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7-30-2008

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Chronic Endometritis Revisited:
A Review of the Pathology and Clinical Findings

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Abstract

Background: Chronic endometritis is a histopathologic diagnosis characterized by endometrial inflammation rich in plasma cells. Through examination of this disease, we hope to further elucidate the meaning of its diagnosis and whether or not it should be more carefully considered when examining specimens.

Methods: A retrospective chart and slide review was conducted that focused on the collection of clinical data and the examination and description of previous tissue samples from endometrial biopsies. A total of 94 chronic endometritis cases and 99 controls were identified. All statistical analyses were conducted using SAS version 9.1.

Results: Women with chronic endometritis were more likely to be within 41-50 year of age (39/95, 41.1%), with 65.3% of cases in the 31-40 and 41-50 age categories (23/95, 39/95). They were also more likely to be perimenopausal (42/92, P-value 0.0015) and multiparous (79.1%, P-value 0.1358). Additionally, hormone use was found to be significantly associated with endometritis (P-value 0.0299). No specific symptoms were found to correlate with chronic endometritis. Our study confirmed that the presence of lymphocytes (P-value <0.0001), neutrophils (P-value 0.0029), and macrophages (P-value 0.0048) are associated with endometritis along with epithelial change/metaplasia (P-value 0.0595).

Discussion: Our study has helped to better understand the demographics of endometritis and its clinical presentation; but as always, more studies are needed to further elucidate the implications of this disease for women.

Introduction

Chronic endometritis is a histopathologic diagnosis characterized by endometrial inflammation rich in lymphocytic cell infiltrates. While the diagnostic criteria for chronic endometritis remains controversial, it is generally agreed upon that the presence of plasma cells within the substance of the stroma is the most useful criteria for diagnosis (1, 2, 3, 4, 5). While this is true, a variety of different features can alert the pathologist to the possible presence of chronic endometritis. Disturbances in normal growth and maturation (focal ares that are out of cycle with other areas), superfical mucosal stromal edema, stromal breakdown, and characteristic spindle cell alteration of the stroma, especially around glands, are all other morphological features that can be seen with chronic endometritis (2, 3, 4, 5, 6, 7).

Plasma cell identification can often be difficult and problematic in the diagnosis of chronic endometritis. Because stromal cells often resemble plasma cells, and vice versa, it has been documented that plasma cells can be unreliable in diagnosising chronic endometritis (3, 5). Because of this, ancillary studies may aid in establishing the diagnosis. Syndecan-1 (CD138) is just such a study. It is a cell surface marker that is expressed on plasma cells, and through immunohistochemical means, it has proven to be an effective adjunct in the identification of plasma cells and the diagnosis of chronic endometritis (2, 5).

In addition to plasma cells, the presence and location of lymphocytes may aid in the diagnosis. Lymphocytes are considered a normal component of endometrial stroma (3, 5, 8). Leukocytes generally account for 10% of stromal cells in normal proliferative

and early secretory phases. These number increase to well over 20% in the mid and late secretory phase (3). The most predominate lymphocytes include T lymphocytes, macrophages, and natural killer cells (3, 5). These cells are generally found within the stratum basalis where they form lymphoid aggregates, in the stratum functionalis where they are scattered singly and in small aggregates around glands and blood vessel, and lastly in an intraepithelial position and within glandular lumina (3). B lymphocytes are a rare cell to be found in the endometrium (3, 5). They account for fewer than 1% of all endometrial leukocytes and are found as lymphoid aggregates in the stratum basalis as well as scattered individually throughout the superficial stratum functionalis (3, 5).

While endometritis can be an incidential finding on endometrial biopsy, it has also been associated with a number of entities. There has been a relationshiop noted between gonorrhea, Chlamydia, bacterial vaginosis, and mycoplasma. Furthermore, in some cases, chronic endometritis has been suggested to be a low-grade form of pelvic inflammatory disease (4, 6, 7, 9, 10, 11, 12). In others, infection does not seem to play a role. It has been variably observed with inflammation associated with structural abnormalities (polyps, submucosal leiomyomata, prolapse). It is also often found in postpartum and post-abortal endometria (6).

From the above, it is evident that a variety of studies have addressed different aspects of chronic endometritis. Current knowledge is based on studies investigating the etiology (gonorrhea, Chlamydia, bacterial vaginosis, or idiopathic infections), correlations with pelvic inflammatory disease, and whether or not these are different stages of the same disease or separate entities. Additionally, further investigations have

revealed the utility and effectiveness of treatments for chronic endometritis and attempted to clarify the pathologic features, epidemiology, and correlation with clinical findings.

Unfortunately, many of the studies examining the pathology of endometritis have either focused solely on the histopathology or used very small cohorts when trying to correlate histopathology with clinical findings. In addition, the epidemiology of endometritis is unclear and currently thought to have no specific predilections in almost all demographic categories. Moreover, there is little in the way of recent updates of the epidemiology of this condition. Current knowledge is fairly well developed in the presentation, common clinical signs and symptoms, and histopathology independently, but crucial data incorporating all of these aspects is lacking.

The meaning and correlations of diseases related to chronic endometritis have been only loosely examined and there is currently no clear and large sample that combines both the histopathology and clinical findings in a statistically significant and clear manner. In addition, the finding of chronic endometritis in both the Hispanic and Native American populations has not been represented. Using an expanded population with a tight linkage between clinical and specific pathologic features will develop a better understanding of multiple facets of the disease including incidence, prevalence, and outcome. We hypothesis that thorough examination of chronic endometritis, its associated histopathologic findings, and clinical history will help to further elucidate the meaning of this diagnosis and whether or not there it should be more carefully considered when examining specimens.

The aims of the study include: updating current information about the epidemiology, clinical presentation and outcome of patients with chronic endometritis, expanding on and/or confirming the currently agreed upon histopathologic findings of chronic endometritis, and correlating the clinical and histopathologic findings in a more diverse patient population than has been previously reported.

Methods

With permission from our institutional review board, we undertook a retrospective chart and slide review that focused on the collection of clinical data and the examination and description of previous tissue samples. A total of 194 cases were identified. Ninety-five women with a diagnosis of chronic endometritis and 99 women of similar age and menstrual status were identified. This was accomplished by searching Power Path®, our pathology electronic database, for previous endometrial biopsies from 2004 to 2007 at The University of New Mexico Hospital and associated clinics, for cases of chronic endometritis in women and women with endometrial biopsies without the diagnosis of chronic endometritis. The diagnosis of chronic endometritis was based on standard criteria available at the time of diagnosis. Cases that were identified as having missing clinical data or scant tissue on endometrial biopsies were included in an effort to preserve random sampling. Cases were excluded if the endometrial samples were not clear biopsies, were part of large resections due to carcinoma, or were not clear cases of endometritis. Once the patients and biopsies were identified unique identifiers were assigned to each case. Subsequently, one investigator undertook a chart review of Power Chart, our electronic medical record system. A variety of information was collected including: demographics and clinical features of endometritis.

At the same time, a separate additional investigator collected and examined previously prepared and stored hematoxylin and eosin stained tissue slides from the cases. A number of defined histologic parameters were evaluated for including variables such as cell types, degrees of inflammation, and presence of various types of metaplasia. Lastly, the data was combined in a spreadsheet including the clinical characteristics and analyzed for any relationships or significant findings.

All statistical analyses were conducted using SAS version 9.1. Chi-square tests were used in the analysis of dichotomous or categorical variables. When expected cell frequencies were <5, the Fisher exact test was used.

Results

The mean age of all patients was 46 with a range from 21-86 years of age (Table 1). In terms of ethnicity, the majority (42%) of patients were Hispanic, followed by Whites (26%) and others. Native American (7%), Asians (3%), and African Americans (1%) were represented in much smaller numbers (Table 2). Premenopausal women represented the largest number of individuals (43%) in the overall sample (Table 3). In addition, 79.8% of the women in our study had been pregnant >1 time. Lastly, out of the entire study population, 24.1% women were using some form of hormones (oral contraceptive pills, hormone replacement therapy, etc) at the time of biopsy. (Table 4).

When considering age, a preponderance of endometritis cases occurred in the 41-50 age category (39/95, 41.1%), with 65.3% of cases in the 31-40 and 41-50 age categories (23/95, 39/95), a handful of cases fell in the 21-30 and 51-60 age categories (13/95, 12/95), and few in the 71-80 and 81-90 categories (2/95, 2/95). (Table 1).

Given our sample population, endometritis was very prevalent in the Hispanic population. Forty-two percent of endometritis cases were in patients of Hispanic ethnicity (40/95), followed by 26.3% of Whites (25/95), 20% others (19/95), 7.4% Native Americans (7/95), 3.2% Asians (3/95), and 1.1% African American (1/95) (Table 2). Despite these findings, no ethnic category was significantly associated with endometritis (P-value 0.3665).

As mentioned above, the bulk of both cases and controls fell within the premenopausal category (82/191; missing data for 3 cases). Interestingly though, the greater part of the endometritis cases were found within the perimenopausal group. There were a total of 42/92 cases considered to be perimenopausal compared to 21/99 controls (45.7% versus 21.2%; P-value 0.0015). (Table 3).

When examining parity and hormone use, an increased number of pregnancies and hormone use were both associated with the occurrence of chronic endometritis, although hormone use was the only statistically significant value. Multiparous women were more likely to have the diagnosis of endometritis then their nulliparous and primiparous counter parts (79.1% versus 4.4% and 16.5; missing data for 4 cases; P-value 0.1358). When this data is compared to the controls, 80.5% were mutiparous, 9.2% primiparous, and 10.3% nulliparous (missing data for 12 controls**.** Additionally, 31.1% of the endometritis cases were using some form of hormonal contraception at the time of biopsy, compared to 17.5% of the controls (missing data for 5 cases; P-value 0.0299) (Table 4).

Data on symptoms included intermenstrual vaginal bleeding, lower abdominal pain, dysmenorrhea, menorrhagia, and menometrorrhagia. When examining these

symptoms individually, no single symptom was significantly linked with endometritis. Although, the diagnosis of endometritis was most closely associated with menometorrhagia, 44% of endometritis cases experienced heavy vaginal bleeding with and without their period contrasted with only 33.3% of controls (missing data for 4 cases; P-value 0.1326). Intermenstrual vaginal bleeding was the next most closely related symptom with endometritis, followed by lower abdominal pain, menorrhagia, and dysmenorrhea. Endometritis cases experienced intermenstrual vaginal bleeding 62.6% of the time, lower abdominal pain 25.3% of the time, and menorrhagia 61.5% of the time. On the other hand, 67.7% of controls experienced intermenstrual vaginal bleeding, 22.2% experienced lower abdominal pain, and 60.6% experienced menorrhagia. Surprisingly, dysmenorrhea was found to correspond with the control group more so than the cases (28.3% versus 15.4%, P-value 0.0323). (Table 5).

Different findings were discovered when symptoms were examined in combination. The most prevalent combination of symptoms in the endometritis cases were intermenstural vaginal bleeding, menorrhagia, and menometorrhagia (21/91, data missing in 4 cases). For the controls, the most prevalent symptom was intermenstrual vaginal bleeding by itself (19/99). When symptom combinations in the cases were compared to the controls, the endometritis cases experienced no symptoms roughly twice as often as the controls (14.3% versus 8.1%). Moreover, it was three and a third times more likely for the controls to experience intermenstrual vaginal bleeding, dysmenorrhea, menorrhagia, and menometorrhagia in combination than the cases (10.1% versus 3.3%). (Table 5).

Form of treatment and resolutions of symptoms were categories that were also looked at. Through the data analysis, it was discovered that resolution of symptoms were greater for those who received treatment (antibiotics or surgery) versus those who received no treatment in both cases (56/61 versus 7/12, missing data for 22 cases; P-value 0.0011) and controls (37/38 versus 24/35, missing data for 26 controls; P-value 0.0009). Likewise, surgery was far superior in terms of resolution of symptoms than antibiotics in the cases, as would be expected (8/11 versus 48/50, missing data for 22 cases). (Table 6).

There were a total of 37 control cases that were found to have normal endometrium (missing data for 20 controls). Of these 37 patients, 3 had plasma cells present. Two of these individuals had 1 plasma cell present, while one individual had 2 plasma cells present. There were 42 abnormal endometrium cases found within the control population; and of these, 12 were found to have plasma cells present. Eight of these controls had less than 5 plasma cells present, while 4 were found to have any where from 16 to 39 plasma cells within the tissue. (Table 7).

The phase of cycle was analyzed to determine if there was a difference in this grouping when plasma cells were present and not present. When normal endometrium was examined, it was found that 63.2% had little or no plasma cells present while 36.8% were abundant in plasma cells. Compare this to 62.7% abnormal endometrium with very little or no plasma cells and 37.3% abundant plasma cells (missing data for 1 case; P-value 0.9684). Hence, this analysis showed there was no difference.

In terms of histology, both cases and controls were scrutinized for the presence of plasma cells within the endometrial tissue. This information was then cross linked with the duration of symptoms. It was found that the majority of endometritis cases (52.6%),

had symptoms for <1 year but >1 month. Of these cases, 87.8% had plasma cells present in the endometrium. When only endometritis cases with identified plasma cells were examined, 53.7% of these patients experienced symptoms for <1 year but >1 month. When compared to controls, this data was not statistically significant (missing data for 17 cases; P-value 0.4086). The bulk of the control patients also experienced symptoms for <1 year but >1 month (56.2%); but, only 22% of these cases had plasma cells present. Also, 64.3% of the controls with identified plasma cells fell within the <1 year, >1 month category (missing data for 26 controls). (Table 7).

In order to further investigate the types of immune cells found in tissue with the diagnosis of chronic endometritis, we looked at the occurrence of lymphocytes, neutrophils, macrophages, and eosinophils in the presence of plasma cells for cases and controls. Lymphocytes were the most significantly associated with plasma cells and the diagnosis of endometritis (data missing for 20 controls; P-value <0.0001). At total of 148 biopsies (84 cases, 64 controls) had identified plasma cells. The vast majority of cases had moderate to florid plasma cells throughout (62/95), whereas there were only 12 controls that were identified with large numbers of plasma cells present. Most controls (67/79) consisted of only mild or no plasma cells within the endometrium. In addition, macrophages and neutrophils were also found to coincide with the presence of plasma cells (P-value 0.0029; P-value 0.0048; data missing for 20 controls in both). Eosinophils, on the other hand, were not associated with the diagnosis of endometritis (P-value 0.1668; missing data for 20 controls). (Table 8).

Lastly, several histological features including spindled cells, epithelial changes/metaplasia, and vasculitis within the endometrium were examined and their

occurrence with plasma cells noted. Within the cases, 50% were noted to have spindled cells. Regrettably, this finding was not significant (P-value 0.2346) in that 66.7% of the identified control also had spindled cells present. Epithelial change/metaplasia was exhibited in 49.5% of cases compared to only 7.2% of controls (P-value 0.0595). Vasculitis, conversely, was not found in either the cases or controls. (Table 9).

Discussion

Many interesting inferences were revealed through retrospective examination of clinical and histopathological data of women who underwent endometrial biopsies with and without evidence of chronic endometritis.

In terms of the demographic make up of women who are given the diagnosis of endometritis in our study, many were found to be within the age range of 31-50 years of age and were perimenopausal. These findings may be due to the irregular menstrual cycle of perimenopause. The proliferative phase of the menstrual cycle has been previously associated with plasma cell endometritis (12); and since womens' cycles tend to lengthen with longer proliferative phases during perimenopause, this may be one reason for our findings. Research done by Crum et al. demonstrated that 2/3 of women under 40 who had recently been pregnant (postpartum or post-abortive), received the diagnosis of endometritis. Furthermore, the majority of women between 41 and 50 presented with unexplained uterine bleeding or a history of intrauterine device use (6). Although these identifiers were not specifically looked at in our study, they could also play into the reason for the high number of endometiritis diagnosis in this group.

In addition, significantly more women in our endometritis group were multiparous compared to those who were in the control. It is not clear why parity may

increase the likelihood of chronic endometritis. Possible reasons may include greater disturbances and changes to the endometrium, which make it more susceptible to infection, damage, or irritation leading to the recruitment of plasma cells and lymphocytes.

Unlike studies in the past, our study found hormone use to be significantly associated with endometritis. According to Ross et al. oral contraceptive pills do not increase the risk of endometritis, but do appear to make infections more likely to be asymptomatic (4). Eckert et al goes further by stating current oral contraceptive use does not have any significant associate with endometritis (12). The difference in our finding may be due to the fact that we included all hormone use, not just oral contraceptive pills. Women who were receiving Depo-lupron, hormone replacement therapy, etc were considered in the hormone use category.

Interestingly, no specific clinical symptom was associated with histologic endometritis in our study. Wiesenfeld et al. and Eckert et al. had similar findings (10, 11). Nevertheless, they did determine that abdominal pain during physical exam was associated with chronic endometritis (10, 11, 12). Even more surprisingly, our study showed women with the diagnosis of chronic endometritis were more likely to be asymptomatic that the controls. This may have something to do with Ross et. al finding of oral contraception making endometritis more likely to be asymptomatic, given that a large number of our endometritis population were using hormones at the time of biopsy. Also, a number of our asymptomatic endometritis cases were discovered following routine pap smear. Unfortunately, our study did not investigate the spatial relationship with pregnancy and biopsy, but it could be these samples were obtained during pregnancy

or following birth. Consequently, the high number of plasma cells could be due to pregnant or post-partum endometrium.

Clinical-pathological studies that have looked at density of plasma cell infiltrate and the severity of clinical symptoms have not been able to show an association between the two (1). Our study confirms these previous findings. When looking at duration of symptoms and the amount of plasma cells present, we were unable to show that patients who had a large number of plasma cells found within the endometrium had a longer duration of symptoms.

According to our results, there are several additional features other than just plasma cells that signify chronic endometritis, or at the very least are associated with its diagnosis. Immune cells that were shown to correlate with endometritis include lymphocytes, neutrophils, and macrophages. These findings are similar to other studies (4,6). It was further established that spindle cell alteration of the stroma and epitheliatal change/metaplasia coincide with endometritis (6).

One major limitation of our study was the small number of endometritis cases with corresponding clinical symptoms available for examination. While we were able to gather 95 cases from 2004 to 2007, many samples were missing the corresponding clinical data. Also, endometrial biopsies for the controls were included despite insufficient tissue for examinination in order to preserve the random sample. This method left many cases with absent histological data. In both cases, during analysis, this data was set to missing, which greatly reduced our sample size and ability to make inferences from the data and to develop statistical significance.

In conclusion, our findings have helped to update information about the epidemiology and clinical presentation of chronic endometritis. We have also confirmed the currently agreed upon histopathologic findings of this entity along with correlating the clinical and histopathologic findings in a more diverse patient population than has been previously reported. Unfortunately, given the lack of power in our study, we were unable to provide more information regarding whether or not endometritis should be more carefully considered when examining specimens. As always, future studies with a similar focus, but larger sample size, are needed to further elaborate on the findings of endometritis.

Acknowledgements

We thank Betty Skipper, MD for her contributions to our statistical analysis.

Table 1: Patient Ages

Age Range	Case	Control
21-30	13	0
31-40	23	19
41-50	39	49
51-60	12	21
61-70	4	6
71-80	2	2
81-90	2	2
Total	95	99

Table 2: Patient Ethnicities

Ethnicity	Case	Control
White	25	32
African American	1	1
Hispanic	40	42
Asian	3	0
Native American	7	3
Other	19	21
Total	95	99

Table 3: Menostrual Status

Menstrual Status	Case	Control
Pre-Menopausal	33	49
Peri-Menopausal	42	21
Post-Menopausal	17	29
Total	92	99

Table 4: Hormone Use

Hormone Use	Case	Control	p-value
Yes	28	17	0.029
No	62	80	
Total	90	97	

Table 5: Symptoms: Menometrorrhagia (A), Intermentsrual Vaginal Bleeding (B), Lower Abdominal Pain (C) , Dysmenorrhea (D), Menorrhagia (E), No symptoms and 4 Symptoms.

	(A)	(B)	(C)	(D)	(E)	No Symptoms	A+B+D+E
Case	40	57	23	14	56	13	3
Control	33	67	22	28	60	8	10

Table 6: Forms of Treatment

Treatment	Case	Control
Antibiotics	8	24
Surgery	48	37

Table 7: Duration of Symptoms and Frequency of Plasma Cells

Duration of Symptoms	Cases w/o plasma cells	Cases w/ plasma cells	Controls w/o plasma cells	Controls w/ plasma cells
< 1 Month	1	13	6	1
< 1 Year	5	36	32	9
> 1 Year	5	18	21	4

Table 9: Cells types associated with Endometritis

	Lymphocytes	Neutrophils	Macrophages	Eosinophils
Cases	84	48	35	38
Controls	64	21	11	31

Table 9: Histologic features associated with Endometritis

Group	Spindeled Stroma	Epithelial Change	Vasculitis
Case	41	38	0
Control	5	5	0

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