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ORIGINAL ARTICLE

Plasma Cells In Endometrium In Chronic Endometritis

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ABSTRACT

Objectives: To establish significance of presence of plasma cells in endometrium and their possible relationship with various underlying morbidities.
Study Design: Retrospective Study
Methods: A total of 50 diagnosed cases of chronic Endometritis, based on presence of stromal plasma cells were identified and retrospectively, they were evaluated for their main presenting complaints between 2011-2014 in KRL General Hospital, Islamabad. Prevalence and factors of chronic Endometritis were assessed. SPSS 22.0 was used to analyze all data.
Results: Out of 50 patients 30 (60%) cases were associated with Abnormal vaginal bleeding, 8 (16%) with subfertility, 6 (12%) with Abortion and 6(12%) with non-specific cervicitis.
Conclusion: Chronic nonspecific endometritis is not uncommon but in fact is under diagnosed condition. It is strongly associated with heavy irregular menstrual bleeding, subfertility and abortions. This important topic is still under research. Further work is needed on diagnosis and definitive treatment of this problem.
Key words: Plasma cells, Endometrium, Endometritis, Abnormal vaginal bleeding, Sub-fertility

INTRODUCTION

Chronic endometritis (CE) means persistent inflammation of the endometrium. It is diagnosed on histopathology of endometrial tissue. The characteristics of chronic endometritis are presence of plasma cells in the histopathological examination report of endometrial tissue.(1,2). Lymphocytes, eosinophils (3) and even lymphoid follicles may be seen but in the absence of plasma cells these are not enough to warrant a histologic diagnosis of chronic endometritis (4). Plasma cells are hallmark of chronic endometritis but are not specific for upper genital tract infection. Other features which can alert a pathologist to make a diagnosis of chronic endometritisare disturbances in normal growth and maturation of glands and stroma, superficial mucosal stromal edema, stromal breakdown and characteristic spindle cell alteration of the stroma (5, 6). In spite of those multiple histologic features, the key feature is the presence of plasma cells. Plasma cells are sometimes not easily seen on routine hematoxilin and eosin staining. Many diagnostic techniques have been used to identify plasma cells, like methyl green pyronin stain, immunohistochemistry (IHC) for immunoglobulin G, or syndecan and in situ hybridization for κ and λ light chains. (5, 6, 7) Syndecan-1 is a cell surface proteoglycan that is expressed on plasma cells (benign and malignant) and on keratinocytes, but it is not expressed by mononuclear cells, lymphocytes or endometrial stromal. In cases of suspected chronic endometritis in which no plasma cells can be found on hematoxilin and eosin stained slides,syndecan-1may be effective adjuvant in the diagnosis of chronic endometritis (8).

Chronic endometritis may be seen in up to 10% of all endometrial biopsies performed for irregular bleeding (1,8). Because of its subtle nature, the actual prevalence of this pathology in the general population is unknown, with estimates ranging from 0.8% to 19.0 %(9). Chronic endometritis may be caused by some infection or if no infection can be found and the condition is known as non-specific endometritis. Chronic endometritis is considered as infectious or reactive process because other than infections it is commonly associated with intrauterine contraceptive devices, sub mucosal leiomyoma's and endometrial polyps. In other words any cause of chronic irritation to the endometrium may result in chronic inflammatory reaction (10). The most common organisms causing infectious type of endometritis are Chlamydia trachomatis, Neisseria gonorrhea, Streptococcus agalactiae, Mycoplasma hominis, tuberculosis and various viruses like cytomegalovirus. Cicinelli et al.(11) found that two third of cases in their study were associated with some infection. This is not surprising considering the high prevalence in the population of bacterial vaginosis and the knowledge that ascending bacteria colonize the uterine cavity (12, 13, and 14).

The clinical presentation of chronic endometritis is very varied and non-specific (2). It is commonly seen with abnormal uterine bleeding, recurrent abortions, preterm labor and infertility (15, 16, and 17).

There are few published studies statistically examining both the histopathological and clinical findings of chronic plasmacytic endometritis. We hypothesized that thorough histopathological examination of the specimen in relation to clinical history of patients can make the clinician to understand the clinical significance and treatment of this important condition.

MATERIAL AND METHODS

We undertook retrospective review of 50 endometrial samples containing plasma cells and their clinical notes were recovered from files to see their main presenting complaints and other associated co-morbidities in KRL General Hospital Islamabad from 2011 to 2014.The stromal cells were identified by H & E staining. Cases from 22 -51 years ages were included. Eleven samples were from post-hysterectomy specimens, rest of the specimens were from endometrial curettage samples.

First, the presence of plasma cells was checked in all biopsies by examining conventional H&E stained slides. We used 10% formalin and paraffin to preserve the specimens. Antigen retrieval was performed by heat treatment in DAKO Target Retrieval solution on sections cut at 4 microns and placed on slides coated with 3-aminopropyltrethoxy-silane (DAKO, Carpenteria, CA). Nonspecific binding was inhibited by horse serum block, and endogenous peroxidase activity was neutralised by 0.3% peroxidase. Using a B-B4 (Serotec, Raleigh, NC) anti-human antibody that identifies an epitope of human syndecan-1 diluted 1:100 with the DAKO Large Volume LSAB2 Alkaline Phosphatase Kit (DAKO), we were able to detect the protein (CD138). Tissue sections were first treated with streptavidin alkaline phosphatase for 30 minutes, then with biotinylated secondary antibody for 30 minutes. We used the DAKO Fast Red Substrate System (DAKO) to see the signal, which showed up as a bright red stain at the location of the antigen of interest. Immunoreactivity for syndecan-1 in the cell membranes of keratinocytes was seen from the basal to the granular layers of normal skin, which served as the positive control tissue. In place of B-B4, we used a 1:100 dilution of the nonspecific isotype-matched

IgG1 mouse antibody MCA 928 (Serotec). All data were analysed using SPSS 22.0. Categorical data were presented as frequencies and percentages, while continuous data were presented as means and standard deviations.

RESULTS

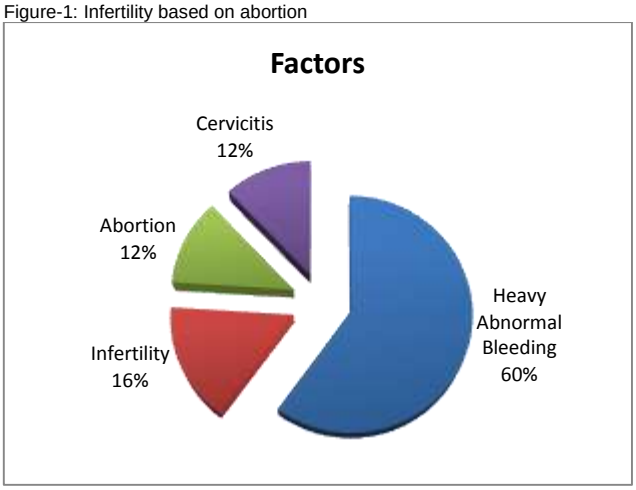
The mean age of the cases were 36.9±10.42 years and had mean BMI 24.2±7.48 kg/m^2. We found that majority of the cases were from rural areas and were illiterate. Mean follicle stimulate hormone (FSH) was 9.7±3.51 mIU/mL. Mean endometrial thickness was 8.6±4.23 mm. There was no any case of smoking history.(table-1)

Table-1: Baseline characteristics of the presented females

Variables	Frequency	Percentages
Mean age (years)	36.9±10.42	
Mean BMI (kg/m^2)	24.2±7.48	
Residence		
Rural	32	64
Urban	18	36
Literacy Level		
Yes	22	44
No	28	56
Mean FSH (mIU/mL)	9.7±3.51	
Mean EM thickness (mm)	8.6±4.23	

We found that 30 (60%) of cases were having abnormal and heavy vaginal bleeding in which other organic causes of heavy menstrual bleeding were ruled out. (Table-1) In the rest, 16% cases were directly or indirectly related to infertility and cases related to abortions were almost 12% in which majority were either recurrent abortions or post septic induced abortions. We also found CE with leiomyoma and polyp in 8% of women. Incidentally we also noted adnexal cyst in 6% of cases but there was no association found in literature. Twelve percentcases were associated with chronic nonspecific cervicitis. This indicates that plasma cells endometritis is definitely associated with these important gynecological morbidities but its actual incidence still needs to be known and because of its non-specific nature, some definitive diagnosis and treatment should be there for this important condition.(figure 1)

Figure-1: Infertility based on abortion



DISCUSSION

Chronic plasmacytic endometritis is a subtle pathology that is difficult to both diagnose and treat .The histopathologicaldiagnosis is characterized by endometrial inflammation rich in plasma cells with or without accompanying acute inflammation and lymphocytes(5). Plasma cells have a clock face chromatin, with an acentric nucleus and a visible perinuclear halo. However many conditions may mimic or interfere the search for a plasma cell on routine H &E staining. Plasma cells may be obscured on H & E by a mononuclear infiltrate, plasmacytoid stromal cells, abundant stromal mitosis, pronounced pre-decidual reaction, menstrual features or secondary changes due to exogenous progesterone treatment prior to biopsy (1, 8). Specific immunostaining of plasma cells by Syndecan 1, not only stains typical plasma cells, but also spindle shaped plasma cells which may be missed on H & E. Use of Syndecan-1 for plasma cells may be helpful in unusual cases where chronic endometritis is suspected as the cause of clinically significant on-going abnormal bleeding (16). It is indicating that CPE is actually an under-diagnosed condition and true incidence is even high. If we are not using special staining modalities then we would be missing some cases of plasmacytic endometritis. Secondly clinical presentation of plasmacytic endometritis is not specific and very varied so chance of under-diagnosis could be a likely possibility. Many studies are showing that it is closely associated with abnormal uterine bleeding, but endometrial biopsy is not performed in every case of heavy and abnormal uterine bleeding especially in young women or if associated with fibroid uterus.

The association between plasma cells and abnormal uterine bleeding still remains to be established. Kitaya et al(17), demonstrated that endometrium in chronic endometritis uniquely expresses the chemokines CXCL1, CXCL13 and adhesion molecules selectin E, implicating that local B lymphocytes are recruited from endometrial microcirculation and differentiate in situ into plasmacytes(17). Such unusual leucocyte composition may disrupt the integrity of the epithelial lining and cause endometrial shedding resulting in abnormal uterine bleeding. In one study by Vidyavathi et al (16) found significant association of plasma cell in disordered proliferative endometrium probably due to the effect of unopposed estrogen in endometrium which predisposes to an inflammatory milieu by the production of cytochymes and growth factors (18). In a recent study by Cicinelli et al(19) demonstrated that hysteroscopy using fluid for distending the uterine cavity is a useful and reliable technique for detecting CE. Taking the presence of hyperemia, mucosal edema, and micropolyps as diagnostic parameters, hysteroscopy showed a diagnostic accuracy of 93.4%. Using these criteria, they found signs of CE in approximately 17.4% of women referred for diagnostic hysteroscopy for various indications

Although it often is clinically silent, it is commonly found in cases of infertility and recurrent abortions (20). CE may also hamper the reproductive capacity of spontaneous and in vitro fertilization (IVF) cycles (21).

The literature does not contain clear guidelines for the management of chronic non-specific endometritis. Empirical treatment usually is antimicrobial therapy and hormonal manipulation. Review of clinical documentation shows that intervention (in terms of antibiotic therapy) was rarely performed in reaction to the CE diagnosis (22). Few studies have emphasized the role of empiric antimicrobial therapy in chronic endometritis and its importance in preventing morbidity of an operative procedure such as hysterectomy. Other options are surgical ablation, curettage or lastly hysterectomy. Though 80% of CE is self-limiting and D and C itself is therapeutic in some cases but certainly what should be the exact treatment is still under research. Failure to diagnose and treat CE may result in persistent abnormal uterine bleeding that does not respond to hormonal treatment alone.

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