinous type followed by endometrioid type, which is similar to the study by Fujiwara et al¹⁵ (1997), who observed mucinous (Endocervical type) to be most common 57% and the study conducted by Farveen Marican Abu Backer et al¹⁴ and Klaus Bodner et al (2010).¹³

In the present study, well differentiated tumours were more common accounting to 63.5%. This was similar to the study conducted by Klaus Bodner et al (2010)¹³ and the study conducted by Farveen Marican Abu Backer et al¹⁴ in which the combination of well and moderately differentiated came to be 62.5 % in the patients of cervical adenocarcinoma.

This study showed a higher proportion of stage II tumours followed by stage I tumours, which did not concur with the studies conducted Klaus Bodner et al (2010)¹³ and Farveen Marican Abu Backer et al¹⁴ who showed a predominance of tumours of stage I in the patients of cervical adenocarcinoma.

Among the 30 cases of endometrioid type, 16 cases showed definite immunophenotype of endocervical origin [i.e., a combination of CEA positivity, VIM negativity, ER negativity] and 9 cases showed definite immunophenotype of endometrial origin [i.e., a combination of CEA negativity, VIM positivity, ER positivity] and in the remaining 4 cases origin could not be made out.

This impression was based on the study conducted by Castrillon et al (2002),⁶ who observed CEA positivity in 62% of endocervical adenocarcinoma, but Vimentin positivity in only 7% of it. He also compared the CEA, VIM expression in endometrial adenocarcinoma, which came to be 27% and 100% respectively. Another study conducted by McCluggage et al(2002)⁷ showed CEA, VIM, ER expression in cervical adenocarcinoma to be 96%, 8%, 38% respectively, while CEA, VIM, ER expression in endometrial adenocarcinoma was found to be 70%, 97%, 93%.

Similar study by A. Alkushi et al (2003)³ showed CEA, VIM, ER positivity in 70%, 11%, 11% of cervical adenocarcinoma respectively and CEA, VIM, ER positivity in 61%, 92%, 73% of endometrial adenocarcinoma.

Limitations of this Study

1. This study was conducted in a large tertiary hospital, so the findings therefore cannot be generalized to the whole community.
2. This panel of IHC markers is useful mainly in the distinction between endocervical adenocarcinoma and a low-grade endometrioid adenocarcinoma of the corpus. High-grade aggressive uterine adenocarcinoma do not express ER.
3. As the exact localisation of the tumour was not made out, the immunological suggestion of the origin of the tumour are not confirmed.

Scope for Future Studies

1. Analysis of HPV association in cervical adenocarcinomas helps to identify the primary, so the immunostains for p16 (INK4A) will be helpful in differentiating these two malignancies.
2. Exact preoperative localization of the tumour by various advanced techniques with proper follow up of the cases might be very useful to identify the role of the above markers as both diagnostic and prognostic factors.

CONCLUSION

The incidence of cervical adenocarcinoma for a period of 4 years in the Institute of Obstetrics and Gynaecology, Madras Medical College is 5.94% of total cervical malignancies with the peak incidence in the age group of 40 to 50 years and the most common histological type noted was mucinous type (Endocervical type) followed by endometrioid type with majority of the cases exhibiting well differentiation, which is similar to several other studies conducted throughout the world.

Among the 30 cases of endometrioid type, 16 cases showed definite immunophenotype of cervical origin and 9 cases showed definite immunophenotype of endometrial origin and in the remaining 4 cases origin could not be made out as they showed aberrant immunophenotype.

To conclude, identifying the expression of CEA, Vimentin, ER and PR in cervical adenocarcinoma can help to identify the origin of the tumour and plan the treatment preoperatively. Future studies with a larger sample size with exact localization of the tumour with proper follow up of the cases might shed more light on the role of the above markers in both diagnosis and treatment of the cervical adenocarcinoma.

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