EXPRESSION OF C-KIT IN BENIGN AND MALIGNANT ENDOMETRIAL LESIONS

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ABSTRACT

Objective: To examine and to compare c-kit expression in benign and malignant endometrial lesions.
Study Design: Comparative, Cross Sectional Study
Place and Duration of Study: Department of Pathology, King Edward Medical University Lahore.
Methodology: Patients undergoing Gynecological procedures (diagnostic dilatation and curettage or hysterectomies due to dysfunctional uterine bleeding). They were further sub classified into benign and malignant lesions. Patients age and histopathological diagnosis were recorded and described.
Conclusion: This study showed, c-kit over expression was seen in 31/68 (45.6%) in endometrial carcinoma and 21/68 (30.9%) in benign endometrial lesions.

Key words: *Benign Endometrial lesions, Malignant Endometrial lesions, C-kit expression*

INTRODUCTION

The common most malignancy of females is endometrial carcinoma (EC). 47,000 new cases and 8,000 deaths in 2012 among women in United States[1]. The 8th leading cause of cancer related mortality in developed world and was responsible for 8190 deaths in 2013 worldwide [2]. Its annual incidence estimated is 10–20 per 100,000 women and it is increasing, a study done at Fatima Memorial College of Medicine and Dentistry, Lahore[3]. The incidence of EC is approximately 4.3-5.9/ 100,000 women in developing countries[4]. It is the third most common malignancy accounting for 16% of all gynecological malignancies of female genital tract in developing countries of Africa and Asia including Pakistan[5]. Another study at lahore Pakistan showing endometrium cancer are 19% of all gynaecological malignancies[6].

Reproductive axis is composed of hypothalamic–pituitary–ovarian axis and the müllerian-derived organs [7]. Changes during menstrual cycle, provide environment for new embryo for its implantation and then removal of lining epithelium followed by regeneration, includes menstrual; postmenstrual repair; proliferative; and secretory phases[8].

19.1% of 20.1 million visits for gynecologic reasons towards doctors are due to menstrual irregularities in America. Commonly present with irregular menstrual bleeding or postmenopausal bleeding. Endometrial cancer patients often exhibit signs and symptoms such as postmenopausal bleeding [9].

Dysfunctional uterine bleeding (DUB) is abnormal uterine bleeding without any specific cause. FIGO classification system for DUB comprises PALM-COEIN: Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory Dysfunctions, Endometrial Disorders, Iatrogenic, and Not Classified. PALM group are (structural) entities and can be measured by visually, by histopathology and by imaging. COEIN group are (nonstructural) cannot be measured by histopathology or by imaging[10].

Endometrial malignancies are divided into two types. Type I (Endometrioid Adenocarcinoma). Continuous estrogen stimulation and followed by endometrial hyperplasia is a feature of type I EC. Type II (Serous adenocarcinoma, Clear cell adenocarcinoma, Undifferentiated carcinoma).These are not associated with estrogen stimulation and occurs in elderly patients and in atrophic endometrium[11]. EC results from a complex process, by activation of oncogenes and inactivation of tumor suppressor genes. Mutations in type I are PTEN, PIK3CA, KRAS and Beta-catenin along with microsatellite instability. Whereas mutations in type II are p53, her-2/neu, p16 and E-Cadherin[12].

Three studies have been compared for c-Kit positivity in various lesions of endometrium. In one study 65 cases were taken out of which 3/10 (30%) showed c-kit positivity in normal endometrium, 9/15 (60%) in simple hyperplasia, 5/10 (50%) in complex hyperplasia without atypia and 8/10 (80%) in complex

hyperplasia with atypia. While 8/10 (80%) in grade I and 10/10 (100%) in grade II EC[13].

The second study done on 50 cases at Department of Obstetrics and Gynecology, Malatya, Turkey showed c-kit expression 6/10 (60%) in normal endometrium, 18/18 (100%) in simple hyperplasia, 5/6 (83%) in complex hyperplasia without atypia and 7/10 (70%) in complex hyperplasia with atypia, however, is reduced as the lesion progresses that is 1/6 (16%) for EC [14].

Third study, done on 44 cases showed 11/14 (79%) positivity in secretory phase, 13/14 (93%) in proliferative phase, 4/7 (57%) in hyperplasias and 4/9 (44.44%) in EC[15].

c-Kit or stem cell factor receptor also called as CD117, is a type III receptor tyrosine kinase and involved in initiation/mediation of different signaling cascades. c-kit also seen in endometrial cells, and associated with a highly proliferative cell type and promote cell survival and migration. Gastrointestinal stromal tumors are known as c-kit positive tumors and well known mesenchymal tumor of GI tract[16]. Specific treatment targeting oncogenic KIT and PDGFRA activation has become available. Target for tyrosine kinase inhibitor therapy is used in locally unresectable and metastatic tumors. Also, used as adjuvant therapy for debulking in resectable tumors. It also prevents postoperative recurrence of tumor. Imatinib mesylate is a competitive inhibitor for kit, PDGFRA and for tyrosine kinases. And can give 80% to complete pathological response[17]. C-kit shows positivity in cytoplasm and in cell membrane. Positivity is labeled as O=negative (sporadically stained <10%), 1+=weak staining(>10%), 2+=moderate staining (focal 10-50%) and 3+=strong staining (diffuse >50%)[18].

METHODOLOGY

This study was carried out in Pathology Department KEMU, Mayo Hospital Lahore from 28-4-2016 to 30-5-2017 after approval of synopsis. The study was Comparative - Cross sectional. Approval of the study was taken by statistical committee of KEMU IRB and ASRB. A total of 136 cases were taken by non-probability purposive sampling technique. Patients undergoing histopathology of biopsy either curretings and hysterectomy, were enrolled in this study. Their demographic features i.e. age, case number and medical records were noted. The biopsies received in the Pathology Department were fixed in the formalin, processed and then slides were stained with hematoxylin and eosin stain. Histological examination was carried out by a consultant histopathologist under light microscope. They were further sub classified into benign or malignant lesions. All these information was recorded on proforma. Sample size of 136 patients (68 patients in each group) is estimated by using 90% confidence level, 10% absolute precision with expected %age of benign as 10.9%(21) and malignant as 19%(22).

Data was entered in SPSS-20. Quantitative variables like age will be presented as mean ± S.D. Qualitative variables like type of diagnosis i.e. benign and malignant and their c-kit positivity will be presented as frequency and percentages. Comparison of two groups benign and malignant apply Chi-Square. P-value ≤ 0.05 will be taken as significant.

RESULTS

The total of 136 surgical specimens of female endometrial lesions were included in the study. Out of 136, 68 (50%) were benign and 68 (50%) were malignant endometrial lesions. The mean age for malignancies was 52.66 years while minimum age noted was 25 and maximum was 85 years. Majority of the patients 73 (53.67%) with benign and malignant lesions fall within age range of 36-50 years while the second most common age range was 51-65 years i.e. 35 (25.73%).

Most common presenting complaint for endometrial carcinoma was postmenopausal bleeding 45.6% and then second most was heavy menstrual bleeding while the most common presenting complaint for benign lesions was heavy menstrual bleeding.

Out of 136 cases 86 (63.2%) were endometrial curettings and 50 (36.8%) were hysterectomy specimen. In 136 cases 52 (38.2%) turned out to be positive (2+ and 3+) for c-kit expression. The remaining 84 (61.8%) were negative (0 and 1+) for c-kit expression.

There were 16 (23.5%) Out of 68 benign cases showing secretory phase changes with 3/16 (18.8%) positive for c-kit protein, 10/68 (14.7%) were showing proliferative phase changes with 3/10 (30%) positive for c-kit protein, 19/68 (27.9%) were showing simple hyperplasia with 10/19 (52.6%) positive for c-kit protein, 12/68 (17.6%) were complex hyperplasia without atypia with (0 0%) positivity for c-kit and 11/68 (16.2%) were with complex hyperplasia with atypia shows 5/11 (45.5%) positivity for c-kit protein. Benign lesions are 21/68 (30.9%) positive and 47/68 (69.1%) negative for c-kit expression. In malignant lesions 31/68 (45.6%) were positive and 37/68 (52.4%) were negative for c-kit expression.

In malignant cases Type I endometrial carcinoma are 60/68 (88.23%) out of which 26/60 (43.3%) are positive for c-kit expression. Type II endometrial carcinoma are 8/68 (11.76%) out of which 5/8 (62.5%) are positive and 3/8 (37.5%) are negative for c-kit

expression. In endometrial carcinomas Type II includes papillary serous adenocarcinoma 4/68 (5.8%) out of which 3/4 (75%) are positive and 1/ 4 (25%) are negative for c-kit expression, Clear cell carcinoma are 2/68 (2.9%) out of which 1/2 (50%) are positive and 1/2 (50%) are negative for c-kit expression, similarly undifferentiated carcinoma are 2/68 (2.9%) out of which 1/2 (50%) are positive and 1/2 (50%) are negative for c-kit expression

Type of Diagnosis				Expression of C-Kit		Total
				Positive	Negative	Positive
Type I Endometrial Carcinoma	Histological Diagnosis	Endometrioid Adenocarcinoma	Count	26	34	60
			Expected Count	26.0	34.0	60.0
			% within Histological Diagnosis	43.3%	56.7%	100.0%
	Total		Count	26	34	60
			Expected Count	26.0	34.0	60.0
			% within Histological Diagnosis	43.3%	56.7%	100.0%
Type II Endometrial Carcinoma	Histological Diagnosis	Papillary Serous Adenocarcinoma	Count	3	1	4
			Expected Count	2.5	1.5	4.0
			% within Histological Diagnosis	75.0%	25.0%	100.0%
		Clear Cell Adenocarcinoma	Count	1	1	2
			Expected Count	1.3	.8	2.0
			% within Histological Diagnosis	50.0%	50.0%	100.0%
		Undifferentiated Carcinoma	Count	1	1	2
			Expected Count	1.3	.8	2.0
			% within Histological Diagnosis	50.0%	50.0%	100.0%
	Total		Count	5	3	8
			Expected Count	5.0	3.0	8.0
			% within Histological Diagnosis	62.5%	37.5%	100.0%
Type of Diagnosis				Expression of C-Kit		Total
				Positive	Negative	Positive
Type I Endometrial Carcinoma	Histological Diagnosis	Endometrioid Adenocarcinoma	Count	26	34	60
			Expected Count	26.0	34.0	60.0
			% within Histological Diagnosis	43.3%	56.7%	100.0%
	Total		Count	26	34	60
			Expected Count	26.0	34.0	60.0
			% within Histological Diagnosis	43.3%	56.7%	100.0%
Type II Endometrial Carcinoma	Histological Diagnosis	Papillary Serous Adenocarcinoma	Count	3	1	4
			Expected Count	2.5	1.5	4.0
			% within Histological Diagnosis	75.0%	25.0%	100.0%
		Clear Cell Adenocarcinoma	Count	1	1	2
			Expected Count	1.3	.8	2.0
			% within Histological Diagnosis	50.0%	50.0%	100.0%
		Undifferentiated Carcinoma	Count	1	1	2
			Expected Count	1.3	.8	2.0
			% within Histological Diagnosis	50.0%	50.0%	100.0%
	Total		Count	5	3	8
			Expected Count	5.0	3.0	8.0
			% within Histological Diagnosis	62.5%	37.5%	100.0%

Table 1: Comparison of c-kit expression in benign and malignant endometrial lesions.

Table 2: Expression of c-kit in all Benign and Malignant Endometrial Lesions

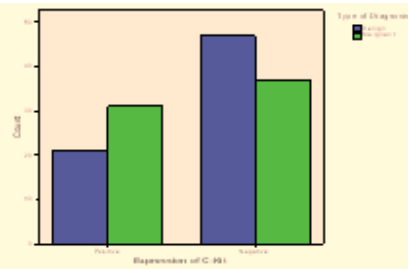


Figure1: Papillary Serous Endometrial Carcinoma H&E 20x

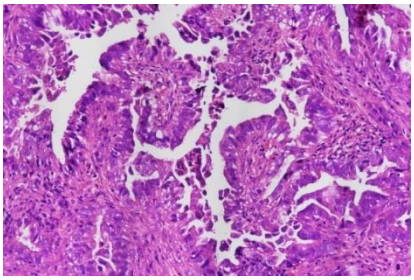
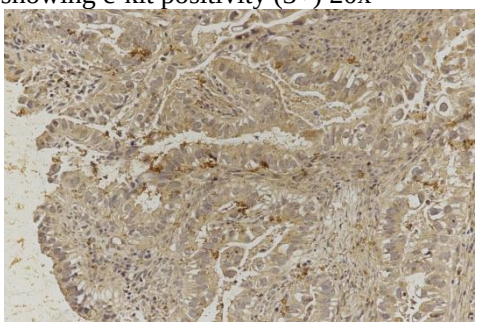


Figure 2: Papillary Serous Endometrial Carcinoma showing c-kit positivity (3+) 20x



DISCUSSION

Most common carcinoma of women genital tract is EC[1]. Previous studies showed, EC to be more common after menopause with age >50 years with presenting complaints of postmenopausal bleeding[9]. However, this study is showing 32 out of 68 (47%) patients of EC in the age range of 36-50 years with median age of 50 years, mostly after menopause and presenting with postmenopausal bleeding. Taking into consideration the significant role of c-kit expression in GIST, the current study has been done to assess c-kit expression in endometrial lesions by immunohistochemistry.

In current study, c-kit expression was analyzed in136 lesions, with 68 being reported as malignant and 68 benign.

Study done by Ibrahim Sehitoglu et al; showed 3/10 (30%) c-kit positivity in normal endometrium, 9/15 (60%) in simple hyperplasia, 5/10 (50%) in complex hyperplasia without atypia and 8/10 (80%) in complex hyperplasia with atypia, While 8/10 (80%) in grade I and 10/10 (100%) in grade II EC in total 65 cases, 47 benign and 18 malignant cases without further specifying their types in grade I and grade II[13].

Study done by Ercan Yilmaz et al; on 50 cases showed c-kit expression 6/10 (60%) in normal endometrium, 18/18 (100%) in simple hyperplasia, 5/6 (83%) in complex hyperplasia without atypia and 7/10 (70%) in complex hyperplasia with atypia, however, the c-kit expression is reduced with progression of lesion that is 1/6 (16%) for EC[14].

Study done by Lynne W et al; on total 44 cases including 35 benign and 9 malignant endometrial carcinoma, showed 11/14 (79%) positivity in secretory phase, 13/14 (93%) in proliferative phase, 4/7 (57%) in hyperplasias and 4/9 (44.44%) in EC all were endometrioid adenocarcinoma[15].

This study is compatible with the study done by Lynne W et al, both in EC and hyperplasias. The rest of two studies have great difference regarding the results of c-kit expression in benign and malignant endometrial lesions.

So, the current study reveals that c-kit positivity is seen in quite a significant percentage in EC. These findings suggest that further studies on a larger scale and clinical trials should be done to assess the role of inhibitors of tyrosine kinase (imitanib) therapy in c-kit positive cases. Regarding the benign lesions, treatment trials can be given with tyrosine kinase inhibitors for symptomatic patients having DUB and are unfit for surgeries. As by literature studies, imitanib treatment has been used for benign desmoid tumors which are intrabdominal, large in size and were unresectable[19].

CONCLUSION

In our study, c-kit over expression was found in 31 out of 68 cases (45.6%) of malignant endometrial lesions and 21 out of 68 cases (30.9%) of benign endometrial lesions.

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