**Research article**

**An immunohistochemical study of CD83 positive dendritic cell density in human benign and malignant uterine specimens**

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**ABSTRACT**

**Introduction and Aim:** Dendritic cells (DCs) are heterogenous group of accessory cells that function as specialized forms of antigen-presenting cells in human body. A thorough knowledge of the DC population of the human uterus, especially the CD83 population would be very useful for an effective understanding of the immune protection of the endometrium during different phases of menstrual cycle and in the pathological conditions of the uterus.

**Materials and Methods:** A prospective study was conducted in a tertiary care referral medical college hospital in South India. Women in the age group of 35 to 50 years, who underwent hysterectomy were included in the study. Immunohistochemical study on the presence of mature CD83+DCs was carried out in the processed uterine specimens. The number of CD83 cells/20 high power fields in each of the specimen was calculated and reviewed by two independent reviewers.

**Results:** About 43 hysterectomy specimens obtained from patients undergoing hysterectomy for benign and malignant conditions of uterus were included in the study. Fibroid uterus was the most common indication for hysterectomy. The minimum and maximum DCs were 12 and 720 DCs per 20 HPF respectively, with an overall mean of 109.28. The mean DCs amongst benign specimens was 1.2 DCs and in the malignant specimens was 22.65 DCs per HPF, with a P value of 0.0001.

**Conclusion:** Mature dendritic cells are seen in abundance in malignant and pre-malignant tissues of human uterus. A reduction in number of CD83+ DCs was observed in patients with proliferative and secretory endometrium.

**Keywords:** Hysterectomy; dendritic cell; endometrium; decidua; uterus.

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**INTRODUCTION**

Dendritic cells (DCs) are heterogenous group of accessory cells that function as specialized forms of antigen-presenting cells in human body (1). Their principal role is to process the antigenic agents and present them onto the T-helper cells of the human body (2). These cells function as mediators between the innate and adaptive immune systems of humans. DCs take their origin from the bone marrow progenitors and subsequently migrate towards the lymphocytes and are responsible for stimulation of these T-helper cells to produce various types of immune responses in our body (3). Based on the mode and path of development, DCs are further sub-classified into myeloid and lymphoid DCs (4,5). Thus, DCs identify, catch hold of the antigens, present them to the lymphoid tissue and trigger the immune response to act against these antigens.

The specialized subset of these DCs, Langerhans cells (LCs) are predominantly seen in the epithelial and endometrial stroma (7). CD83 is a marker for mature DCs. It is one of the glycoprotein member of the immunoglobulin family that is up-regulated during maturation of DCs.

Various studies have suggested the role of such DCs in peripheral tissue immune tolerance (8,9). Thus, DCs play a dual role in acting as antigen-presenting cells and in induction of peripheral tolerance. DCs thus mediate a crucial role in balancing maternal defensive immune responses to foreign antigens and also aid in tolerance to the fetal embryo in the human decidua. While the immature DCs (CD1a) are excellent in antigen uptake, mature cells (CD83) are good in antigen presenting. A thorough knowledge of the DC population of the human uterus, especially the CD83 population would be very useful for an effective understanding of the immune protection of the endometrium during various phases of menstrual cycle and in the pathological conditions of uterus. The objectives of the present research work were to study the distribution and morphology of CD83 (mature) Dendritic cells (DC) in the body of the uterus using various Immuno Histochemical (IHC) techniques and to determine the effects of dysplastic and neoplastic epithelium and endometrial stroma (7). CD83 is a marker for mature DCs. It is one of the glycoprotein member of the immunoglobulin family that is up-regulated during maturation of DCs.

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cells on the CD83 cell density in normal and pathological lesions of the body of uterus using IHC techniques.

Though many researchers have studied the presence and their role of DCs in human uterus, not much of evidence (through larger sample sizes) is there in medical literature on the actual pattern of distribution of CD83 DCs in human uterus. Our study focuses on the pattern and distribution of CD83 density in various normal and abnormal uterine specimens and on the effects of neoplastic changes on the distribution of CD83 cells in human uterus.

**MATERIALS AND METHODS**

After obtaining clearance from the Institutional Ethical committee from the tertiary care referral medical institution to which the author was earlier associated with, a prospective study was conducted on the uterine specimens. Women in the age group of 35 to 50 years, who underwent hysterectomy for various clinical conditions like prolapsed of uterus, abnormal uterine bleeding, fibroid uterus, adenomyosis were included in the study. Other indications for hysterectomy including endometrial hyperplasia, cellular atypia, endometrial adenocarcinoma were also included in the study. A detailed menstrual cycle staging was done in all the patients under study using an idealized 28-day cycle and specimens were classified as proliferative or secretory phases.

All specimens were processed by routine histological techniques and stained with Haematoxylin-Eosin stain. Thin sections each measuring 3 μm in thickness were made. A single senior technician with more than 12 years of experience in tissue cutting, processing and immune-staining was used to prepare slides. This procedure is carried out for identification of Ag present in formalin fixed paraffin embedded tissue. First epitope retrieval prior to staining was done for sections taken on charged slides. Endogenous peroxidase activity was neutralized using the peroxidase block. Immunostaining of the sections was done using monoclonal antibodies for anti CD83. After this, post primary block (target binder) was used to enhance penetration of the subsequent polymer reagent (Polymer HRP + Secondary Ab). Then the nova link polymer recognizes& detects any tissue bound primary antibody. Then sections were incubated with substrate/ Chromogen, 3,3 diaminobenzidine (DAB). Reaction of DAB with peroxidase produced visible brown precipitate at antigen site. Sections were counter stained with hematoxylin. Skin was used as control. DCs were identified in the uterine specimens. The number of CD83 positive cells was counted per 20 high power field (40X objective and 10X eyepiece). From this, the mean number of CD83 positive cells per high power field was subsequently calculated. An adequately sized nucleated cell with visible processes that extend and project from each of the cells were defined as the morphological anatomy of the DCs. All the immune-stained cells were reviewed by 2 independent observers and the photographs were all taken using high definition camera. SPSS version 16 was used to perform statistical analysis. Descriptive data including mean, median, range and standard deviation were obtained and analysed. Student independent t-test and Fischer’s exact test were used to compare the number of cells in proliferative phase, secretory phase, hyperplasia and adenocarcinoma specimens.

**RESULTS**

Hysterectomy specimens from 43 women aged 35 to 50 were included in the study. CD83 DCs were present in the endometrial cells and stromal cells of the uterus in all examined specimens. Table 1 illustrates the demographic data of specimens studied.

### Table 1: Demographic data of the specimens studied (n=43)

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative endometrium</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory endometrium</td>
<td></td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno carcinoma</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial Hyperplasia with cellular atypia</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dendritic cells/20 HPF (40Xmagnification)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Overall mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>720</td>
<td>23.5</td>
<td>109.28</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dendritic cells/20 HPF (40Xmagnification)</th>
<th>Mean amongst benign endometrium (n=37)</th>
<th>Mean amongst cellular atypia/ malignant tissue(n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23.5</td>
<td>453</td>
</tr>
</tbody>
</table>

Fibroid uterus was the most common indication for hysterectomy followed by bleeding per vaginum and adenomyosis. The minimum and the maximum age at presentation were 36 and 56 years respectively, with the mean age of 45.7 years. DCs were present in the functional and basal layers of the endometrium in all the 43 specimens studied. Maximum DCs of 720 per 20 HPF were seen in a 54 year old lady who presented with bleeding per vaginum and had adenocarcinoma of uterus. The overall mean DCs in 43 specimens was 109.3 DCs per 20 HPF. The mean DCs in the benign (n=37) and malignant/premalignant (n=6) specimens were 23.5 and 453 DCs per 20HPF.
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Table 2. Number and distribution of DCs according to pathological diagnosis (n=43)

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Mean DCs/20 HPF</th>
<th>Mean DCs/HPF</th>
<th>Mean DCs/HPF (Benign/Malignant)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative endometrium</td>
<td>20</td>
<td>28</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Secretory endometrium</td>
<td>17</td>
<td>19</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Adeno carcinoma</td>
<td>2</td>
<td>628</td>
<td>31.4</td>
<td>22.65</td>
</tr>
<tr>
<td>Hyperplasia with cellular atypia</td>
<td>4</td>
<td>278</td>
<td>13.9</td>
<td></td>
</tr>
</tbody>
</table>

The number of DCs per 20 HPF in the adenocarcinoma and atypia were 628 and 278 DCs per 20 HPF respectively. On the other hand, the CD83 positive DCs in the proliferative and secretory phases of benign endometrium were 28 and 19 per 20 HPF.

The mean DCs/HPF in those with adenocarcinoma and cellular atypia were 31.4 and 13.9 respectively. On the other hand, the mean DCs per HPF in the proliferative and secretory endometrium were 1.4 and 0.95 respectively. The benign (n=37) and the malignant/premalignant (n=6) groups had 1.2 and 22.7 CD83 positive DCs per HPF respectively. The difference between the two groups is statistically significant (p=0.0001), which suggests that those specimens with malignant/pre-malignant lesions had an over expression of the CD83+ dendritic cells while the DCs in the benign specimens were very scarce.

Fig 1: The number and distribution of CD83 positive DCs per 20 HPF.

Fig 2. CD83+ dendritic cells in specimens studied

DISCUSSION

Dendritic cells are specialized cells that initiate, maintain and control immune responses and mediate immunity and immune tolerance (10). Dendritic cells play a key role in hosting an immune response and hence they are the main focus in the study of many clinical conditions of T cells such as transplantation, allergy, auto immune disease, immune deficiency, tumours and vaccines. In rheumatoid arthritis and in psoriasis which are auto immune diseases there are activated and increased number of dendritic cells.

Dendritic cells seen in the lung has a role in allergy and asthma (11). These cells serve as liaison between the adaptive and innate immunity. DCs are heterogenous in origin and function and are distributed across various organs in the body. They serve as immunostimulatory or immune tolerant, based on the local environment. DCs in the uterus are responsible for both immunosuppression and immunostimulation. The implanted embryo is
allogenic in nature. It is shielded and protected by the human uterus from the immune system of the host (mother). Even in non-pregnant women, these DCs act as mediators during the regular menstrual cycles. Human CD83 serves as a marker for mature dendritic cells and are expressed on the activated T helper and B cells (12). CD83 expression on T cells enhances the immune responses by activation of DCs. CD83 DCs have been proven to be a well-established cell-surface marker for mature DCs (13, 14). Under-expression of CD83 on human DCs causes a reduction of allogenic T cell proliferation.

CD83 DCs have been proven to be a well-established cell-surface marker for mature DCs. Various researchers have studied the presence and immunostimulatory role of CD83+DCs in the uterine decidua (15). Qian ZD et al studied the role of mature DCs in decidua of women with recurrent spontaneous abortions (16). Furihata studied its prognostic role in patients with gall bladder carcinoma and observed that patients with higher CD83 index had a better prognosis than in those with lower index (17).

Several authors have found an increase in CD 83 positive dendritic cells in gall bladder carcinoma; laryngeal papilloma and some have observed that with higher CD83 index there was better prognosis than in those with lower index. Hence a higher number of CD 83 cells in malignant specimens seen in our study can be an indicator of better prognosis. Similar studies have shown a strong association of CD83+DCs with laryngeal papilloma(18). However, there is not much published data on the distribution of CD83+ DCs in the endometrial carcinoma and other pathological conditions that affect the human uterus. Hayati AR has studied the role of CD83+DCs in cervical neoplasia and observed that the number and distribution of these DCs are upregulated in the cervical neoplasia than in non-specific cervicitis (19). Our study has shown a statistically significant rise in numbers and distribution of CD83+DCs in uterine adenocarcinoma and endometrial cellular atypia than in patients with proliferative and secretory endometrium.

Bell et al., in their study of CD1a and CD83 DCs in breast carcinoma, observed that the CD83 cell population was located more in abundance in the peritumour areas while CD1a population was more often seen within the tumour tissue (20). The author, in her earlier publication on CD1a cell distribution in human uterus and cervix observed a decrease in CD1a population in malignancies of uterus and cervix while a higher concentration was noted in the benign and inflammatory conditions affecting the cervix and uterus. Perimenopausal bleeding is becoming a common problem in women visiting primary care centers. They account for roughly 30% of all gynaecological visits (21). Endometrial cancers account for a significant number of such bleeds.

DNA vaccines symbolize a newer modality in protecting against various infections, thereby improving animal and human welfare (22). Similarly, future areas of research include utilization of antigen-presenting properties of DCs for the development of vaccines and immune therapeutics against cancer in humans (23). Our subsequent studies would focus on the comparison of CD1a and CD83 in human cervix and uterus.

CONCLUSION

Our study established the incidence and pattern of distribution of CD83+DCs in the endometrium of hysterectomy specimens, both in malignant and normal uterine specimens. Mature dendritic cells are seen in abundance in malignant and pre-malignant tissues of human uterus. A reduction in number of CD83+ DCs was observed in patients with proliferative and secretory endometrium. Comparison of pattern of distribution of mature and immature DCs in human uterus and cervix would give a better understanding of the role of immune responses in various pathological conditions of uterus and cervix.

REFERENCES