Type II endometrial cancers: A case series

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ABSTRACT

Introduction: Endometrial carcinoma ranks 3rd in India among gynecological malignancies. Endometrial cancer (EC) can be classified into two distinct groups – type I and type II, based on histology, which differs in molecular, clinical and histopathological profiles. Type II is nonestrogen dependent, nonendometrioid, more aggressive and carries poor prognosis. Although type II cancers contribute only about 10% of EC incidence, they present at advanced age and cause approximately 50% recurrence and deaths with a low 5-year, overall survival rate. Type II EC are also characterized by genetic alterations in p53, human epidermal growth factor-2/neu, p16 and E-cadherin.
Materials and Methods: Endometrial carcinomas diagnosed from endometrial biopsies and hysterectomy specimens received in the Department of Pathology, Kasturba Medical College, Mangalore, from January 2007 to June 2012 were included in the study. Clinicopathological analysis of the 84 cases of EC was done with emphasis on morphology. p53 immunostaining was performed in two cases of serous carcinoma.
Results: Out of a total of 84 cases of EC, ten cases were of type II (11.9%). Out of which, eight were serous carcinoma (9.5%) and two clear cell (2.4%). p53 immunostain was strongly positive in the serous papillary carcinomas. The age of the patients ranged from 45 to 75 years. Myometrial invasion was more than half. Treatment was hysterectomy followed by aggressive chemotherapy.
Conclusion: Of the type II EC, serous carcinoma is the most common type. Clinical presentation and prognosis differs in comparison to type I EC, thus the recognition of this type of EC is pivotal.

Key Words: Clear cell carcinoma, serous papillary, type II endometrial cancer

INTRODUCTION

Endometrial carcinoma ranks 3rd in India amongst the gynecological malignancies.[1] Endometrial cancer (EC) can be classified into two distinct groups – type I and type II, based on histology, which differs in molecular as well as in clinical and histopathological profiles.[2] Type II is nonestrogen dependent, nonendometrioid, with higher grade histologies, more aggressive and carries an adverse prognosis.[3,4] Although type II cancers contribute only about 10% of EC incidence, they present at advanced age

and cause approximately 50% recurrence and deaths with a low 5-year, overall survival rate of 35%.[5,6] Type II cancers typically arise in an atrophic endometrial background, and often have deep myometrial penetration and demonstrate lymph node spread. Type II EC is also characterized by genetic alterations in p53, human epidermal growth factor (HER)-2/neu, p16 and E-cadherin.[7]

MATERIALS AND METHODS

Endometrial carcinomas diagnosed from endometrial biopsies and hysterectomy specimens received in the Department of Pathology, Kasturba Medical College,

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Mangalore, from January 2007 to June 2012 were included in the study. All specimens were fixed in 10% neutral buffered formalin and paraffin embedded for histological examination with hematoxylin and eosin staining. The clinicopathological analysis of the cases of EC was done with emphasis on morphology. p53 immunostaining was performed in two cases of serous carcinoma; using mouse monoclonal antibody. p53 immunoreactivity was regarded as positive when brown staining was localized to the tumor cell nuclei.

RESULTS

During the study period, a total of 84 cases of EC were reported. Of these, ten cases were classified as type II EC (11.9%) as per histology. Out of which, eight were serous carcinoma (9.5%) and two clear cell (2.4%). The age of the patients ranged from 45 to 75 years, with mean age being 62 years. Grossly, the type II EC frequently appeared bulky on a background of an atrophic endometrium, with tumor filling almost the entire cavity [Figure 1]. Myometrial invasion was more than half in seven of the cases. p53 immunostain was performed in two of the serous papillary carcinomas which showed strongly positive (>75% of tumor cells nuclei) staining in the nuclei. The tumor, node, metastasis staging and FIGO staging (2008) was done for all the cases, with four cases of stage III disease [Table 1].

Treatment was surgical hysterectomy in all cases, with one case being followed with aggressive chemotherapy due to metastases in the liver.

DISCUSSION

Type II endometrial carcinomas are nonestrogen related, nonendometrioid type. These generally occur in women a decade later than type I carcinoma, and in contrast to type I carcinoma they usually arise in the setting

Figure 1: Endometrial serous carcinoma gross specimen: Uterus with fleshy tumor filling the endometrial cavity with papillary excrescences

Table 1: Clinical profile and pathological features of type II endometrial cancers

S.No	Age (years)	Nature of specimen	Diagnosis	Grade/Stage	Gross features	Myometrial invasion
1.	58	Endometrial biopsy	Endometrial serous carcinoma	FIGO Stage Ib. TNM - T1bN0M0	Multiple dark brown tissue bits	> 50%
2.	75	Endometrial curettage	Endometrial serous carcinoma	FIGO Stage Ib. TNM - T1bN0M0	Multiple dark brown tissue bits	>50%
3.	45	TAH+BSO+ lymph node dissection	Clear cell carcinoma with squamous differentiation	FIGO Stage Ib. TNM - T1bN0M0	Grey white sessile growth arising in the posterior wall near right cornua	>50%
4.	69	TAH+BSO+ lymph node dissection	Clear cell carcinoma	FIGO Stage IIIc. TNM - T3bN1M0	Bulky uterus on a background of an atrophic endometrium, with tumour filling almost the entire cavity	>50%
5.	65	TAH+BSO+ lymph node dissection	Endometrial serous carcinoma	FIGO Stage IIIc. TNM - T3bN1M0	Enlarged uterus with tumour in entire cavity	>50%
6.	64	TAH+BSO+ lymph node dissection	Endometrial serous carcinoma	FIGO Stage Ia. TNM - T1aN0M0	Fleshy endometrium with large polyp in the cavity	<50%
7.	67	TAH+BSO+ lymph node dissection	Endometrial serous carcinoma	FIGO Stage IIIc. TNM - T3bN1M0	Fleshy endometrium with papillary excrescences; tumour filling entire cavity	>50%
8.	62	TAH+BSO+ lymph node dissection	Endometrial serous carcinoma	FIGO Stage Ia. TNM - T1aN0M0	Bulky uterus on a background of an atrophic endometrium, with tumour almost filling the entire cavity	<50%
9.	59	TAH+BSO+ lymph node dissection	Endometrial serous carcinoma	FIGO Stage Ia. TNM - T1aN0M0	Fleshy endometrium with polyp in the cavity	<50%
10.	60	TAH+BSO+ lymph node dissection	Endometrial serous carcinoma	FIGO Stage IV TNM - T3bN1M1	Bulky uterus on a background of an atrophic endometrium, with tumour almost filling the entire cavity	>50%

*TAH: Total Abdominal Hysterectomy   *BSO: Bilateral salphingo-oophorectomy

of endometrial atrophy. Of the type II EC, serous carcinoma is the most common type. Endometrial serous carcinomas (ESCs) constitute only 10% of ECs but have a substantially higher case-fatality rate than their more common endometrioid counterparts.[8] This is attributable, at least in part, to the advanced stage at which many patients with ESC present.[8]

The patient's age at the time of diagnosis is often a critical factor in determining the prognosis of a patient with endometrial carcinoma.[9] Generally, endometrial carcinoma in younger women, particularly before the menopause, is associated with a 5-year survival approaching 100%. One study found a 5-year survival of 96% for women aged 40–49 years compared with only 53% for women of 70–79 years.[10] Increasing age is associated with a higher grade and stage of endometrioid tumors and the likelihood of a nonendometrioid type tumor, but this accounts for only part of the difference in survival. An additional factor may be that a relative lack of immunocompetence is more prevalent in older patients.[11] In our series too, the mean age was 62 years, and the histomorphological features were of high grade (poorly differentiated).

Out of the 84 cases of EC reported during the study period, eight were serous carcinoma and two were clear cell carcinoma. This showed that serous carcinomas were the most common type of type II ECs. This was in concordance with studies and case reviews done earlier in literature.[4-8] Uterine bleeding in the postmenopausal woman was the presenting feature in all the cases.

ESCs are morphologically characterized by a complex pattern of papillae with cellular budding, cytologic pleomorphism, frequent lymphovascular and/or myometrial invasion, and not infrequently containing psammoma bodies.[12] Histologically, clear, glycogen-filled cells and hobnail cells that project individually into lumens and papillary spaces, and large, highly pleomorphic nuclei characterize the typical clear cell adenocarcinoma.[12]

In our study, ESC showed complex, branching papillae with fibrovascular core [Figure 2]. The papillae are covered by a stratified epithelium with a prominent and characteristic tufting or budding pattern. One case also showed a glandular pattern, lined by polygonal cells. Marked nuclear pleomorphism and large macronucleoli along with occasional bizarre and hyperchromatic giant nuclei was seen. Lymphovascular invasion and deep myometrial invasion was also present. In the clear cell carcinoma, the cells had clear cytoplasm with regular cell outline. The enlarged and pleomorphic nuclei were appearing to protrude into the lumens, presenting a "hobnail" appearance.
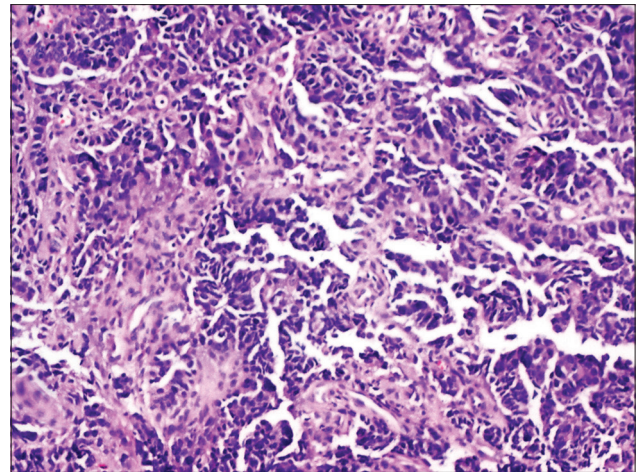

Figure 2: Endometrial serous carcinoma. Complex branching papillae (H and E; ×10)

The precursor of serous carcinoma, endometrial intraepithelial carcinoma, consists of cells identical to those of serous carcinoma but lacks identifiable stromal invasion.[13] Mutations in p53 are found in approximately 75% of these lesions, suggesting that mutation of p53 is an early event in serous endometrial carcinoma.[13] Thus, serous carcinoma presumably begins as a surface epithelial neoplasm that extends into adjacent gland structures and later invades endometrial stroma. Their generally poorer prognosis is thought to be a consequence of a propensity to exfoliate, undergo transtubal spread, and implant on peritoneal surfaces like their ovarian counterparts.

Myoinvasion is described by the presence of a constellation of features, including irregular, jagged contours of the neoplastic glands, single tumor cells or clusters in the myometrium, desmoplastic stroma, haphazard distribution of neoplastic glands in myometrium, etc.[14] Once the presence of myoinvasion is established, the depth of invasion is measured using the deepest undulation of endomyometrial junction. Other authors also advocate this approach.[14] Patients with more than 50% myometrial thickness invasion are at increased risk for extrauterine metastases, including pelvic and para-aortic lymph node metastases. These patients often require more aggressive surgical staging, which may include pelvic and para-aortic lymphadenectomy, as well as postoperative adjunctive therapy.[15] In our findings, seven of the cases (70%) had more than half of myometrial thickness invasion. One of the cases had distant metastases to the liver. For all the cases, Wertheim's hysterectomy was done. Postoperative chemotherapy was given additionally to the case with distant metastases.

The molecular changes of p53 mutation in 80–90% of serous carcinomas is reflected in p53 immunohistochemistry, which typically shows a diffuse and intense nuclear staining
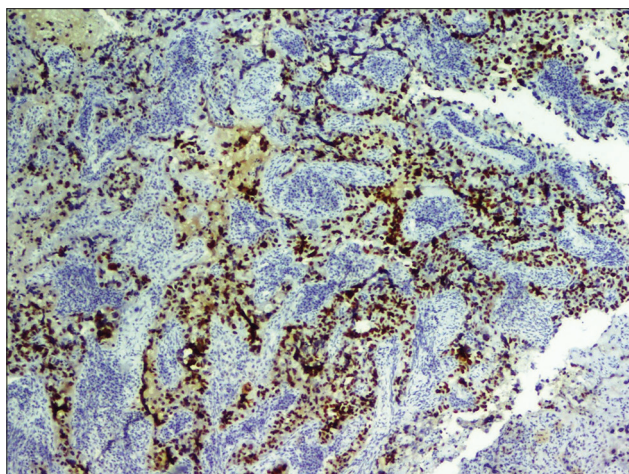
Figure 3: Endometrial serous carcinoma. Immunohistochemistry p53 staining. Diffuse strong positivity seen in the tumor cell nuclei

pattern involving almost all tumor cells.[16] In our study too, intense p53 staining was seen in 2 of the cases diagnosed as ESC and progesterone receptor marker was negative [Figure 3]. Thus, there is a significant association between p53 overexpression and ESC.

CONCLUSION

Our case series shows that the incidence of type II EC is less than that of type I. Among the type II EC, serous carcinomas are higher in number. The aggressiveness and the poorer survival rates of type II EC makes the diagnosis of this type very crucial for the histopathologist and the clinician.

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Conflicts of interest
There are no conflicts of interest.

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