IJPRP

Indian Journal of Pathology: Research and Practice
Volume 7 Number 11, November 2018
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.71118.8

Original Research Article

Histomorphology and Immunohistochemistry in Endometrial Carcinomas

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Received on 09.10.2018,
Accepted on 31.10.2018

Abstract

Context: Endometrial carcinoma is one of the most common malignancies occurring in postmenopausal females. Endometrial carcinomas are of two types, type I and type II. Type I is the most common encountered type of endometrial carcinoma. *Aim:* The aim of this study was to study the spectrum of histomorphology of endometrial carcinomas with special reference to immunohistochemical findings including ER PR and p 53. *Methods and Material:* This was a prospective study conducted over a period of eighteen months. Thirty cases of endometrial carcinomas were included in the study. The diagnosis of endometrial carcinoma was confirmed after microscopic examination. Immunohistochemical expression of ER, PR and P53 was studied. *Statistical analysis:* Correlation between the histopathological results and immunohistochemistry results were calculated by using chi-square tests and test of sample proportion. *Results:* The association of histologic type I of endometrial carcinoma with estrogen receptor and progesterone receptor was significant with the p value less than 0.01 and 0.05 respectively. The association of histologic type II of endometrial carcinoma with p53 was significant with the p value less than 0.05. *Conclusion:* In the present study, significant association was noted between estrogen and progesterone receptor in type I endometrial carcinoma and between type II endometrial carcinoma and p53. The expression of ER and PR were found to be related to disease recurrence, reports suggest that ER, PR and p53 status, as determined by IHC, can be used as an independent predictor for disease recurrence.

Keywords: EndometrialCarcinoma;Types;Immunohistochemical Study of ER; PR P53.

Introduction

Endometrial carcinoma is the 4th most common among the carcinomas in women, and accounts for 6% of female cancers with 75% cases occurring in postmenopausal women with an average age being

61 years [1]. Most commonly the patients presented with postmenopausal bleeding.

Endometrial carcinoma accounts to 150,000 new cases per worldwide with 7,470 deaths per year [1]. Endometrial carcinoma has an incidence of 2,88,387 cases worldwide. It is one of the commonest invasive carcinoma of the female genital tract constituting 5.9 cases per 100,000 per year with a mortality rate of 1.7 per 100,000 in India [1].

These neoplasms accounts for 7% of all invasive cancers in women excluding skin cancer [2]. It constitutes the second most common malignancy in females next to cervical carcinomas. The difference noted in epidemiology, presentation and biologic behavior of the endometrial carcinomas suggest that there are two fundamentally different pathologic types of disease.

Endometrial carcinoma has two basic clinicopathologic forms, type I and type II. Type I carcinomas occur in the younger age, in the background of hyperplastic endometrium [3,4,5]. They account for 80-85% of all endometrial carcinomas and are generally low grade. They result from unopposed estrogenic stimulation and prognosis is generally good with a five year survival of 80% or better.

Type II carcinomas are high grade neoplasms which occur in the older age in the background of atrophic endometrium and are not related to sustained estrogen stimulation [6,7,8]. They account for 15%-20% of all endometrial carcinomas and occurs in postmenopausal women. They show high degree of nuclear pleomorphism, deeper myometrial invasion with increased lymphatic spread and decreased sensitivity to progesterone.

Endometrioid carcinoma like any other adenocarcinoma expresses pancytokeratins and glycoprotein associated markers CA125 [4], Ber-EP4 [9,10] B72.3 [11]. Nearly all endometrioid carcinomas are CK 7 positive and CK20 negative [10,11,12].

Type I carcinomas show expression of ER, PR, Bcl2, Beta catenin and PTEN whereas uterine papillary serous, clear cell carcinomas show immunopositivity for p53, p16 and Ki67.

In Type l carcinomas, ER and PR will be positive and the treatment consisting of hysterectomy will be sufficient, whereas in cases of Type II carcinomas (since the tumor is aggressive) p53 will be positive, hence along with hysterectomy, the need for chemotherapy and radiotherapy and further follow up arises. Some cases of endometrial carcinomas may appear endometrioid (Type l) in histology but when correlated with immunohistochemistry appears that of high grade or mimics that of Type II hence the difference in the management of the patient.

In our study, the histomorphology of endometrial carcinoma were confirmed with immunohistochemistry using the panel of markers constituting ER, PR and p53.

The following were the objectives of this study

1. To correlate the clinical features and histopathological features of endometrial carcinoma.

2. To analyze the spectrum of histopathological features of endometrial carcinomas.

3. To correlate the expression of ER, PR and p53 with the histopathological grade of endometrial carcinomas.

Subjects and Methods

This study was a prospective study conducted over a period of eighteen months from February 2013 to July 2014 at Coimbatore Medical College and Hospital, Coimbatore, India. The ethical clearance was obtained from the Institutional Ethics Committee.

Thirty cases of endometrial carcinomas were analysed. All specimens of endometrial carcinomas received in the department were included in the study. Patients who received prior radiotherapy and chemotherapy and cases of endocervical carcinomas were excluded from the study.

Processing and staining

The endometrial specimens were fixed in 10% formalin and subjected to routine tissue processing and 4-6 μm were cut on a glass slide for routine Haematoxylin and Eosin staining. The diagnosis of endometrial carcinoma were made by analysing characteristic histopathologic features.

Sections were then deparaffinized in xylene and dehydrated in graded alcohol and water. Antigen retrieval was done. Sections were treated with peroxide block followed by application of primary antibody (supplied by biogenex) and superenhancer. Then DAB chromogen was applied with substrate buffer and counterstaining was done with Haematoxylin.

Evaluation

The slides were examined and the immunohistochemical reactivity was evaluated:

Positive staining of both ER and PR was seen as fine granular staining in nuclei of glands and stroma. A total of 100 cells were counted under oil immersion and semi-quantitative grading of staining was done as absent 0, Weak 1, Moderate 2, Intense 3.

An immunohistochemical score was calculated as Σ Pi (i+1) [13]

{i=intensity (0, 1, 2, 3) and Pi = percentage of stained cells (0–100%) of each

tissue component (glands/stroma) in each intensity category}. Tumours were divided into three categories depending on the immunohistochemical score. Category I corresponded to a score of 2, Category II to a score of 3 or 4, and Category III to a score of 5 or 6.

p53 staining

The reaction for p53 was recorded as percentage of tumour cells showing nuclear staining.

Statistical analysis

Correlation between the histopathological results and immunohistochemistry results were calculated by using chi-square tests and test of sample proportion.

Results

Age distribution

Usually endometrial carcinomas are found to be distributed in postmenopausal age group which in the present study constitutes 76.66%, the remaining were found to be perimenopausal and premenopausal comprising 23.33%.

In our study, the mean age of patients with endometrial carcinoma was 52.7 years. Most common age group according to the present study is 50-69 years.

According to the present study population, women in their postmenopausal age group were more vulnerable to develop endometrial carcinomas than women in the other age group.

Presentation

The most common presentation of endometrial carcinomas was bleeding per vagina followed by pain abdomen, amenorrhea, menorrhagia, mass per abdomen and difficulty in passing urine.

The depth of invasion of endometrial carcinomas were found confined to less than half of the myometrium or there was minimal involvement of the myometrium in around 60% of the cases. About 40% of the cases showed more than half of the myometrial invasion.

Architectural pattern

Most common architectural pattern in the present study is the admixture of cells arranged in glands and sheets comprising 40%, next in the grading were tumours composed entirely of glands consisting of 30% and then 26.67% of the tumours were entirely composed of sheets / solid pattern.

Types

In the present study, type I constituted 53.33% which is the most common histologic type among endometrial carcinomas and 46.66% were among type II (Table 1).

Expression of ER: In the present study, out of 16 cases in type I -13 cases were positive and 3 cases were negative, compared to the 14 cases of type II wherein 3 cases were positive and 11 cases were negative (Table 2 and Table 5).

Table 1: Showing the number of Type I and Type II Carcinoma Cases in our Study

Histologic Type	Number of Cases	Percentage
Type I carcinoma	16	53.33%
Type II carcinoma	14	46.66%

Table 2: Expression of Estrogen Receptor in Type I and Type II Endometrial Carcinoma

Expression of Estrogen Receptor	Number (Percentage) of Positive Cases	Number (Percentage) of Negative Cases
Type I	13 (81.25%)	03(18.75%)
Type II	03(21.43%)	11(78.57%)

Expression of PR: In the above study out of 16 cases in type I - 12 cases were positive and 4 cases were negative compared to 14 cases of type II wherein 4 cases were positive and 10 cases were negative(Table 3 and Table 6).

Expression of p53: In the present study out of 16 cases in type I – 7 cases were positive constituting 43.75% and 9 cases were negative which constitutes 56.25%, compared to 14 cases of type II – 11 cases were positive comprising 78.57% and 3 were negative constituting 21.43% in type II (Table 4 and Table 7).

The association of histologic types with estrogen receptor was tested using chi-square analysis, the value was found to be 10.75 with the p value less than 0.01 (significant at 1% level) which implies a significant association between the type I carcinoma and expression of estrogen receptor.

The association of histologic types with progesterone receptor was tested using chi-square analysis, the value was found to be 6.53 with the p value less than 0.05 (significant at 5% level) which implies a significant association between the type I carcinoma and expression of progesterone receptor.

The association of histologic types with p53 was tested using chi-square analysis, the value was found to be 3.77 with the p value less than 0.05 (significant at 5% level) which implies a significant association between the type II carcinoma and expression of p53.

Table 3: Expression of Progesterone Receptor in type I and type II Endometrial Carcinoma

Expresssion of Progesterone Receptor	Number(Percentage) of Positive Cases	Number(Percentage) of Negative Cases
Type I	12(75%)	04(25%)
Type II	04(28.75%)	10(71.42%)

Table 4: Expression of p53 in type I and type II endometrial carcinoma

Expression of P53	Number(Percentage) of Positive Cases	Number(Percentage) of Negative Cases
Type I	07(43.75 %)	09(56.25%)
Type II	11(78.57%)	03(21.43%)

Table 5: Expression of ER by immunohistochemical score

	Negative	Positive		Total
	Category 1	Category 2	Category 3	
Type I	03	05	08	16
Type II	11	02	01	14

Table 6: Expression of PR by immunohistochemical score

	Negative	Positive		Total
	Category 1	Category 2	Category 3	
Type I	04	05	07	16
Type II	10	02	02	14

Table 7: Expression of p53 by immunohistochemical score

	Negative Negative	Positive	Total
Type I	9	7	16
Type II	3	11	14

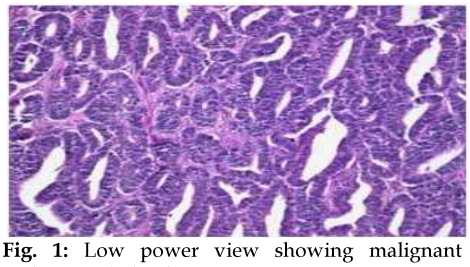

Fig. 1: Low power view showing malignant endometrial gland

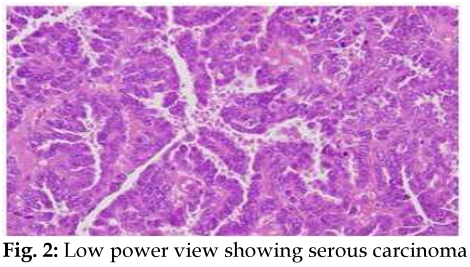

Fig. 2: Low power view showing serous carcinoma

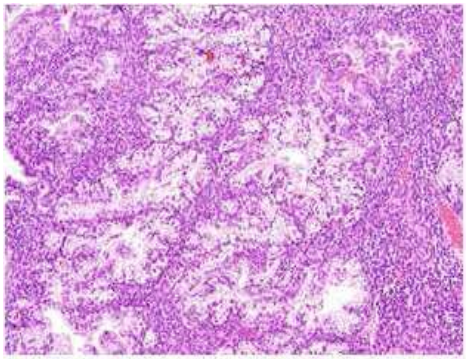

Fig. 3: Low power view showing clear cell variant

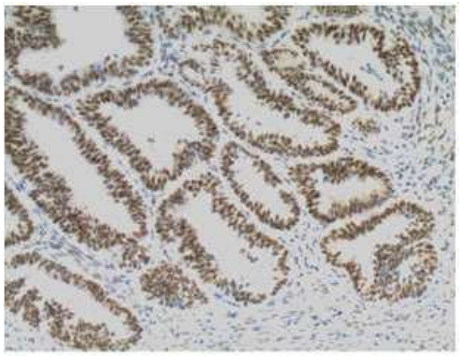

Fig. 4: Low power showing ER positivity in endometrial glands

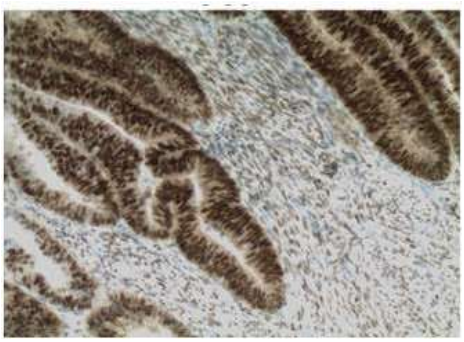

Fig. 5: Low power view showing PR positivity

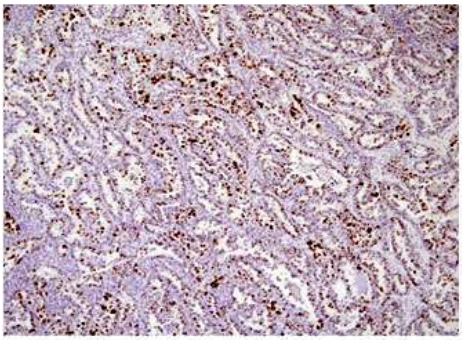

Fig. 6: Low power showing clear cell carcinoma demonstrating p53 positivity

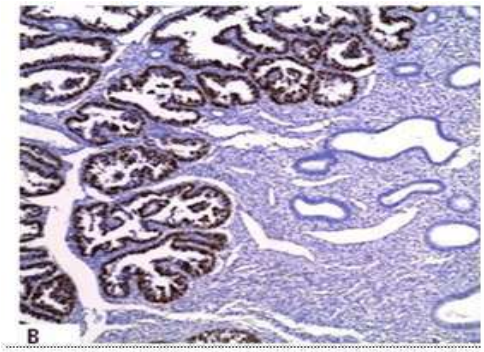

Fig. 7: Low power showing p53 positivity in serous carcinoma

Discussion

Endometrial carcinomas are class of neoplasms in which pathologic factors play an important role in determining the prognosis of the patient. Basically endometrial carcinomas are of two types: type I- estrogen dependent tumours and type II – non estrogen dependent tumours.

Type I are usually seen in premenopausal and perimenopausal women in patients with hyperplastic endometrium, usually does not involve the myometrium. Most of them are well to moderately differentiated and rarely presents with distant metastasis and hence usually have a better prognosis.

In comparison to type II which is usually seen to occur in females little older than the estrogen dependent type. They are usually of higher grades and presents with distant metastasis and are associated with poor prognosis.

Type I tumours appeared to be steroid hormone receptor positive and they show immunopositivity for ER and PR. But as the grade of the tumour increased, there immunopositivity decreased. In contrast to higher grade tumours which showed p53 positivity and less immunopositivity to ER and PR.

There are few well established prognostic factors which includes, stage of the tumour, grade of the tumour and the depth of invasion of the myometrium.

Recently nuclear grade of the tumour and vascular invasion of the tumour were also recognized as important prognostic factors.

The advent of immunohistochemistry proved to be of significance in many malignancies like the breast, soft tissue tumours etc., to arrive to a diagnosis and were helpful in the management of the patients.

There are numerous studies showing inverse correlation between the steroid hormone receptor status and the grade of the tumour and direct relationship of p53 positivity with higher grade of tumours.

In the present study: A total of thirty cases of endometrial carcinomas were studied histologically and the immunohistochemistry expression for ER, PR and p53 were correlated. Among the thirty cases sixteen were type I and fourteen were type II.

The association of histologic types with estrogen receptor was tested using chi-square analysis, the value was found to be 10.75 with the p value less than 0.01 (significant at 1% level) which implies a significant association between the type I carcinoma and expression of estrogen receptor.

According to Halperin R [14], et al. a study of 64 cases on endometrial carcinomas - ER positivity was observed in 85.7%.

As per Sidonia Catalina Stoian [15] et al. a retrospective analysis on endometrial carcinomas, ER positivity was seen in 86.3% of the cases and 13.4% of the cases were found to be negative.

The association of histologic types with progesterone receptor was tested using chi-square analysis, the value was found to be 6.53 with the p value less than 0.05 (significant at 5% level) which implies a significant association between the type I carcinoma and expression of progesterone receptor.

According to Halperin R, et al. [14], a study of 64 cases on endometrial carcinomas showed PR positivity in 78.6%.

Sidonia Catalina Stoian [15] et al. analysed 22 cases retrospectively and observed 81.1% of the cases to be positive for PR while 18.9% of the cases were reported to be negative.

Expression of p53

In the present study, from a total of 16 cases in type I (endometrioid type) – 7 cases were positive constituting 43.75%.

The proportion of p53 cases between type I and type II were compared using test of sample proportions, the critical ratio was 1.942 which is less than the table value of 1.96 at 5% level suggests that the two sample proportions are not significantly different.

A study conducted by Nicola Ragina [16] et al., on 240 specimens of endometrial carcinomas showed that nearly 100% of the uterine papillary serous tumours were positive for p53 when compared to 60% of the endometrioid tumours. There was a trend for immunopositivity in advanced stage tumours constituting 86.2% while compared to 64.3% in early stage tumours. However no correlation between the expression of p53 and the histological grade has been made so far. Positive p53staining was observed in 111 of the 182 (61%) endometrioid tumours and in 47 of the 58 (81.0%) non-endometrioid tumours. p53 expression was significantly higher in papillary serous carcinomas than in the endometrioid type.

According to Ozsaran [17] AA et al., p53 staining was detected in 20 out of the 35 cases of endometrial carcinoma. Eleven of the 21 endometrioid tumors stained positive, while 9 out of 14 tumors with more aggressive histology stained positive for p53.

The expression of ER and PR were found to be related to disease recurrence, reports suggest that ER, PR and p53 status, as determined by IHC, can be used as an independent predictor for disease recurrence.

Limitation

The numbers in this study were small to make a definitive statement on the importance of hormone receptors and p53.

Conclusion

The status of steroid hormone receptor in breast carcinomas has been well documented but in the breast tissue only low levels of estrogen receptors unlike the endometrium which will have considerable amount of these receptors normally. Hence by using immunohistochemical studies the distribution of proportion in each tissue element can be assessed and measured in a semiquantitative manner.

The presence of ER and PR provides a hope for the likelihood of the response to therapy for endometrial carcinomas. The presence of p53 points to an aggressive form of the tumour which will need further follow up of the patients with extensive surgery, hence tumours which might be of low grade in histopathology might show positivity for p53 in immunohistochemical studies implying the varying molecular genetics of the endometrial carcinomas.

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