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Epidermal growth factor receptor (EGFR) overexpression in endometrial carcinoma: association with histopathologic parameters

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Abstract

Background: Epidermal growth factor receptor (EGFR) is a cellular oncoprotein which is overexpressed in many human cancers including a subset of endometrial cancers. Immunohistochemical (IHC) expression of EGFR has been investigated in previous studies; Role of EGFR in endometrial carcinoma as a prognostic biomarker has not been studied in our population; therefore we aimed to evaluate the expression of EGFR in cases of endometrial carcinoma in loco-regional population and its association with histologic variables.

Methods: Total 89 cases of endometrial carcinoma were selected from records of pathology department archives. All patients underwent surgeries at Liaquat National hospital, Karachi from January 2012 till December 2017 over a period of 6 years. Slides of all cases were retrieved and reviewed by two senior histopathologists and pathologic characteristics were evaluated. Moreover, representative tissue blocks of all 89 cases were selected for EGFR immunohistochemistry.

Results: 73% (65 cases) showed no EGFR expression, while 21.3% (19 cases) showed low EGFR expression and 5.6% (5 cases) revealed high EGFR expression. Significant association of EGFR expression was noted with histologic type. Serous carcinoma and carcinosarcoma showed high expression of EGFR. On the other hand, no significant association of EGFR with other histopathologic parameters was found.

Conclusion: Overall, we found a low EGFR expression in endometrial carcinoma in our population without any significant pathological association except for its high expression in serous carcinoma and carcinosarcoma; however, more large scale studies are warranted to validate these findings.

Keywords: Endometrial carcinoma, Epidermal growth factor receptor, EGFR, Serous carcinoma, Carcinosarcoma

Introduction

Epidermal growth factor receptor (EGFR) is a cellular oncoprotein overexpressed in many human cancers including a subset of endometrial cancers (Battaglia et al., 1989; Bauknecht et al., 1989; Miyazawa, 1992). EGFR is also used as a prognostic biomarker and therapeutic target in many cancers including head and neck, breast, bladder and lung cancers (Ali Hashmi et al., 2018; Hashmi et al., 2018)

Endometrial carcinoma is one of the most common gynaecological malignancies in women. There are two major types of endometrial carcinoma (type I and II) on the basis of genetic alteration and phenotypic appearance. Type I endometrial carcinoma is hormone driven and include endometroid subtype. On the other hand, type II endometrial cancers are caused by p53 gene mutations. Major prognostic parameters of endometrial cancers include histologic subtype, grade, depth of myometrial invasion and extrauterine spread (Ambros & Kurman, 1992; Kurman & Norris, 1987) Immunohistochemical (IHC) expression of EGFR has been investigated in previous studies; however its prognostic significance has not been validated yet in Pakistan. Role of EGFR in endometrial carcinoma as a prognostic biomarker has not been studied in our population; therefore we aimed to evaluate the expression of EGFR in cases of

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endometrial carcinoma in loco-regional population and its association with histologic variables.

Methods

Case selection

Total 89 cases of endometrial carcinoma were selected from the files of pathology department archives. All patients had surgeries at Liaquat National hospital, Karachi from January 2012 till December 2017 over a period of 6 years. The study was approved by research and ethical review committee of Liaquat National Hospital. Informed written consent was taken antecedent to surgery. Hematoxylin and eosin stained slides and paraffin blocks were retrieved. Slides of all cases were re-evaluated by two senior histopathologists and pathologic characteristics were recorded. Representative tissue blocks of all cases were selected for EGFR immunohistochemistry.

Immunohistochemistry

EGFR immunohistochemistry was performed using DAKO EnVision method using DAKO Monoclonal Mouse Anti-human Epidermal growth factor Receptor (EGFR), clone H11 according to manufacturers protocol. Both membranous and cytoplasmic staining for EGFR were evaluated. Intensity of staining was categorized into no staining (0), weak (1+), intermediate (2+), strong (3+) while percentage of positively stained cells were scored as continuous variable (Fig. 1). Intensity and percentage cores were multiplied to generate an H-score ranging from 0 to 300. A cut off score of 10 i.e. at-least weak expression (intensity score 1+) of EGFR in 10% of tumor cells was taken as positive EGFR expression. On the other hand, cut-off value of 200 was used to categorize positive EGFR expression into low and high. Cases above 200 H-score was considered high EGFR expression. H-scoring system in evaluating biomarker testing is widely used in different cancers (McCarty Jr. et al., 1985).

Statistical analysis

Statistical package for social sciences (SPSS 21) was used for data compilation and analysis. *P*-value ≤0.05 was taken as significant. Mean and standard deviation were calculated for quantitative variables. Frequency and percentage were calculated for qualitative variables. Fisher exact test was applied to determine association.

Results

Demographic patient characteristics

Mean age of the patients involved in the study was 55.76 + 9.17. Endometroid carcinoma was the most common subtype (86.5%), followed by serous (7.9%) and carcinosarcoma (4.5%). Most of the cases were of either grade I or II (39.3 and 42.7% respectively). Fifty-two cases (58.4%) showed more than half of myometrial invasion. Cervical invasion, adnexal involvement and nodal

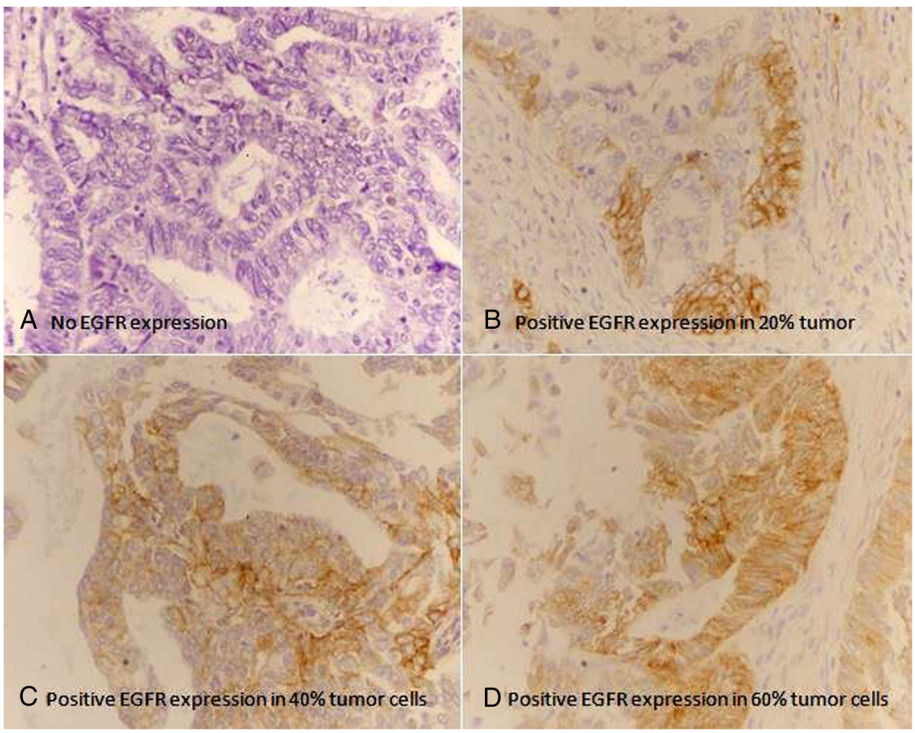

Fig. 1 Epidermal growth factor receptor (EGFR) expression in Endometrial carcinoma

metastasis were seen in 25.8, 10.1 and 5.6% cases respectively. 12.4% cases were found to be at high T stage (T3/T4). Similarly, high FIGO stage (III/IV) was noted in 12.4% cases (Table 1).

EGFR expression in endometrial carcinoma

73% (65 cases) showed no EGFR expression, while 21.3% (19 cases) showed low EGFR expression and 5.6% (5 cases) revealed high EGFR expression. Significant association of EGFR expression was noted with histologic type.

Table 1 Clinico-pathologic parameters of patients involved in the study

		n (%)
Age(years)		55.76 ± 9.17
EFGR IHC Score		15.39 ± 41.52
Menopausal Status	Pre Menopausal	17 (19.1)
	Post Menopausal	72 (80.9)
Histological Type	endometroid	77 (86.5)
	serous	7 (7.9)
	clear cell	1 (1.1)
	carcinosarcoma	4 (4.5)
Grade	Grade I	35 (39.3)
	Grade II	38 (42.7)
	Grade III	16 (18)
Myometial Invasion	Limited To Endometrium	6 (6.7)
	Less Than Half Of Myometrium	31 (34.8)
	More Than Half Of Myometrium	52 (58.4)
Cervical Invasion	Present	23 (25.8)
	Absent	66 (74.2)
Adnexal Involvement	Present	9 (10.1)
	Absent	80 (89.9)
Nodal Status	N0	84 (94.4)
	N1	4 (4.5)
	N2	1 (1.1)
Lymphovascular Invasion	Present	6 (6.7)
	Absent	83 (93.3)
T Stage	T1	62 (69.7)
	T2	16 (18)
	T3	8 (9)
	T4	3 (3.4)
FIGO Stage	Stage IA	34 (38.2)
	Stage IB	27 (30.3)
	Stage II	17 (19.1)
	Stage IIIA	7 (7.9)
	Stage IIIB	1 (1.1)
	Stage IV	3 (3.4)

Serous carcinoma and carcinosarcoma showed high expression of EGFR. Median IHC score for endometroid carcinoma was 0 with standard error 4.5; median IHC score for serous carcinoma was 8.0 with standard error of 7.2 while median IHC score for carcinosarcoma was 80.0 with standard error 34.7. Non parametric Kruskal-Wallis Test was used to compare mean difference. We found significant mean difference between EFGR IHC scores of various histologic subtypes of EC ($p = 0.013$).On the other hand, no significant association of EGFR with other histopathologic parameters was found (Table 2).

Discussion

In the present study, we found a low overall expression (26.9%) of EGFR in endometrial carcinoma. Moreover, no significant association of EGFR expression was noted with tumor grade and other histologic parameters.

Comparison of our results with reported literature revealed that most of the authors found a relatively high expression of EGFR in endometrial carcinoma. Niikura H et al., found 67.1% expression of EGFR in a study involving 140 patients of endometrial carcinoma. They found significant association of EGFR expression with grade and age, however no significant association was noted with other prognostic parameters like depth of myometrial invasion and tumor stage (Niikura et al., 1995). On the other hand, in another study involving 96 and 40 cases of endometrial carcinoma, revealed 74 and 67.5% EGFR expression with no significant association with tumor grade and depth of invasion (Berchuck et al., 1989a; Nyholm et al., 1993). Similarly, Berchuck A et al., didn't find any significant association of EGFR expression with histologic grade and depth of myometrial invasion (Berchuck et al., 1989b). Khalifa MA et al., found EGFR expression in 49% cases of endometrial carcinoma and found that EGFR expression as a significant predictor of survival (Khalifa et al., 1994).

Cai S et al., in a study involving 152 cases of endometrial carcinoma concluded that, EGFR along with COX-2 and VEGF-C expression can help in predicting FIGO stage, degree of differentiation, and depth of myometrial invasion in endometrial carcinoma (Cai et al., 2017). Ramalingam P et al., investigated expression of various biomarkers in undifferentiated and basal like EC. They noted EGFR expression in 22% cases of undifferentiated EC; on the other hand, basal like EC lack EGFR expression.

In this era of personalized medicine and changing trends of cancer management, more and more molecular targets are being identified. Apart from WHO classified histologic subtypes of EC, two distinct molecular pathways of EC are well known with type II EC frequently having p53 and EGFR mutations. Therefore, there is need for a molecular based classification of EC that can

Table 2 Association of Epidermal growth factor receptor (EGFR) expression with clinico-pathologic parameters of Endometrial carcinoma

		n(%)			P-Value
		Negative (n=65)	Low (n=19)	High (n=5)	
Menopausal Status	Pre Menopausal	13 (20)	4 (21.1)	0 (0)	0.792
	Post Menopausal	52 (80)	15 (78.9)	5 (100)	
Histological Type	endometroid	60 (92.3)	14 (73.7)	3 (60)	0.009
	serous	3 (4.6)	4 (21.1)	0 (0)	
	clear cell	1 (1.5)	0 (0)	0 (0)	
	carcinosarcoma	1 (1.5)	1 (5.3)	2 (40)	
Grade	Grade I	28 (43.1)	6 (31.6)	1 (20)	0.055
	Grade II	30 (46.2)	6 (31.6)	2 (40)	
	Grade III	7 (10.8)	7 (36.8)	2 (40)	
Myometial Invasion	Limited To Endometrium	6 (9.2)	0 (0)	0 (0)	0.753
	<1/2 Of Myometrium	23 (35.4)	6 (31.6)	2 (40)	
	>1/2 Of Myometrium	36 (55.4)	13 (68.4)	3 (60)	
Cervical Invasion	Present	15 (23.1)	6 (31.6)	2 (40)	0.524
	Absent	50 (76.9)	13 (68.4)	3 (60)	
Nodal Status	N0	61 (93.8)	18 (94.7)	5 (100)	1.000
	N1	3 (4.6)	1 (5.3)	0 (0)	
	N2	1 (1.5)	0 (0)	0 (0)	
Lymphovascular Invasion	Present	3 (4.6)	3 (15.8)	0 (0)	0.278
	Absent	62 (95.4)	16 (84.2)	5 (100)	
T Stage	T1	47 (72.3)	13 (68.4)	62 (69.7)	0.094
	T2	12 (18.5)	2 (10.5)	16 (18)	
	T3	4 (6.2)	4 (21.1)	8 (9)	
	T4	2 (3.1)	0 (0)	3 (3.4)	
FIGO Stage	Stage IA	26 (40)	6 (31.6)	2 (40)	0.155
	Stage IB	20 (30.8)	7 (36.8)	0 (0)	
	Stage II	13 (20)	2 (10.5)	2 (40)	
	Stage IIIA	4 (6.2)	3 (15.8)	0 (0)	
	Stage IIIB	0 (0)	1 (5.3)	0 (0)	
	Stage IV	2 (3.1)	0 (0)	1 (20)	
Adnexal involvement	Present	5 (7.7)	3 (15.8)	1 (20)	0.321
	Absent	60 (92.3)	16 (84.2)	4 (80)	

Fisher exact test applied
P-value ≤ 0.05, considered as significant

help in personalizing targeted therapy in EC. Although, molecular classifications of EC have been proposed in the past, however they have not been implemented yet. Jones NL et al., correlated histologic types with gene mutations and described EGFR mutations in EC including mucinous subtype (Jones et al., 2017). Thoury A et al., investigated gene expression and molecular targets in low and high grade EC and proposed role of anti-EGFR agents and rapamycin derivatives (anti-m-TOR) for low grade and anti c-MET/ligand complex in high grade EC (Thoury et al., 2014). On the other hand, Jones NL et al., suggested hormonal receptors, as well as genes implicated in cell proliferation, DNA repair, and cell cycle pathways as possible therapeutic targets in EC (Jones et al., 2015)

In addition to the prognostic significance of EGFR, predictive role of EGFR in anti-EGFR targeted therapy was also suggested in a few studies. Nishimura T et al., proposed possible role of Erlotinib in EGFR over-expressed EC (Nishimura et al., 2015)

The main limitation of the study was that long term follow-up of the patients was not available to evaluate association of EGFR expression with recurrence and disease free survival. In addition, the number of cases of non-endometroid cancers was low. Therefore, we recommend large scale studies to evaluate EGFR expression in endometrial carcinoma in our population.

Conclusion

Overall, we found a low EGFR expression in endometrial carcinoma in our population without any significant pathological association except for its high expression in serous carcinoma and carcinosarcoma, however, more large scale studies are warranted to validate these findings.

Abbreviations

EGFR: Epidermal growth factor receptor; IHC: Immunohistochemistry

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Availability of data and materials

Please contact author for data requests.

Authors' contributions

AAH, ZFH and MI: main author of manuscript, have made substantial contributions to conception and design of study. MN, SKH, HA, SB and NF: been involved in drafting the manuscript, revising it critically for important intellectual content. MN, SKH, HA, SB and NF have been involved in analysis of the data and gave final approval and revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics committee of Liaquat National Hospital, Karachi, Pakistan approved the study. Written informed consent was obtained from the patients for the participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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