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Case Series

A case series on endometrial cancer in multipara and their prognostication based on IHC markers

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ABSTRACT

Endometrial carcinoma is one of the leading gynecological malignancies across the globe. With advent of molecular analysis, establishing an accurate treatment plan and improving patient outcome has become eminent. In resource limited settings like India, surrogate IHC markers like hormonal receptor expression are congruous substitutes that aid to accurately predict patient prognosis. In this case series, expression of hormonal receptors in multiparous women and it's association with patient outcome seen as disease free survival at a span of 2 years was compared. This study opines inclusion of hormonal receptors in evaluation of endometrial carcinoma patients to accurately comment on patient outcome.

1. Introduction

Endometrial cancer ranks third after cancer cervix and cancer ovary in India with an incidence of 1.2% and mortality rate of 0.75% (GLOBOCON2022).[1] Despite an increasing trend in the incidence of endometrial carcinoma, a low mortality rate is ascribed to the fact that >80% endometrial cancers present as post menopausal bleeding when confined corpus uteri. The conventional histopathological classification of endometrial carcinoma given by Bokhman is now considered inadequate to predict patient outcome. The ProMise trial proved that molecular subgroups given by TGCA were present across all the histological types and were associated with patient prognosis, influencing clinical outcomes. India, being a resource limited settings, hormonal receptors used as surrogate immunohistochemical markers, seems to be appealing due to the well established role of ER that aids endometrial proliferation under the mitogenic effect of estrogen and PR that promotes endometrial differentiation under the influence of progesterone.[2] Therefore estrogen receptor, progesterone receptor, and combined estrogen receptor/progesterone receptor status were significant independent prognostic factors, replacing histologic assessment of glandular or nuclear differentiation.[3]

Various studies on breast cancer and its association with parity have proved that increased parity increases the expression of estrogen receptors thus influencing treatment modality and patient outcome. Although endometrial carcinoma is most often associated with infertility and nulliparity,[4,5] in this case series we have tried to establish a similar correlation, wherein increased parity, which increases hormonal receptor expression and therefore have favourable outcome.[6]

In this study, histologically confirmed cases of endometrial carcinoma, operated and followed in the institute, were chosen. All postoperatively obtained specimens were subjected to histological examination

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and were designated histological staging according to the revised FIGO staging for endometrial carcinoma 2023 update.[7] Histopathological slides fixed in 10% formalin were subjected to Immunohistochemical staining. Primary antibodies used included ER(alpha) and PR by Dako manufacturers. Evaluation was based on Allred scoring.

2. Objective

To analyse the expression of hormonal receptors in histologically confirmed cases of endometrial carcinoma in multiparous females and its relation with patient prognosis.

3. Case 1

1. A 66 years old, P3L3, known case of diabetes and hypertension with post menopausal bleeding underwent hysteroscopic dilation and curettage which confirmed endometrioid adnecarcinoma.
2. She underwent Modified Radical Hysterectomy. Specimen was extracted sent for histological examination which suggested villoglandular type of adenocarcinoma with involvement of inner half of myometrium with no lymphovascular space invasion and pelvic lymph nodes free of tumor, designated FIGO Stage 1A2. Histopathology slides subjected to immunohistochemistry for ER α and PR were strongly positive for the expression of both the receptors.
3. Her postoperative course was uneventful. 2yrs follow up gynecological examination suggested no abnormality. She was referred to Cancer center for 2 cycles of External beam radiation therapy. Telephonic follow up suggested no complaints.

4. Case 2

1. A 45 year old P1L1, known case of hypertension presenting with heavy menstrual bleeding and simple hyperplastic endometrial polyp, was histologically confirmed case of complex endometrial hyperplasia with atypia on hysteroscopic dialation and curettage.
2. She underwent total abdominal hysterectomy with bilateral salphingoopherectomy. Specimen retrieved was sent for histopathological examination post operatively. Reports suggested: villoglandular type of adenocarcinoma with no involvement of myometrium, lymphovascular space or lymph nodes. FIGO stage 1A was assigned to this patient. Immunohistochemistry performed on specimen slides stained weakly positive for hormonal receptors. Post operatively patient required resuturing of her wound and was discharged after appropriate wound care.
3. Patient was followed up for two years, wherein she had no complaints, her gynecological examination suggested no abnormality and her follow up MRI revealed no recurrence of the disease.

5. Case 3

1. A67 year old P1L1, known case of hypertension and diabetes, presenting with post menopausal bleeding was histologically confirmed to have adenocarcinoma on hysteroscopic dialation and curettage.
2. She underwent modified radical hysterectomy and her postoperative specimen was subjected to histopathological examination which revealed well differentiated Adenocarcinoma with no involvement of myometrium, lymphovascular space or lymph nodes. FIGO Stage 1A was assigned to this patient and her slides were were subjected to immunohistochemical staining. These stained positive for both ER and PR receptors. Her post operative period was uneventful and patient was not advised any further investigation.
3. She had 2 follow visits in one year span, wherein she didnot have any new complaints and her examination showed no signs of recurrence.

6. Case 4

1. A 66 year old, P2L2, known case of hypothyroidism with postmenopausal bleeding was histologically confirmed case of endometrioid adenocarcinoma.
2. She was posted for Modified Radical Hysterectomy and specimen was sent for histological examination postoperatively. Her histopathological report suggested well differentiated endometrioid adnecarcinoma, with inner myometrium involved. Lymphovascular space and lymph nodes were free of tumor and the patient was designated Stage 1A1. Her immunohistochemistry for hormonal markers was strongly positive for ER α and PR. Her post operative course was uneventful.
3. She was followed up for 2 yrs, during which she had no complaints, her gynecological examination revealed no abnormality and her USG and FDG scans revealed no recurrence off tumor.

7. Case 5

1. A 44 years old, P1L1, with heavy menstrual bleeding not relieved by medications, was histologically confirmed to have endometrial hyperplasia with foci of atypia on hysteroscopic dialation and curettage.
2. She underwent total abdominal hysterectomy with bilateral salphingoopherectomy and the specimen obtained was sent for histological examination and immunohistochemical staining. Histopathology report suggested well differentiated Adenocarcinoma with no involvement of myometrium, lymphovascular space or lymph nodes and FIGO stage 1A1 was assigned to her. IHC markers stained focally positive for both the hormonal receptors. Her post operative course was uneventful.

3. She was followed up for 2 years. She had no complaints and her gynecological examination revealed no signs of recurrence.

8. Case 6

1. A 49year old, P3L3, known case of diabetes with hepatic cyst, with postmenopausal PV spotting, was histologically confirmed to have well differentiated Adenocarcinoma following on hysteroscopic dialation and curettage.
2. She underwent Modified Radical Hysterectomy with omental biopsy and the specimen was sent for histological examination. Reports suggested villoglandular type of adenocarcinoma with adenomyosis of myometrium. No LVSI or lymph nodes involvement was seen and she was assigned FIGO Stage 1A1. Her IHC markers were strongly positive for ER α and PR. Her post operative course was uneventful.
3. She was followed up for 2 years during which she had 4visits. She had no complaints and her gynecological examination revealed no abnormality. Her repeat CT scan revealed hepatic cyst with no recurrence of the disease.

9. Case 7

1. A 61years old, P2L2, hypertensive and obese (BMI: 35) patient, complaining of post menopausal bleeding was histologically confirmed to have papillary endometrial adenocarcinoma on hysteroscopic dialation and curettage..
2. She was posted for Modified Radical Hysterectomy. Her specimen examined histologically showed papillary endometrial adenocarcinoma with no involvement of myometrium or lymphovascular space, however one pelvic lymph node involvement was seen and she was assigned FIGO stage 3C1. She was stained ER α and PR negative on immunohistochemistry. Postoperatively she developed DVT with hyperkalemia.
3. She was followed up for 2 years, wherein, she received 3 cycles of chemoradiation therapy. She had no complaints and her gynecological examination suggested no abnormality.

10. Case 8

1. A 47 year old P3L3, known case of diabetes and hypertension, with the complaints of foul smelling PV discharge, with pap smear suggesting Low-grade squamous intraepithelial lesion was histologically confirmed to have moderately differentiated Adenocarcinoma along with adenosquamous carcinoma of cervix on hysteroscopic dialation and curettage with cervical biopsy.
2. Modified Radical Hysterectomy was performed postoperative specimen was histologically examined to reveal moderate to poorly differentiated Adenocarcinoma with inner half of myometrium involved. No LVSI or lymph node involvement was noted. She was designated FIGO Stage 1A. IHC staining was strongly positive for hormone receptors (ER α and PR).
3. After an uneventful postoperative course, patient was followed up for 1year during which she had 2 visits which revealed no evidence of recurring disease. She was followed up for another one year telephonically for which she had no complaints and her repeat USG suggests no recurrence of the disease.

11. Case 9

1. A 53 year old, P3L3, known case of hypertension, came with postmenopausal bleeding. Histopathology report on hysteroscopic dialation and curettage confirmed endometrioid adnecarcinoma.
2. She was posted for Modified Radical Hysterectomy. Specimen sent for histopathological examination suggested well differentiated endometrioid adnecarcinoma with inner half of myometrium involved and no lymphovascular space invasion. Her pelvic lymph nodes were free of tumor and she was designated Stage 1A2. On IHC staining, her slides were strongly positive for both hormonal receptors.
3. After discharge, she received 3 cycles of external beam Radiation therapy. She had regular visits wherein her gynaecological examination revealed no abnormality and her USG showed no recurrence of the disease.

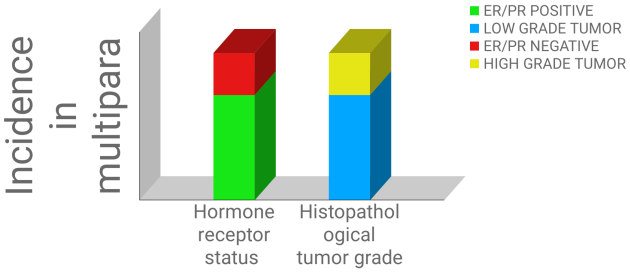

Figure 1:

12. Case 10

1. A 53 years old P4L3D1A1, known hypertensive and diabetic, complaining of post menopausal bleeding, was histologically confirmed case of villoglandular adenocarcinoma on hysteroscopic dialation and curettage.

Table 1:

Case no.	Parity	FIGO Stage	HPE type	ER status	PR status	Additional therapy	2 years survival
1	P3L3	1A2	Villoglandular	Strongly positive	Strongly positive	EBRT 2 cycles	No recurrence
2	P1L1	1A	Villoglandular	Weakly positive	Weakly positive	Nil	No recurrence
3	P1L1	1A	Well differentiated Adenocarcinoma	Positive	Positive	Nil	No recurrence
4	P2L2	1A1	Well differentiated Adenocarcinoma	Strongly positive	Strongly positive	Nil	No recurrence
5	P1L1	1A1	Well differentiated Adenocarcinoma	Focally positive	Focally positive	Nil	No recurrence
6	P3L3	1A1	Villoglandular	Strongly positive	Strongly positive	Nil	No recurrence
7	P2L2	3C1	Papillary endometrial carcinoma	Negative	Negative	3 cycles of chemoradiation	No recurrence at present
8	P3L3	1A	Moderate to poorly differentiated Adenocarcinoma	Strongly positive	Strongly positive	Nil	No recurrence
9	P3L3	1A2	Well differentiated Adenocarcinoma	Strongly positive	Strongly positive	EBRT 3 cycles	No recurrence
10	P4L3D1A1	2C	Papillary serous endometrial cancer	Negative	Negative	EBRT 3 cycles Chemotherapy 3 cycles	No recurrence at present

2. Modified Radical Hysterectomy was performed and specimen underwent histological examination and immunohistochemical staining. Reports revealed papillary serous endometrial carcinoma with more than half myometrium involvement and presence of lymphovascular emboli. Lymph nodes were free of tumor. She was assigned FIGO Stage 2C. Further, IHC markers stained negative for both hormonal receptors. Postoperatively she developed deep vein thrombosis and was discharged after treating the same..
3. She was followed up for 9 months, wherein she received 3 doses of external beam radiation therapy and 3 cycles of chemotherapy and her examinations suggested no recurrence. She has no complaints on telephonic follow up thereafter.

13. Discussion

Multiparous and primiparous cases, matched for their specific ages, have been compared for histological stage, hormonal receptors status and 2years prognosis. The most common associated comorbidity seen across all the cases is hypertension followed by diabetes. Most of these patients presented with post menopausal bleeding and were evaluated according to ACOG guidelines.[8] Modified Radical Hysterectomy was the chosen operative modality complying ESMO guidelines, for most of them. Cases 1, 2, 3, 4, 5, 6, 8 and 9 had tumors confined to uterine corpus with none to less than half myometrium involvement and no lymphovascular space or lymph node involvement, suggesting these were low grades of Endometrial carcinoma. Out of these, only three patients including cases 2, 3 and 5 are primiparous, while cases 1, 4, 6, 8 and 9 are multiparous. IHC staining amongst these low grade tumors showed a strongly positive staining for both the hormonal receptors in multiparous women compared to weak and focal positivity seen in primiparous females. In contrast to the study of Anna et al,[9] this uniformly implied lower stage seen amongst multiparous females in our study. Multiparous females in case 7 and 10 were seen to have higher stage of Endometrial carcinoma, 3C1 and 2C, respectively. However these cases were stained negative for both the hormonal receptors. These cases were also associated with increased risk of postoperative deep vein thrombosis. Our findings are consistent with the study of Tomica et al that suggested ER/PR expression in endometrial Carcinoma has a favourable prognosis.[10]

Primiparous cases had variable staining for ER and PR receptors. Histologically these patients had lower grade of tumor. These patients have 2yrs of disease free survival.

Amongst multiparous patients having staining strongly positive for both hormonal receptors, lower histological stage was noticed. These had a uniform pattern of Co-expression of ER and PR receptors. 2 cases with stage 1A2 disease required external beam radiation therapy while others were routinely followed up at a 6 monthly interval. For 3 out of 5 patients, transabdominal ultrasound was the radiological modality used to asses any recurrence and 1 patient underwent CT scan. An uneventful postoperative

period and disease free survival of 2 years was seen across all of these cases.

Multiparous females staining negative for ER and PR, noticed to have higher stage of endometrial carcinoma, were advised minimum 3 doses of additional chemoradiation therapy. Disease free survival of 2years is consistently seen in these patients as well.

14. Conclusion

Multiparous females with hormone receptors positive tumors, by virtue of higher parity, express more number of hormonal receptors. These also have uniform pattern of co-expression of ER and PR receptors and thus have well differentiated endometrial carcinomas detected at an earlier stage and with 2 yearly favourable outcome. Our study conceeds with the opinion expressed in the study of Guan et al[11] to integrate immunohistochemical evaluation with hormonal receptors for better patient prognostication. However, extended follow up is needed to comment on the prognosis of higher grade tumors and hormonal receptor negative tumors.

15. Source of Funding

None.

16. Conflict of Interest

None.

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