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TO ASSESS MICROVESSEL DENSITY USING ENDOGLIN (CD 105) IN CYCLIC ENDOMETRIUM, ENDOMETRIAL HYPERPLASIA AND CARCINOMA

Pathology

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ABSTRACT

Background- Endometrial angiogenesis is characterized by proliferation of vascular endothelial cells during proliferative phase, coiling of arterial system in secretory phase and repair of vascular bed during menstruation. Vascular endothelial growth factors, acidic and basic fibroblast growth factors and platelet derived growth factor which is structurally similar to vascular endothelial growth factor, appear to be the most important promoters of angiogenesis.

Aims and objectives— 1) To evaluate the importance of immunohistochemical marker CD105 by assessing microvessel density in cyclic endometrium, endometrial hyperplasia and carcinoma and 2) To correlate histomorphological changes and characteristics of micro vessel density parameters like vessel number and area.

Material and methods- The present study was conducted on 55 hysterectomy specimens consisting of 30 cases of proliferative, secretory and atrophic endometrium (10 of each) ,10 cases of endometrial hyperplasia and 15 cases of endometrial carcinoma. Microvessel density (MVD) analysis was performed on paraffin embedded representative tissue sections stained with monoclonal antibodies to CD105 at 200x magnification. Two parameters – vessel number and area were studied using automatic image analyzer. Ten microscopic fields of each lesion type were examined and mean of all was calculated.

Results- Microvessel density remained same throughout different phase i.e. cyclic endometrium while it was less in atrophic endometrium. Mean MVD in simple hyperplasia and complex hyperplasia was 42.81±2.57 and 53.27±1.55 respectively. Mean microvessel density varies from 55.27±6.55 in grade 1 to 69.96±4.23 in grade 2 and 107.60±5.57 in grade 3 carcinoma of endometrium. Mean MVD was significantly associated with tumor invasion depth in myometrium, lymph node metastasis, and staging of endometrial carcinoma. Mean area of blood vessels in proliferative, secretory and atrophic endometrium, endometrial hyperplasia and carcinoma was variable with maximum in cases of complex hyperplasia.

Conclusion— It was concluded that Endoglin (CD105) is a useful marker for evaluation of microvessel density in endometrial hyperplasia and carcinoma. Increased angiogenicity activity was associated with tumor invasion of more than half depth in myometrium, lymph node metastasis, and staging of endometrial carcinoma. Higher endometrial tumor grade directly correlated with higher angiogenic activity.

KEYWORDS

CD 105, Microvessel density, Cyclic Endometrium, Endometrial Hyperplasia, Endometrial Carcinoma.

INTRODUCTION

Endometrial angiogenesis is characterised by proliferation of vascular endothelial cells during proliferative phase, coiling of arterial system in secretory phase and repair of vascular bed during menstruation[1] Vascular endothelial growth factors, acidic and basic fibroblast growth factors and platelet derived growth factor which are structurally similar to vascular endothelial growth factor, appear to be the most important promoters of angiogenesis.[2-4] Angiogenesis is essential for tumor growth and metastatic spread by supplying metabolic requirements for the growing tumor and providing a vascular pathway for haematogenous spread to distant sites.[5,6] Tumour angiogenesis is currently considered to be the result of an imbalance between proangiogenic and antiangiogenic factors produced by both the malignant tumour and the host's normal cells.

One of the studies has suggested that the angiogenic potential of a tumour may be inferred from its vascularity measured in histological sections.[7]

Microvessel density (MVD) is reportedly a prognostic indicator in a variety of human malignant tumours, a higher MVD correlating with disease progression and with shorter overall and disease-free survival rates. Presently, there are many endothelial cell specific markers available which can detect angiogenesis with adequate specificity. Markers such as CD31, CD34, and von Willebrand's factor are pan endothelial markers that are expressed in normal vasculature and also in tumour vasculature. On the contrary, CD105 is expressed on endothelial cells of tumours, but weakly or not at all expressed in normal tissue, thus making this marker superior in detecting tumour angiogenesis.[8] CD105 is specifically proliferation associated endothelial marker of tumour neo-vasculature.

Various studies in the literature reviewed have demonstrated increased expression of CD105 being associated with poor prognosis in various carcinomas.[9,10] To quantitate tumoral angiogenesis, determination of microvessel density by monoclonal antibody has been generally used. The specificity of used marker is very important to detect true tumoral microvessels.

Recently, endoglin (CD105) was introduced with specific staining characteristics for tumoral vessels without false positivity for other blood vessels, lymphatic or inflammatory cells.[11,12] Endoglin (CD105) is a disulphide-linked, proliferation-associated, hypoxia-inducible homodimeric cell membrane glycoprotein weighing 180kDa. This protein is greatly related to the transforming height factors TGFß1 and TGFß3, which participate in differentiation and proliferation regulation of different types of cells. Combining CD105 with TGF-ß stops protein phosphorylation, whereas the level of its expression modulates the effects of TGF with the antagonistic influence. In clinical studies, CD105 antibodies have shown a greater specificity for the tumour vasculature than pan-endothelial markers[13] It has been observed that CD105 antibodies reacted preferentially with the active endothelial cells of angiogenic tissues, whereas antibodies against pan endothelial antigen might react not only with newly forming vessels, but also with stable vessels trapped inside the tumour. Assessing neovascularization by CD105 staining was found to have a prognostic value in various solid malignant tumours, such as breast carcinoma, cervical and colorectal cancers, endometrial and gastric carcinomas,

melanoma, non-seminomatous testicular germ cell tumours, non small cell lung cancer, prostate cancer, renal cell carcinoma, and oral carcinoma.[14] Generally, it is claimed that the histological examination of the microvessels is a standard and relatively effective way of determining vascularisation in cancer tumours.[15]

The present study was carried out with the aims and objectives to evaluate microvessel density by using immunohistochemical methods and computer assisted quantitative image analysis in cyclic endometrium, endometrial hyperplasia and carcinoma with correlation between histomorphological changes and characteristics of microvessel density parameters like vessel number and area. Literature reviewed show very few studies defining the role of angiogenesis using CD105 as an immune-histochemical marker to demonstrate microvessel density as a prognostic marker in endometrial malignancy.

MATERIALAND METHODS

Endometrial samples from 55 hysterectomy specimens, performed due to various benign or malignant causes, submitted in the Department of Pathology in a tertiary care hospital for histopathological examination, were further subjected to immunohistochemistry and morphometry studies. These 55 cases were classified into three groups. Group I - consisted of 30 cases of proliferative, secretory and atrophic endometrium (10 of each) from hysterectomies carried out due to non endometrial pathological causes like uterine fibroids and prolapse etc. Group II comprised of 10 cases of endometrial hyperplasia and Group III comprised of 15 cases of endometrial carcinoma. The uterine tissue was examined grossly in toto.

The histopathological cases of endometrial hyperplasia and adenocarcinoma were classified according to accepted criteria.16 Areas immediately surrounding glands were examined in cyclic, atrophic and hyperplasic endometrium. In neoplastic lesions, intratumoral stroma was examined avoiding epithelial components. All the sections were stained with haematoxylin and eosin as per standard method and microvessel density (MVD) analysis was performed on paraffin embedded representative tissue sections stained with monoclonal antibodies to CD 105.

Automated Image Analysis:

The quantitative morphometric studies were done by image analysis. Images provided by a charged device video camera coupled with Olympus BX51 microscope at a magnification 200x were stored on a host computer based on Pentium 4 processor with operating system Microsoft Windows Vista through a digital frame grabber and processing was done by image analysis software Image Proplus Version 6.3.Microvessel (MV) was defined as any highlighted endothelial cell or endothelial cell cluster clearly separate from adjacent microvessels, tumor cells and other connective tissue elements. Vessel lumen was not necessary for a structure to be defined as microvessel. Two observers independently performed quantitative analysis of the intratumoral micro vessel density by light microscopy in representative areas of sections with highest numbers of capillaries and small venules (neovascular "hot spots") according to the method that was first described by Weidner et al.[17] The sections were scanned first at low magnification (100x), and after the most intense area of neovascularisation (hot spot) were identified in sections, microvessel (MV) counts were done on a 200x magnification. Computer assisted image analysis was performed on all cells, tissues and vessels expressing antibody staining, avoiding confounding background and including all positive staining vessels. Appropriate areas totalling most of the epithelium or most of the adjacent stroma, fulfilling morphologic criteria were analyzed, whereas contaminating areas were excluded using the specific computer function.

The parameters which were studied include vessel number and area. For all these parameters ten microscopic fields of each lesion type were examined. For number of vessels, all vascular structures and cells stained with CD105 were analysed in each microscopic field of 200x magnification. These were highlighted by outlining their digitalized images on monitor screen with help of computer mouse. After all cells expressing antibody staining were selected, results were analysed. After examining 10 fields mean of all was calculated. Determination of vessel area was also done using the image analysis software Image Pro plus Version 6.3. Total area of CD 105 stained vessels in morphologically classified lesion was measured in endometrial stromal area and in tumour. The results were presented as size of area of positive staining. Its measurement was also generated by computer. Results were expressed as the number of microvessels in proliferative, secretory, atrophic endometrium,endometrial hyperplasia and carcinoma, in different histopathological groups and in different group of grading and staging along with vessel area. Mean of 10 fields was calculated and finally tabulated in excel sheet. Standard deviation and median were also calculated. Data were collected, tabulated and statistically analyzed using SPSS (Statistical package for social studies) statistical programme version 18. In all tests 'p' values below 0.05 were regarded as significant. For comparison between two groups like hyperplasia and carcinoma independent sample 't' test was applied. For comparison among all groups analysis of variance (ANOVA) test was applied.

RESULTS

Out of total 55 cases, 10 (18.18%) cases were of proliferative phase, 10 (18.18%) of secretory phase, 10 (18.18%) of atrophic endometrium, 10 (18.18%) of endometrial hyperplasia and 15 (27.27%) cases were of endometrial carcinoma. The mean age of total patients was 45.8±7.4 years with age range of 21-80 years. Majority of cases of proliferative and secretory phase were in range of 21-50 years whereas cases of atrophic endometrium were in an age range of 41-70 years. Mean age for patients of endometrial hyperplasia was 50.1±12.3 years and majority of patients belonged to age group of 31-40 years while patients of endometrial carcinoma were in the age group of 51-60 years. Post menopausal bleeding was the chief complaint of the patients of endometrial carcinoma followed by abdominal distension, discharge per vagina, pain abdomen and something coming out of vagina.

All cases of endometrial carcinoma were classified according to FIGO grade. Seven cases were of grade 1; 4 cases of grade 2 and 4 cases were of grade 3. Four cases had positive lymph node metastasis while eleven cases were negative for lymph node metastasis. Ten cases (66.7%) showed invasion of more than half of the myometrium thickness, while 5 cases (33.3%) had equal to or less than half involvement. Five cases (33.3%) were of stage 1b; 5 cases (33.3%) of stage 1c; 1 case of stage 2b; and 4 cases of stage 3c. A total of 26855 number of vessels were analyzed by automated image analysis in all of 55 cases, including 4751 number of vessels in proliferative endometrium, 4902 in secretory endometrium, 2463 in atrophic endometrium, 4232 in endometrial hyperplasia and 10507 numbers of vessels in endometrial carcinoma. (Table 1)

Table No. 1 Showing Total Number Of Microvessels Measured By Computer Assisted Image Analysis In Various Lesions

Type of lesions	Number of lesions	Number of vessels
1. Proliferative Endometrium	10	4751
2. Secretory Endometrium	10	4902
3. Atrophic Endometrium	10	2463
4. Endometrial Hyperplasia	10	4232
A) Simple	7	2620
B) Complex	3	1612
5. Endometrial Carcinoma	15	10507
a) GRADE 1	7	3051
b) GRADE 2	4	2885
c) GRADE 3	4	4571
Total	**55**	**26855**

Mean MVD in proliferative endometrium (51.46±4.46) was almost similar to that of secretory endometrium (50.97±4.71) in comparison to atrophic endometrium which showed low MVD (31.56±4.31) (Fig. 1, 2, 3). Mean MVD in hyperplasia was 45.95±5.52 (Fig. 4) as compared to carcinoma which showed a mean of 73.14±23.53 (Fig. 5.) with p value< 0.05 confirming statistical significance.

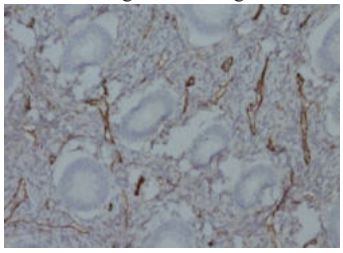

FIG 1. Microvessels in proliferative endometrium. (CD105; 200x).

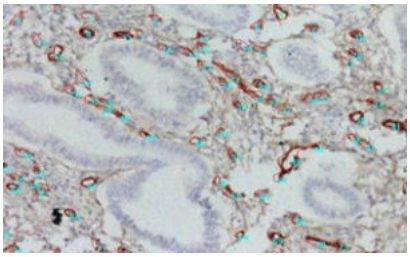

FIG 2. Morphometric presentation of microvessels in secretory endometrium. (CD105; 200x).

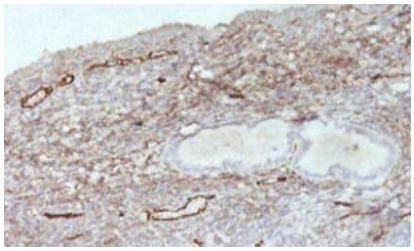

FIG 3. Microvessels in Atrophic endometrium. (CD105; 200x).

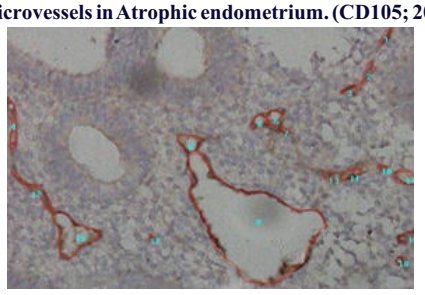

FIG 4. Morphometric presentation of microvessels in simple hyperplasia of endometrium. (CD105; 200x).

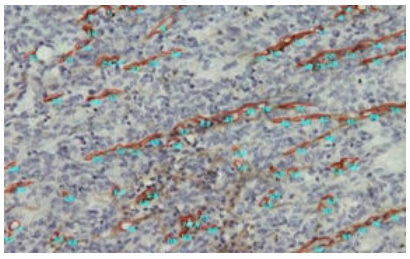

Fig 5. Morphometric presentation of microvessels in carcinoma endometrium. (grade 3) (CD105; 200x).

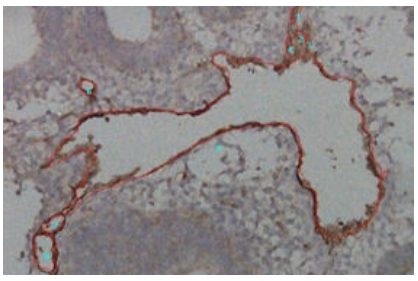

FIG 6. Morphometric presentation of microvessels in complex hyperplasia of endometrium. (CD105; 200x).

MVD in cases of endometrial carcinoma was highest as compared to proliferative, secretory, atrophic endometrium and endometrial hyperplasia. Mean microvessel area was almost similar in proliferative (31.78±1.72), secretory (29.28±8.12), atrophic endometrium (25.97±1.92) and endometrium carcinoma (24.94±6.00) but was low as compared to that in hyperplasia (106.44±73.37). (Table 2)

TABLE NO. 2

Showing comparison of microvessel density and microvessel area in proliferative endometrium, secretary endometrium, atrophic endometrium, complex hyperplasia and endometrial carcinoma (Grade 1, 2 and 3)

CATEGORIES	MICROVESSEL DENSITY (no/mm^2)				AREA (µm^2)			
	MEAN	SD	MEDIAN	RANGE	MEAN	SD	MEDIAN	RANGE
Proliferative Endometrium	51.46	4.46	52.16	43-59	31.78	1.72	32.27	28.25-33.63
Secretory Phase	50.97	4.71	50.43	43-58	29.28	8.12	26.62	21.04-41.77
Atrophic Endometrium	31.56	4.31	32.5	25-38	25.97	1.92	25.85	23.45-28.99
Complex Hyperplasia	53.27	1.55	52.8	52-55	188.18	90.54	168.90	108-286
Carcinoma (Grade 1)	55.27	6.55	55	23-98	23.94	4.78	22.23	18- 30
Carcinoma (Grade 2)	69.96	4.23	73	31-120	22.19	2.32	21.71	20-25
Carcinoma (Grade 3)	107.60	5.57	97.5	40-169	30.61	7.45	30.20	23-38

Significant statistical difference was observed in degree of hyperplasia affecting the vessel number and area. Mean microvessel area in simple hyperplasia was 71.42±23.90 as compared to complex hyperplasia which showed mean of 188.18±90.54 (Fig. 6), showing a significant difference in area with p value <0.05 confirming statistical significance. Hyperplasia cases showed low MVD as compared to carcinoma but area of the blood vessels was far more because of presence of large and irregularly shaped blood vessels in comparison to numerous small and less irregular shaped blood vessels in carcinoma.

The occurrence and pattern of vessel distribution in endometrial carcinoma was associated with degree of differentiation. Mean MVD increased from 55.27 in grade 1 to 69.96±4.23 in Grade 2 followed by maximum mean of 107.60 in grade 3, with p value < 0.05 confirming statistical significance. (Table 2) No statistical significance was observed in mean micro vessel area in different grades of carcinoma ranging from 23.94±4.78 in grade 1, 22.19±2.32 in grade 2 and 30.61±7.45 in grade 3 respectively.Mean microvessel density in cases of endometrial carcinoma with myometrium invasion less than half of thickness was low i.e. 59.16±7.47 as compared to cases with myometrium invasion more than half which showed a mean of 80.13±10.11 with p value < 0.05 confirming statistical significance. Area in cases with myometrial invasion less than half, showed a mean of 23.80±4.64 as compared to cases with myometrial invasion more than half, which showed mean of 25.51±6.73 with p value >0.05 showing no statistical significance. Mean MVD in lymph node positive cases was 107.60±5.57 as compared to lymph node negative cases which was 60.61±6.58 with p value <0.05 showing a significant difference. Mean area in lymph node positive cases was 30.61±7.45 as compared to lymph node negative cases which showed a mean of 22.88±4.03 with p value > 0.05 showing no statistical significance.

DISCUSSION

Endometrium is characterized by extensive vascular remodelling, principally involving steroid sensitive spiral arteries and sub epithelial capillary plexus throughout the menstrual cycle.[12] Angiogenesis in endometrium was shown to be weakest during the menstrual phase followed by a rapid increase in the early proliferative phase before gradually decreasing toward cycle end.[18] Ovarian steroids and a number of angiogenesis promoting growth factors, including VEGF are known to regulate changes in the vascularisation of the human endometrium. Excessive angiogenesis is seen in a variety of pathologic situations such as endometriosis and solid tumour growth.[19] Differences in angiogenesis of the endometrium in normal menstrual cycle and diseased conditions such as endometrial hyperplasia might contribute to the neoplastic changes in the endometrium leading to carcinoma. Potential tumor growth and metastasis depends on the angiogenesis in a variety of tumors such as endometrial carcinoma. In angiogenic phase of the tumors, with the increase in microvessel count, more likely is that the tumor cells will enter the circulation or the lymphatics. Although immunohistochemical staining for pan-endothelial markers clearly highlights the vascular endothelium, endoglin (CD105) is suggested to be useful marker for evaluating the angiogenesis.[20] Present study showed that microvessel density in proliferative endometrium was almost similar to secretory endometrium. Similar findings were observed by Makhija et al[1] and Rogers et al[21] who conducted a study on endometrial angiogenesis and revealed that endothelial cell proliferation occurs throughout the cycle with no statistically significant elevation at any particular stage. Blood

vessels were poorly developed in atrophic endometrium as compared to proliferative and secretory phase.[22] Current study revealed low microvessel density which was observed by Nayha et al who detected low number of micro vessels.[23]

In endometrial hyperplasia, degree and atypia significantly affected vessel number. Present study revealed that mean of microvessel density in simple hyperplasia was low as compared to complex hyperplasia with a significant p value <0.05. Several authors have also observed that the total number of vessels increased markedly from simple to complex hyperplasia with p value <0.02 confirming statistical significance.[19,24] It may be assumed that increased vascularity of the hyperplastic endometria may be due to the state of prolonged estrogen stimulation.[6]

The assessment of angiogenic factors in cancer patients may have important clinical implications in many malignant tumors. Several researchers have measured angiogenesis by correlating micro vessel counts with tumour angiogenesis. The degree of angiogenesis could allow for the identification of patients at high risk of recurrence who may benefit from aggressive surgical procedures and/ or neo adjuvant therapy.[25] Occurrence and pattern of vessel distribution in endometrial carcinoma was associated with degree of differentiation. It was observed from the study that mean MVD increased from grade 1 to grade 3 carcinoma with p value < 0.05 confirming statistical significance. Studies carried out by various authors have shown a significant increase in microvessel density with increasing grades confirming an increasing trend of angiogenesis in different organs.[26- 30] (Table 3)

Table No. 3 Comparison Of Micro Vessel Density In Carcinoma Of Various Organs With Different Grades.

		Micro vessel Density		
Authors	**Organ**	**Grade 1**	**Grade 2**	**Grade 3**
Nayha et al[23]	Endometrium	117	152	232
Abulafia et al[26]	Endometrium	44	96	98.5
Kaku et al[27]	Endometrium	60.40	64.04	78.15
Laitakari et al[28]	Larynx	129	136	219
Netto et al[29]	Brain (Oligoden droglioma)	—	10.00	11.67
Mahzouni et al[30]	Brain (Astrocytoma)	10.87 (Grade 1+2)	12.31 (Grade 3)	21.25 (Grade 4)
Present Study	**Endometrium**	**55.27**	**69.96**	**107.60**

As far as the correlation between the microvessel density and the depth of tumour invasion was concerned, the current study showed a significant difference in microvessel density in cases of endometrial carcinoma with myometrium invasion less than half as compared to myometrium invasion more than half revealing an increased MVD (p value <0.05). Various authors had also confirmed the similar findings indicating increased microvessel counts in depth of tumour invasion.[13,30] Various studies have been carried out to know the comparison of microvessel density in normal endometrium, hyperplastic endometrium and grade 1 endometrial carcinoma which showed increase in blood vessel number. Erdem et al compared the microvessel density in proliferative endometrium, complex hyperplasia with atypia and grade1 endometrial carcinoma and found that there was a significant difference in microvessel density between proliferative endometrium and complex hyperplasia with atypia with p<0.05 whereas no significant difference was seen in microvessel density between complex hyperplasia with atypia and grade 1 endometrial carcinoma.[31] Nahya et al has also revealed that there was a striking increase in concentration of blood vessels in the stroma of well differentiated endometrial carcinoma compared with normal and a range of hyperplastic endometria representing angiogenesis associated with tumour.[23]

Similar findings were observed by Jikihara et al that the microvessel density was highly correlated with clinical stage, myometrium invasion and lymph node involvement.[32] The increased number of microvessel count which was associated with tumour depth of invasion and lymph node involvement could be explained by the requirement for neovascularisation to achieve tumour invasion and metastasis, since the tumour cells require blood vessel to support their growth with oxygen and nutrients as well as increase the opportunity for tumour cells to metastasize. Therefore, intratumorally microvessel count could be used as predictor to select patients at higher risk for tumour metastasis and /or recurrences. Lymph node involvement has been considered an important prognostic indicator of cancer. Mean microvessel density in lymph node positive cases was high as compared to lymph node negative cases showing a significant difference in microvessel density (p value <0.05). Saad et al also found that micro vessel counts using CD105 correlated significantly with the presence of lymph node metastasis (p<0.01).[13] There was a strong correlation with number of microvessels with different stages of endometrial carcinomas indicating a significant difference in microvessel density i.e. with increase in FIGO staging, MVD increased from stage 1 to stage 3 with p value < 0.05 confirming statistical significance. Present study was also supported by observations of various researchers who showed that microvessel counts correlated significantly with staging.[13,33] Weidner et al analysed microvessel counts in their studies on breast cancer by using factor VIII related antigen and found them to be statistically significant in cases with metastasis with p value<0.003.17 Similar studies which were carried out in carcinomas of different organs like colon, lung, cervix and precancerous lesions of cervix respectively showed a significant correlation of microvessel counts with status of lymph node metastasis.[34-37]

Present study showed similar findings i.e. angiogenesis being a crucial factor in the metastatic process and thus for the progression of a malignant disease. Contrary to the present study, Kaku et al[19] and Erdem et al[31] revealed that there was no significant relationship of microvessel count with lymph node status in endometrial carcinoma. Transition from endometrial hyperplasia to endometrial cancer was accompanied by microvessel density changes.[26] Studies carried out on patients of precancerous lesions of cervix and cervical cancers revealed an increase in mean MVD in cases of low grade to high grade dysplasia and demonstrated that MVD is an independant prognostic marker for patient free survival in patients with stage IB and IIA cervical carcinoma.[36,37] Pawar et al also demonstrated that MVD and microvessel area using CD105 antibody in cervical dysplasia and carcinoma exhibits potent angiogenic activity which increased significantly and highly correlated with increasing grades and invasion of tumour. Our findings also correlated with the study performed by various researchers who showed that increase in microvessel density indicates transition from endometrial hyperplasia to carcinoma.[24,37,14]

CD105 is a promising marker of recent years which helps in determining the angiogenic factor in tumor progression through MVD. Microvessel density in the present study was also determined using CD105 in cyclic endometrium, hyperplasia and carcinoma of endometrium. So far, the ensity and number of micro vessels are one of the most thoroughly examined parameters for angiogenesis.[38] Very few studies regarding calculation of vessel area and size using CD 105 as angiogenesis markers exist in the literature reviewed. Similar results were observed by Nayha et al who showed that vessel size and area get increased with variation in degree of hyperplasia i.e. from simple and complex to atypical hyperplasia.[23] Laitakari et al showed that there was alteration in size and shape of vessels in preneoplastic conditions like dysplasia of squamous epithelium, which showed prominent enlarged and branched blood vessels as compared to small and round vessels in the subepithelial layer. Aberrant angiogenesis was observed in poorly differentiated squamous cell carcinoma which revealed an increased number of irregular vascular structures. Small regular vessels were common in benign lesions and large irregular vessels in malignant neoplasms.

In normal tissue and slowly growing low grade tumours the microvessels were well branched and showed a high surface to vessel ratio whereas microvessels in high grade highly malignant lesions were plump and nonbranched showing a low surface to vessel ratio.[28] Tumour vessels provide a useful target for antineoplastic therapies, as a variety of anti-angiogenic substances have resulted in effective inhibition of tumor growth in vitro. A variety of experimental studies have demonstrated that angiogenesis inhibitors such as TNP- 470 and angiostatin mediate the inhibitory effect on tumor growth and metastasis. The inhibitory effect of medroxyprogesterone acetate on angiogenesis induced by endometrial carcinoma was also reported.[38] Targeting of CD 105 for the treatment of solid tumors has been experimentally validated in mice; in fact, radiolabelled or immunotoxin conjugated anti-CD105 monoclonal antibody demonstrated a high antitumor efficacy in severe combined immunodeficiency mice bearing human breast carcinomas, likely mediated by the inhibition of tumor associated angiogenesis and/or by

the destruction of tumour associated vasculature.[14] Such agents may prove to be valuable antitumor chemotherapeutic drugs. Tumor angiogenesis, assessed with quantitative pathology using microvessel counting was found to be an independent and important prognostic indicator of endometrial carcinoma in a retrospective study.[27]

CONCLUSION

The present study concluded that endometrial carcinoma was characterized by increased neovascularisation as evident by increased microvessel density as compared with normal endometrium and endometrial hyperplasia. Microvessel density was highly correlated with tumor grade, myometrial invasion, lymph node status and FIGO staging confirming that the tumor progression might be related to angiogenesis. These findings further suggested the potential significance of characteristics of microvessel density and area as potential prognostic markers as well as their application in improved selection of patients for antiangiogenic and other treatments. This study showed a positive correlation between endometrial angiogenesis and menstrual disorders. In the present era of newer anti- angiogenic therapies, endometrial angiogenesis and alteration in vascular morphology definitely has prognostic significance and thus helps to improve the treatment modalities and patient care.

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