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Clinical Research

Re-evaluation of Cases Diagnosed as Endometrial Hyperplasia: in 19 Years

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ABSTRACT

Aim: Endometrial hyperplasias (EH) are precancerous lesions. They are quite often misdiagnosed in surgical pathology. For the correct diagnosis of EH, the criteria for the differential diagnosis should be determined and the causes of misdiagnosis should be eliminated. For this reason, we decided to re-evaluate the cases that we had formerly diagnosed as EH.
Material and Method: We re-evaluated 1000 cases who were diagnosed as endometrial hyperplasia in our clinic between January 1995 and April 2014 in terms of the correct diagnosis and factors which lead to misdiagnosis.
Results: During the first examination, 439 of simple hyperplasia without atypia and 61 of simple hyperplasia with atypia were found. But when they were re-evaluated, it was found that only 14 of the cases were simple hyperplasia with atypia but 47 of cases were not containing atypia. Of the 439 cases formerly diagnosed as simple EH without atypia, %31 (n=136) were evaluated as proliferative endometrium, %32 (n=140) as irregular proliferation, %0.7 (n=3) as metaplastic changes, %6.3 (n=28) as endometrial polyp, %25 (n=110) as simple EH and %5 (n=22) as insufficient. When 33 cases which were diagnosed with complex atypical hyperplasia were re-evaluated, complex atypical hyperplasia was found only in 4 cases. When atypical cases were examined evidence of invasion have been detected and diagnosed as adenocarcinoma. Of the 467 cases formerly diagnosed as complex hyperplasia without atypia, %37.7 (n=176) were evaluated as secretory endometrium, %6.6 (n=31) as proliferative endometrium, %8.6 (n=40) as endometrial polyp, %4.9 (n=23) as dysfunctional uterine bleeding, %2.4 (n=11) as Areas-Stella reaction, %4.5 (n=21) as metaplastic changes, %0.2 (n=1) as adenocarcinoma, %33 (n=154) as complex EH and %2.1 (n=10) as insufficient.
Conclusion: Inadequate sampling, technical problems and lack of experience may be assumed as the main factors causing diagnostic discordance.

Key Words: *Endometrium, hyperplasia, diagnostic disagreement*

ÖZET

Endometrial Hiperplazi Tanısı Almış Olguların Tekrar Gözden Geçirilmesi

Amaç: Endometrial hiperplaziler prekanseröz lezyonlardır. Cerrahi patoloji içerisinde oldukça sık yanlış tanı verilen lezyonlardır. Ayırıcı tanıda kriterlerin belirlenmesi ve doğru tanıyı engelleyecek sebeplerin ortadan kaldırılması amaçlandı.
Gereç Yöntem: Ocak 1995-Nisan 2014 yılları arasında kliniğimizde hiperplazi tanısı alan toplam 1000 olguyu doğru tanı ve tanıyı engelleyen nedenler yönünden tekrar değerlendirildi.
Bulgular: İlk bakıda 439 basit atipisiz hiperplazi ve 61 basit atipili hiperplazi tanısı alan olgular tekrar değerlendirildiğinde olguların sadece 14'ünün basit atipili hiperplazi olduğu, 47 olgunun ise atipi içermediği görüldü. Basit atipisiz hiperplazi tanısı olan 439 olgunun %5 (n=22)'u yetersiz, % 31 (n=136)'i proliferatif endometrium, %32 (n=140)'u düzensiz proliferasyon, %0.7 (n=3)'si metaplazik değişiklikler, %6.3 (n=28)'ü endometrial polip ve %25 (n=110)'i basit atipisiz hiperplazisi olarak değerlendirildi. Kompleks atipili hiperplazi tanısı almış 33 olgu yeniden değerlendirildiğinde sadece 4 olguda kompleks atipili hiperplazi olduğu saptandı. Atipili olgular incelendiğinde invazyon bulguları saptandı ve adenokarsinom olduğuna karar verildi. Kompleks atipisiz hiperplazi tanısı olan 467 olgunun %2.1 (n=10)'i yetersiz, %37.7 (n=176)'si sekretuvar endometrium, %6.6 (n=31)'sı proliferatif endometrium, %8.6 (n=40)'sı endometrial polip, %4.9 (n=23)'u disfonksiyonel uterus kanaması, %2.4 (n=11)'ü Arias-Stella reaksiyonu, %4.5 (n=21)'i metaplazik değişiklikler, %0.2 (n=1)'si adenokarsinom ve %33 (n=154)'ü kompleks atipisiz hiperplazisi tanısı aldı.
Sonuç: Yetersiz örnekleme, teknik sorunlar ve deneyim eksikliği tanı uyumsuzluklarının başlıca nedenlerini oluşturmaktadır.

Anahtar Kelimeler: *Endometrium, hiperplazi, yanlış tanı*

According to the classification of the World Health Organization (WHO) in 2003, endometrial hyperplasias are endometrial disorders with a wide spectrum ranging from benign to premalignant changes. Abnormal hormone levels are responsible for these changes (1). In western countries, 150.000-200.000 new cases of EH are diagnosed every year. They are frequently seen lesions (2). The WHO has classified EHs as simple hyperplasias without atypia, complex hyperplasias without atypia, simple atypical hyperplasias and complex atypical hyperplasias (1).

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The correct diagnosis of EH's and their differential diagnosis in a wide spectrum also including endometrial carcinoma are very important (3). Because of the high rate of misdiagnosis in cases of EH, we decided to re-evaluate the cases that we had formerly diagnosed as EH.

MATERIAL AND METHOD

Five hundred cases of simple hyperplasia and 500 cases of complex hyperplasia making a total of 1000 cases of EH that had been diagnosed in our laboratory between January 1995 and April 2014 were randomly selected and re-evaluated. Power analysis applied prior to study showed that at least 60 cases would be enough to be able to determine 15 percent variance with power of 90 percent, from the point of true diagnosis and reasons which prevent diagnosis (α=0.05, β=0.1). Patientswere between30-75years of age (Table 1).The former hematoxylin-eosin stained sections of the cases were studied under the light microscope by the same pathologist for re-diagnosis. Due to the fact that we use the EH classification of WHO published in 2003, all cases were evaluated according to this classification in our clinic. First of all, the sufficiency of the samples was assessed. In case of sufficient endometrial tissue pieces comprising one or more glands or stromas, it was accepted as sufficient, and biopsy samples containing only blood, cervical mucus and pieces belonging to the cervical mucus, or curettage material containing endometrial glands within wide blood masses, were accepted as insufficient (4). Hyperplastic foci, glandular congestion, cytological atypia, metaplastic changes and presence of endometrial polyps were evaluated (5). For the diagnosis of simple hyperplasia, an increase in the gland/stroma ratio in favor of the gland, significant differences in the shape and the size of the glands, pseudostratification, and increase in stromal cellularity were evaluated. As for complex hyperplasia, increased gland/stroma ratio, irregular formations in the glandular component, papillary intraluminal protrusions, increase in alignment, loss of polarity, increase in mitosis, and the presence of apopitotic bodies were taken into consideration (1). Furthermore, the criteria of atypia including nucleolar prominence, chromatin roughening and vesicular apperance, irregularity in the cellular borders, and cytoplasmic eosinophilia were evaluated (6).

RESULTS

During the first examination, 439 of simple hyperplasia without atypia and 61 of simple hyperplasia with atypia were found but when they were re-evaluated, it was found that only 14 of the cases were simple hyperplasia with atypia but 47 of cases were not containing atypia.

Of the 47 cases formerly diagnosed as without atypia %15 (n=7) were evaluated as proliferative endometrium, %55.3 (n=26) as irregular proliferation, %21.3 (n=10) as metaplastic changes, %2.1 (n=1) as endometrial polyp and %6.4 (n=3) simple EH (Table 1).

Of the 439 cases formerly diagnosed as simple EH without atypia, %31 (n=136) were evaluated as proliferative endometrium, %32 (n=140) as irregular proliferation, %0.7 (n=3) as metaplastic changes, %6.3 (n=28) as endometrial polyp %25 (n=110) as simple EH and %5 (n=22) as insufficient (Table 2).

Table 1. *Range of patients's ages without any statistical consideration*

First exemination results	30-40 age	40-50 age	50-60 age	Over 60 age
Simple endometrial hyperplasia without atypia	62	231	109	37
Simple endometrial hyperplasia with atypia	3	11	22	25
Complex endometrial hyperplasia without atypia	37	54	258	118
Complex endometrial hyperplasia with atypia	4	8	17	4

Table 2. *Simple Endometrial Hyperplasia Cases without Atypia*

Simple Hyperplasia Cases without Atypia	*Number of Cases*
Proliferation phase	%31 (n=136)
Irregularproliferation	%32 (n=140)
Changes ofmetaplasia	% 0.7 (n=3)
Endometrial polyps	% 6.3 (n=28)
Simple endometrial hyperplasia	%25 (n=110)
Insufficient	%5 (n=22)
Total	%100 (n=439)

By re-evaluating 33 cases which were diagnosed with complex atypical hyperplasia, complex atypical hyperplasia was found in only 4 cases. When atypical cases were examined they showed evidence of invasion and have been diagnosed as adenocarcinoma. Other 29 cases formerly diagnosed as without atypia, %6.9 (n=2) as endometrial polyp, %10.3 (n=3) as dysfunctional uterine bleeding, %10.3 (n=3) as metaplastic changes and %72.4 (n=21) as complex EH.

Of the 467 cases formerly diagnosed as complex hyperplasia without atypia, %37.7 (n=176) were evaluated as secretory endometrium, %6.6 (n=31) as proliferative endometrium, % 8.6 (n=40) as endometrial polyp, %4.9 (n=23) as dysfunctional uterine bleeding, % 2.4 (n=11) as Areas-Stella reaction, %4.5 (n=21) as metaplastic changes, %0.2 (n=1) as adenocarcinoma, %33 (n=154) as complex Endometrial hyperplasias and %2.1 (n=10) insufficient(Table 3).

Table 3. *Complex Endometrial Hyperplasia Cases without Atypia*

Complex Hyperplasia Cases without Atypia	***Number of Cases***
Secretion phase	%37.7 (n=176)
Proliferation phase	%6.6 (n=31)
Endometrial polyps	%8.6 (n=40)
Dysfunctional uterine bleeding	%4.9 (n=23)
Arias-Stella reaction	%2.4 (n=11)
Changes of metaplasia	%4.5 (n=21)
Adenocarcinoma	%0.2 (n=1)
Complex endometrial hyperplasia	% 33 (n=154)
Insufficient	%2.1 (n=10)
Total	%100 (n=467)

DISCUSSION

Endometrial hyperplasias is a pathological condition characterized with hyperplastic changes in the endometrial glandular and stromal structures lining the uterine cavity (7). The disorder is generally seen in the 50-54 age group of women and rare under the age of 30. Although its etiology has not been fully clarified, it is implicated that most cases of EH result from high levels of estrogens, combined with insufficient levels of progesterone (8,9). EH is more frequently seen in women with a body mass index of over 30 (5). In postmenopausal women, it frequently manifests itself with abnormal uterine bleeding (8). It was diagnosed by histopathological examination of biopsy, curettage or hysterectomy material (5).

According to the classification of the WHO, EHs are divided into 4 groups as simple hyperplasias without atypia, complex hyperplasias without atypia, simple atypical hyperplasias and complex atypical hyperplasias (10). Since they are precancerous and require treatments different than other diseases causing menometrorrhagia, they should be differentiated from adenocarcinomas and other endometrial disorders, as well as their types to be differentiated from other types of EH (3).

Simple hyperplasia can be confused with proliferative endometrium by its pseudostratified epithelium, increased mitosis and active stroma. The cystic glands in senile cystic atrophy, cohesive endometrial glands in endometrial polyp, and focal hyperplastic changes in irregular proliferation may cause confusion in the diagnosis. However, the presence of stromal structure in senile atrophy and thick-walled vessels in endometrial polyp can be helpful in the differential diagnosis (3, 11). Complex hyperplasias should be differentiated from simple hyperplasia, atypical polypoid adenomyoma and endometrial adenocarcinoma (3).

When it is the case that glands are demonstrating disintegration and stromal collapse in the curretage material and menstrual bleeding, this is evaluated as glandular irregularity and congestion, which may be misdiagnosed as hyperplasia. Furthermore, due to the fact that disintegrated proliferative and late secretory glands are observed as close to each other, this may be evaluated as glandular congestion. We think that this is the source of disagreement in the majority of cases diagnosed as dysfunctional uterine bleeding, secretory endometrium and irregular proliferation on the re-evaluation of cases already diagnosed with hyperplasia. Irregular proliferative endometrium may particularly be misdiagnosed as simple hyperplasia because of the demonstration of focal glandular irregularity due to estrogen stimulation. Another lesion that may be mixed up with hyperplasia is endometrial polyp. Some polyps demonstrate focal hyperplasia areas. The presence ofdense stroma and vessels with thick walls is helpful in the differential diagnosis (6). In our study we observed that, the main number of endometrial polyps have been diagnosed as hyperplasia due to comprised fixation problems, mistakes in sections, and excessively bleeding curettages. The new sections applied to the cases were quite helpful. In the new sections, the thick-walled vessels belonging to the polyp and the stromal characteristics of the stroma could be visualized with more easily, and the diagnosis of endometrial polyp was made

Endometrial hyperplasias are quite often misdiagnosed lesions in surgical pathology (3). Consequently, the criteria for the differential diagnosis of these lesions should be determined, and inhibiting factors for correct diagnosis should be eliminated. In a study by Winkler et al. (12) 100 cases formerly diagnosed as EH were re-evaluated by a reference pathologist, and only 24 cases received the diagnosis of EH in this second examination. Of the remaining cases, 25 were diagnosed as polyp, 17 as normal cyclic endometrium, and the rest as metaplastic changes and endometritis. In the study of Allison et al. (5) 2601 cases thought to be EH were evaluated by three academic pathologists. Although the diagnoses of the first two pathologists were consistent with each other, the diagnoses of the third pathologist were 27.7% and 43.9% consistent with the diagnoses of the first and second pathologist, respectively. The highest consistency in the diagnosis was obtained in cases without hyperplasia and the lowest consistency in cases with simple hyperplasia. When the cause of diagnostic inconsistency was assessed, it was seen that specimens smaller and larger than 0.5 cc yielded a diagnostic inconsistency of 64.6% and 56.5%, respectively. In determining the focus of hyperplasia, specimens smaller and larger than 0.5 cc yielded a diagnostic inconsistency of 61.9% and 38.8%, respectively. Furthermore, the diagnostic inconsistency related to endometrial polyp and metaplastic changes was reported, but this was insiginificant. In the present study, Of the 439 cases formerly diagnosed as simple EH without atypia, %31 (n=136) were evaluated as proliferative endometrium, %32 (n=140) as irregular proliferation, %0.7 (n=3) as metaplastic changes, %6.3 (n=28) as endometrial polyp %25(n=110) as simple EH

and %5 (n=22) as insufficient. Of the 467 cases formerly diagnosed as complex hyperplasia without atypia, %37.7 (n=176) were evaluated as secretory endometrium, %6.6 (n=31) as proliferative endometrium, %8.6 (n=40) as endometrial polyp, %4.9 (n=23) as dysfunctional uterine bleeding, %2.4 (n=11) as Areas-Stella reaction, %4.5 (n=21) as metaplastic changes, %0.2 (n=1) as adenocarcinoma, %33 (n=154) as complex EH and %2.1 (n=10) as insufficient.

The criteria for atypia in EHs include loss of cellular polarity, increased irregular lining, anisocytosis, nucleomegaly, hyperchromatism, chromatin coarsening, and prominent nucleolus (3, 13). Moreover, an eosinophilic cytoplasm may be seen in some cases. Although cytoplasmic eosinophilia may be an alert for pathologist, it is not absolutely the necessarycriteria for the diagnosis ofatypia. These changes in cells can be confused with metaplastic changes (3). Formerly, 94 cases out of a total of 1000 cases had been found to have atypia, whereas in the re-evaluation of cases, atypia was confirmed in only 18 cases. The diagnostic consistency for atypia was 38% in the study of Zaino et al. (4) and 16.1% in the study of Allison et al. (11) According to the WHO, many of the diagnostic criteria for atypia (nuclear irregularity, loss of polarity, prominent nucleolus, chromatin coarsening) can also be observed in hormonal irregularities, regeneration and metaplastic changes (14). However, in our study, most of the diagnostic inconsistencies for atypia were associated with technical problems, such as insuitable fixation and insufficient staining quality.

There are some factors limiting the diagnosis in endometrial curettage material. Some of these factors comprise insufficient clinical data, curettage performed in the wrong cycle phase, insuitable fixation of the specimen, mistakes in histopathological sampling, sectioning and insufficient experience (15). Since the diagnoses were confirmed in 23.2% of simple hyperplasia and in 34.2 % of complex hyperplasia cases, we assessed the factors limiting a correct diagnosis. The main causes of misdiagnosis were determined to be insufficient or moderately sufficient in sampling, not sampling the whole of the material, mistakes in fixation and subsequent procedures, improper sectioning and staining, and lack of experience. Some studies have reported that insufficient material is the foremost cause of misdiagnosis (5). However, there is a serious inconsequence between pathologists with regard to the decision of sufficiency. In a study performed on 1280 cases, a diagnosis of insufficiency had been made by the general pathologists in 62 of the cases. These cases that had received insufficient diagnoses, were re-evaluated by the reference group who were Gynaecopathologists and an insufficient diagnosis was made in only 33 of the cases (16). A total of 32 cases we had integrated into our study were evaluated as insufficient. A diagnosis of hyperplasia had been made for these cases. The majority of these cases comprised disintegrated endometrial glands. However, there were cervical epithelium demonstrating immature dysplasia in 2 cases.

In conclusion, for the diagnosis of endometrial specimens from women with the clinical prediagnosis of EH, continuous in-service training should be provided to avoid all deficiencies in the pre-analytic processes (sampling sufficient matherial, matherial fixation, etc.) and analytic processes (proper processing of the matherial, sectioning, staining-cover, diagnosis) to provide clinicopathological correlation and to increasingexperience.

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