Original Article

E-Cadherin Expression in Endometrial Carcinoma

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DOI: 10.21276/APALM.3221

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Submitted: 06-Oct-2022
Final Revision: 01-Nov-2023
Acceptance: 08-Dec-2023
Publication: 05-Feb-2024

Abstract

Background

In this study, we wanted to determine the proportion of negative E-cadherin expression in endometrial carcinoma cases received in the Department of Pathology and evaluate the E-cadherin expression in different histological subtypes of endometrial carcinoma.

Methods

This was a cross-sectional study conducted over one year in the Department of Pathology, Government Medical College, Thiruvananthapuram, Kerala. 52 specimens histopathologically diagnosed as endometrial carcinoma in the Department of Pathology, were studied. Age, histological subtype, grade, stage and E-cadherin staining were recorded. Data were entered into an Excel sheet and analysed with SPSS.

Result

Clinicopathological features of were studied and the median age group of the patients was between 51-60 years. The majority of cases were of endometrioid type and presented at stage IA (69.2 %). Negative E cadherin expression was seen more commonly in Type II endometrial carcinomas (50 & 33.3 % of serous and clear cell carcinoma respectively). Among the Type I carcinoma, grade 3 tumours showed the most proportion of negative E-cadherin staining pattern (33.3 %).

Conclusion:

The study concluded that most of the tumours occurred in the postmenopausal age group and the majority of cases were in stage IA, most cases were of endometrioid type. E-cadherin was lost most commonly in high-grade endometrioid carcinoma and Type 2 carcinomas. Among the 3 grades of endometrioid carcinoma, grade 3 (33.3 %) had the highest proportion of negative staining and grade 1 had the highest proportion of positive staining characteristics. (57.1 %).

Keywords:

Endometrial carcinoma, E-cadherin expression, histological subtypes, Stage, Grade

Introduction

According to the World Cancer Research Fund International, endometrial cancer (EC) is the sixth most common women's malignancy worldwide.[1] The highest incidence of EC is seen in menopausal women, especially between 50 and 59 years of age.[2] Most patients usually present with early-stage symptoms and therefore have a good prognosis. Endometrial carcinoma in

terms of histopathological characteristics is divided into several main and most frequent subtypes: serous carcinoma, clear-cell carcinoma, endometrioid adenocarcinoma and carcinosarcoma.[3] Based on the histopathological classification, type I tumours are usually low-grade endometrioid cancers, whereas type II are usually high-grade serous or clear-cell carcinomas. Molecular evidence shows that there are discrete features of the two EC types in terms of gene copy numbers. Multiple studies based on molecular studies of EC proved that endometrioid carcinomas are highly mutated tumours regarding PI3K/AKT/mTOR and Wnt/β-catenin signaling pathways.

PTEN is considered to be one of the most important negative regulators of the PI3K/AKT/mTOR. Dysfunction of PTEN is present in the majority of endometrioid carcinomas. As PTEN loss is also frequently seen in endometrial hyperplasia, it is hypothesized that it may be an initial and early step in the pathogenesis of endometrioid carcinoma. PIK3CA mutations are also associated with the disturbances in the same pathway leading to disintegration of cell proliferation and apoptosis.[4,5].Endometrial hyperplasia with atypia or endometrioid intraepithelial neoplasia has a high propensity to develop endometrial carcinoma.

The newer molecular classification divides endometrial carcinoma into 4 groups: POLE ultramutated, Mismatch repair-deficient, P53 mutant, no specific molecular profile based on the mutation type and has prognostic significance. Treatment strategies according to the specific molecular type are being developed.

Surgery remains the mainstay of treatment for most women with endometrial cancer. The International Federation of Gynaecology and Obstetrics (FIGO) necessitates staging of endometrial cancer surgically. Surgery includes hysterectomy with possible removal of fallopian tubes and ovaries bilaterally and consideration of lymph node assessment. [6]

Adjuvant chemotherapy includes anti-angiogenic agents, EGFR inhibitors, and PI3K-PTEN-AKT-mTOR inhibitors. Programmed cell death protein-1 (PD-1) is found to have very high expression in endometrial cancer and studies on treatment are on trial.

E-cadherin is a calcium-dependent epithelial adhesion molecule that is linked to cytoskeletal actin filaments through α- and β- (or γ-) catenin. Loss of E-cadherin expression has been encountered in many malignancies. E-cadherin plays an important role in epithelial cell survival.

E-cadherin mutations alter the apoptotic behaviour of tumour cells. Loss of expression in tumour cells, in relation to the epithelial-mesenchymal transition (EMT), is associated with alterations in E-cadherin expression linked to decreased cell-cell adhesion, metastatic potential, tumour dedifferentiation, and deep myometrial invasion in endometrial and other carcinomas. [7,8]

Materials and Methods

This was a cross-sectional study conducted over one year in the Department of Pathology, Government Medical College, Thiruvananthapuram, Kerala after obtaining clearance from the institutional ethical committee. 52 specimens histopathologically diagnosed as endometrial carcinoma (from endometrial curettage and hysterectomies) in the Department of Pathology, were studied. Inadequate samples were excluded.

Inclusion criteria: endometrial curettage and hysterectomies. Age, histological subtype, grade, stage, E cadherin staining were recorded.

Sample Size

Sample size calculated using the formula. 4pq n = d2, p = Prevalence (from previous study) q = 100-p, d = maximum variability that can be afforded (taken as 20 % of p), P value= 43.3 % as per previous study n = 133. This was the minimum number of cases

required for the study. All consecutive specimens received during the study period were included in the study.

Study Instruments

Formalin-fixed paraffin-embedded tissue blocks. Hematoxylin and eosin-stained sections. IHC Marker- E-cadherin and Hospital records.

Methods of Data Collection

Clinical details of the patients were recorded from case sheets. H&E sections were studied for a histopathological grade, histological subtype, and stage of the tumour. Formalin-fixed paraffin-embedded blocks were used for IHC staining using primary antibody – E-cadherin.

Statistical Methods

Data were entered into an Excel sheet. Categorical variables were expressed as proportions and quantitative variables were expressed as mean and standard deviation. Chi-square test for categorical variables and Students t-test for quantitative variables were used as statistical tests of significance. Analysis of data was done using appropriate statistical software (SPSS).

Ethical Considerations

Institutional ethical committee clearance was obtained. Confidentiality was ensured and maintained throughout the study.

Results

The age ranged from 30 to 90 years with the majority of patients between 51 and 60 years of age.

Histological Grade

The most commonly sampled tumours were of endometrioid type of FIGO grade 1 which comprised 40.4 % of the cases. Among the non-endometrioid tumours, serous carcinoma predominated (19.2 %) over clear cell carcinoma (5.8 %).

Proportion of Negative E-cadherin Expression in Endometrial Carcinoma Cases

The majority of tumours showed grade 3 staining pattern (40.4 %) followed by 36.5 % that showed grade 2 staining pattern. Only 15.4 % of cases showed complete loss of E-cadherin staining.

Proportion of Negative E-cadherin Expression in Endometrial Carcinoma Cases

15.4 % of cases showed a negative E-cadherin staining pattern whereas the majority of cases showed a positive staining pattern. This might have been due to the increased prevalence of stage IA tumours.

Table 1: Proportion of negative E-cadherin expression in endometrial carcinoma cases

E-cadherin Staining Pattern	Number of Cases	Percent	95 % CI
Negative E-cadherin expression	8	15.4	5.6 – 25.2
Positive E-cadherin expression	44	84.6	

Stage of Endometrial Carcinoma Cases

The majority of cases were of stage IA (69.2 %) and the least number of cases in stage III (1.9 %). Stage IB constituted 25% and Stage II constituted 3.8%

Association of E-cadherin Expression in Endometrial Carcinoma Cases with Selected Variables

Grade 2 and grade 3 staining patterns were equally predominant in patients less than 60 years (both 39.4 %). Grade 3 staining pattern was predominant in patients over 60 years.

Table 2: Comparison of E-cadherin expression based on age

E-cadherin staining pattern	≤ 60		> 60		Z#	P
	Number of cases	Percent	Number of cases	Percent		
Grade 0	5	15.2	3	15.8		
Grade 1	2	6.1	2	10.5		
Grade 2	13	39.4	6	31.6		
Grade 3	13	39.4	8	42.1	2.59**	0.010
# Mann-Whitney U Test, **: - Significant at 0.01 level						

Distribution of E-cadherin Expression Based on Histological Diagnosis with Grade

It was seen that most of the serous carcinomas (50 %) and grade 3 (33.3 %) showed negative E-cadherin staining. Grade 1 staining was also most predominantly seen in grade 3 endometrioid carcinoma. Grade 2 staining pattern was seen most predominantly in grade 2 endometrioid carcinoma. Among the 3 cases of clear cell carcinoma, 3 of them showed different staining patterns with 33.3 % showing grade 0, 33.3 % showing grade 1 and 33.3 % showing grade 2 staining patterns.

Table 3: Distribution of E-cadherin expression based on histological diagnosis with grade

E-cadherin staining pattern	Grade 1	Grade 2	Grade 3	Serous	Clear cell
Grade 0	0 (0)	0 (0)	2 (33.3)	5 (50)	1 (33.3)
Grade 1	0 (0)	2 (16.7)	1 (16.7)	0 (0)	1 (33.3)
Grade 2	9 (42.9)	4 (33.3)	3 (50)	2 (20)	1 (33.3)
Grade 3	12 (57.1)	6 (50)	0 (0)	3 (30)	0 (0)

Comparison of E-cadherin Expression among Type 1 and Type 2 Tumours

It was found that there was a difference in E-cadherin expression pattern among Type 1 and type 2 tumours.Type 1 tumours mostly showed grade 3 staining and type 1 showed a negative staining pattern.

Table 4: Comparison of E-cadherin expression between type 1 and type 2 tumours

E-cadherin staining pattern	Type 1		Type 2		Z#	p
	Number of cases	Percent	Number of cases	Percent		
Grade 0	2	5.1	6	46.2		
Grade 1	3	7.7	1	7.7		
Grade 2	16	41.0	3	23.1		
Grade 3	18	46.2	3	23.1	2.59**	0.010
(# Mann-Whitney U Test**: - Significant at 0.01 level)						

Table 5: Comparison of E-cadherin expression based on the stage of carcinoma

E-cadherin staining pattern	IA/IB		II/III		Z#	p
	Number of cases	Percent	Number of cases	Percent		
Grade 0	8	16.3	0	0.0		
Grade 1	3	6.1	1	33.3		
Grade 2	17	34.7	2	66.7		
Grade 3	21	42.9	0	0.0	1.04	0.296
(# Mann-Whitney U Test)						

Distribution of E-cadherin Expression Based on Stage of Carcinoma

Comparing the E-cadherin staining pattern with the grade of the tumour it was found that most of the stage IA tumours showed grade 3 staining (47.2 %), most of the IB tumours showed either grade 2 or grade 3 staining (61.8 % of total). Stage II tumours showed equal to grade 1 and 2 staining patterns. Most of the stage III tumours showed grade 2 staining pattern taking the total of stage I cases, most of the grade 3 staining pattern (42.9 %) and most of stage II/III tumours (66.7 %) showed grade 2 staining patterns

Comparison of Stage of the Carcinoma with Age

Most of the patients below 60 years (72.7 %) and above 60 years (63.2 %) had stage IA carcinoma. There was no significant association between stage and the age of the patient (p 0.417).

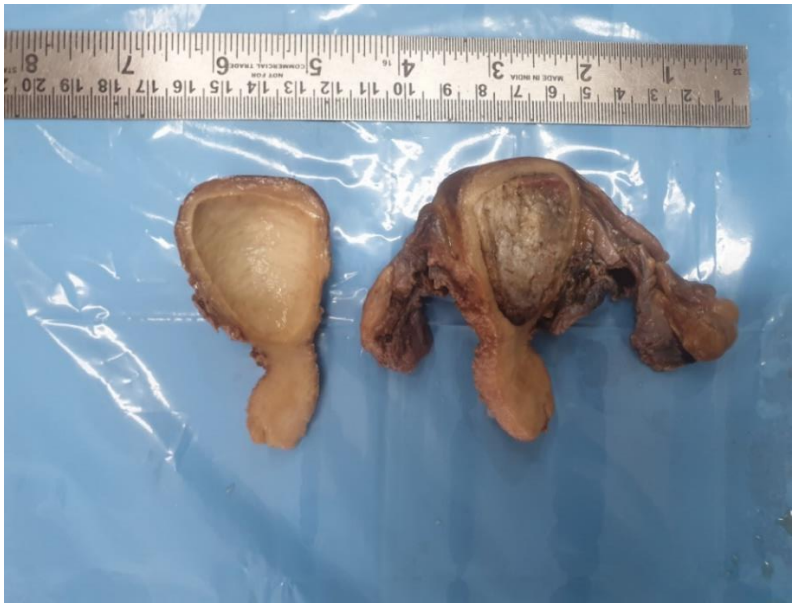

Figure 1: gross appearance of endometrial carcinoma presenting as a polyp with dilatation of endometrial cavity.

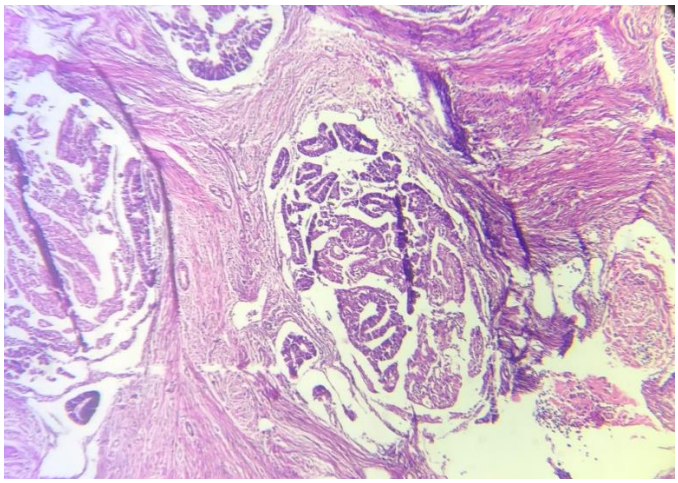

Figure 2: Endometrioid carcinoma grade 2

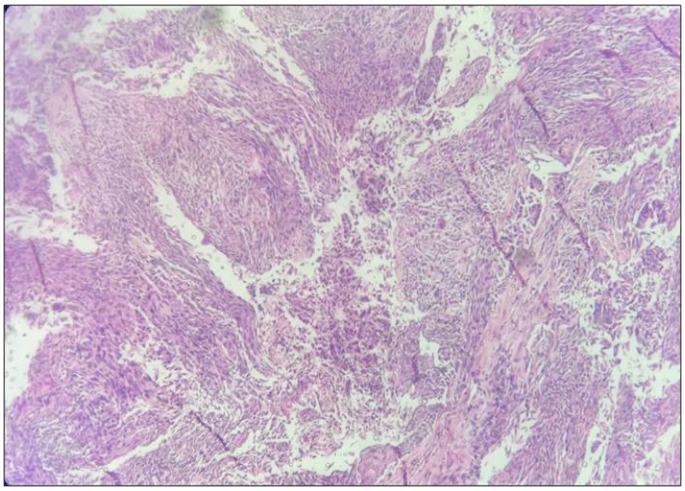

Figure 3: Grade 3 endometrioid carcinoma with >50% solid component

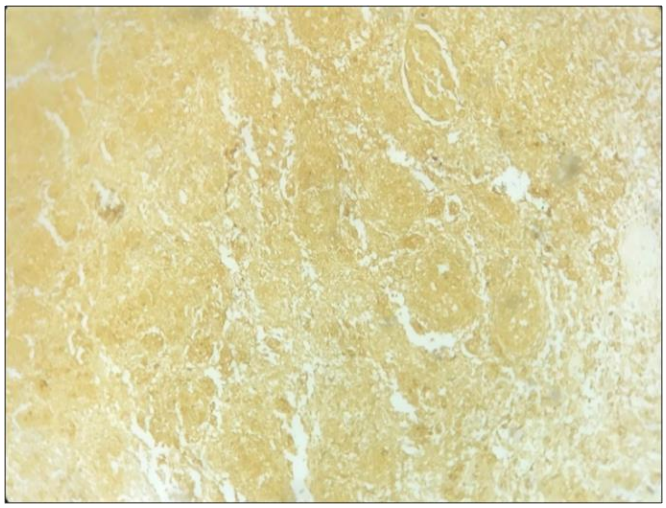

Figure 4: grade 3 staining pattern of e cadherin in grade 1 endometrial carcinoma.

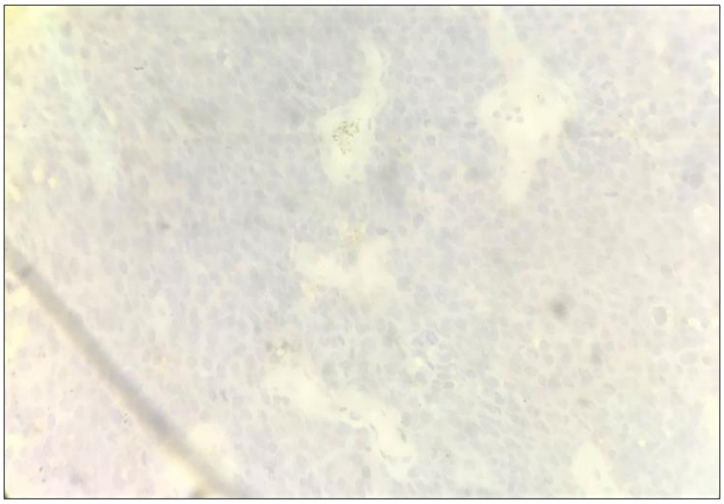

Figure 5: grade 0 staining pattern in serous carcinoma

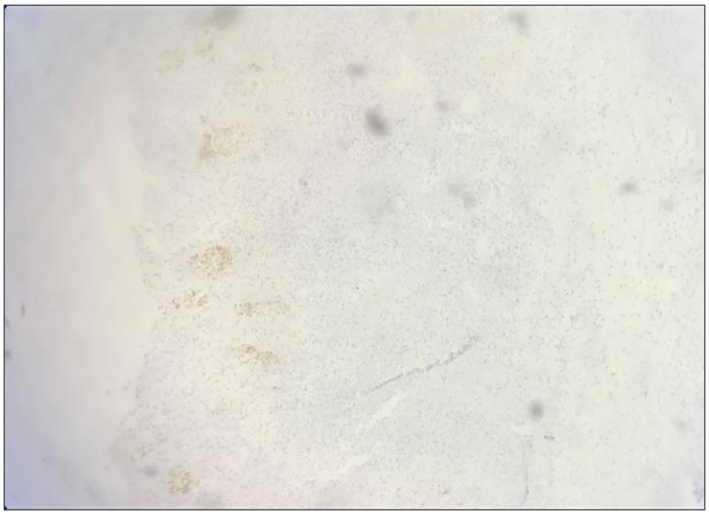

Figure 6: grade 1 e cadherin staining pattern in grade 3 endometrioid carcinoma

Discussion

Age

The age group ranged from 30-90 years with the youngest patient being 37 years and the eldest being 90 years. A maximum number of patients were in the 51-60 years age group. This was in concordance with a study done by Bharatnur S, Kustagi P.[9] Patients who were less than 60 years of age showed a grade 3 staining pattern in the majority of cases. Patients who were less than 60 years showed an equal predominance of grade 2 and grade 3 E cadherin staining pattern.

Histological Subtype

The most common histological subtype was endometrioid carcinoma comprising 40.4 % of the total study population. The least common histological subtype was clear cell carcinoma of the endometrium. In a study done by T Yalta et.al.[10] also the predominant population was endometrioid type (23 out of 32 cases) and the least common was clear cell type (5 out of 32 cases).

Stage of the Endometrial Carcinoma

In our study, it was found that the majority were of stage IA (69.2 %). Comparing stage with age all cases irrespective of age were in stage IA.

Age is known to be an important factor that determines the prognosis. In a retrospective review done by Ganesh et al.[11] of 263 patients conducted to assess the relationship between selected clinical and pathological factors and disease-free survival (DFS) and overall survival (OS) in endometrioid endometrial cancer patients, it was observed that the worse OS was related to younger age at menopause (HR=0.932; 95% CI=0.873-0.996; P=0.039) (Gottwald, 2011). E-cadherin expression showed a grade 3 expression in stage IA/IB tumours (42.9 %) and the majority of stage II/III tumours showed a grade 2 staining pattern. In a study done by Loren K Mell et al, it was found that there was a negative correlation of E-cadherin expression based on stage.[12]

Proportion of Negative E-cadherin Expression in Endometrial Carcinoma Cases

It was seen in our study that the proportion of negative expression of E-cadherin among all cases was significantly lower than the number of cases showing positive staining patterns. This was in discordance with the study done by Jee Hyun Park et al. that had a higher prevalence of negative expression among endometrioid carcinoma (43.3 %).[13]

Apoptosis is a tightly regulated cell cycle process. Expression of E-cadherin is a critical mechanism for the regulation of intercellular cohesiveness, and also for the regulation of the apoptosis of tumour cells. E-cadherin is a calcium-dependent epithelial adhesion molecule. 9 Loss of E-cadherin expression has been encountered in various types of human malignancies including endometrial carcinoma.[14]

E-cadherin Staining According to Histological Subtype

It was statistically significant that type I /endometrioid type tumours showed retainment of E-cadherin expression (94.9 %) as compared to most of the type 2 carcinomas showing loss of E-cadherin expression. This was a significant finding in the study done by T Yalta et al.[10] as well.

It was found in our study that among the 3 grades of endometrioid carcinoma, grade 3 (33.3 %) had the highest proportion of negative staining and grade 1 had the highest proportion of positive staining characteristics. (57.1%).

Conclusion

Endometrial carcinoma is one of the most common female genital tract tumours. It was concluded in our study that E-cadherin expression was predominantly lower among the higher grade endometrioid carcinoma as compared to lower grade (33.3 and 57.1 %) and there was a significantly decreased staining pattern in Type 2 tumours as compared to Type 1 tumours. It was also found that irrespective of the age, most of the study population was of predominantly stage IA disease and a majority of stage I/II cases showed a good expression of E-cadherin as compared to higher stages. Most of the cases in our study presented as stage IA disease (69.2 %). These findings might help in personalized targeted therapy with E-cadherin inhibitors in higher stage and higher-grade tumours in addition to the conventional treatment protocols and would probably help in increasing the overall survival of patients irrespective of the histological subtype.

Acknowledgements: I take this opportunity to express my gratitude to all the people whose invaluable support made it possible to complete this study including my mentor Dr. Sheela K M, technical support by Sudharma and Bindu Thomas and our Head of department Dr. Krishna G for all the guidance.

Funding: None

Competing Interests: None declared

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