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IS PRE-OPERATIVE BLOCK CONSULTATION NECESSARY IN ATYPICAL ENDOMETRIAL HYPERPLASIA?

ATİPİLİ ENDOMETRİAL HİPERPLAZİLERDE CERRAHİ ÖNCESİ BLOK KONSÜLTASYONU GEREKLİ MİDİR?

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SUMMARY

Introduction: *This study aimed to investigate the need to re-evaluate paraffin block pathology preparations of endometrial biopsy samples taken from patients diagnosed with atypical endometrial hyperplasia (AEH) at different institutions by expert gynaecologic pathologists before surgery at a tertiary hospital.*

Materials and Methods: *This study included 116 patients diagnosed with AEH based on endometrial biopsy samples taken at different institutions between January 2017 and January 2021 and operated on at our clinic. The paraffin blocks of all patient samples included in the study were re-evaluated at the Pathology Department of our hospital (block consultation). Patients were divided into two groups as follows: those diagnosed with AEH based on endometrial biopsy at an external centre (all patients) and those diagnosed with AEH based on paraffin block examination. The post-operative pathology results of the two groups were compared.*

Results: *Block consultation indicated AEH in 77 (66.4%) of the patients with AEH diagnosed at an external centre. Post-operative pathology results revealed that 15 (12.9%) patients had benign, 42 (36.2%) had AEH and 59 (50.9%) had malignant. On comparing the post-operative pathology results of the two groups, no significant difference was observed (p = 0.252). There was no significant difference between the two groups in terms of the grade and stage of the malignancy detected on post-operative pathological evaluation (p = 0.603 and p = 0.552, respectively).*

Conclusion: *Although re-examination of the paraffin blocks of patients diagnosed with AEH based on endometrial biopsy samples taken at different institutions by gynaecologic pathologists (block consultation) led to*

different results, no significant difference was noted on comparing the post-operative pathology results. To ensure that workload does not increase and to save time, patients diagnosed with AEH based on endometrial biopsy can be operated on without re-examining the paraffin blocks to confirm the diagnosis.

ÖZ

Giriş: *Farklı kurumlarda alınan endometrial biyopsi sonucunda atipili endometrial hiperplazi (AEH) tanısı konmuş hastaların hazır parafin blok patoloji preparatlarının 3. basamak bir hastanede cerrahi öncesi uzman jinekolog patologlar tarafından tekrar değerlendirilmesinin gerekliliğini araştırmayı amaçladık.*

Gereç ve Yöntem: *Bu çalışmaya Ocak 2017-Ocak 2021 tarihleri arasında farklı kurumlarda endometrial biyopsi sonucunda AEH tanısı konarak kliniğimizde opere edilmiş 116 hasta dahil edildi. Çalışmaya alınan tüm hastalara ait parafin bloklar hastanemiz Patoloji Bölümü'nde yeniden değerlendirildi (blok konsültasyon). Tüm hastalar kliniğimizde opere edildi. Hastalar dış merkezde endometrial biyopsi sonucunda AEH tanısı alanlar (tüm hastalar) ve parafin blok konsültasyon sonucu AEH tanısı alanlar olmak üzere 2 gruba ayrıldı. Bu iki grup postoperatif patoloji sonuçları açısından karşılaştırıldı.*

Bulgular: *Çalışmaya alınan dış merkez AEH tanılı hastanın blok konsültasyonu sonucu 77 (%66.4) AEH tanısı aldı. Postoperatif (cerrahi sonrası) patoloji sonucunda 15 (%12.9) hasta benign, 42 (%36.2) hasta AEH ve 59 (%50.9) hasta malignite tanısı aldı. İki grup postoperatif patoloji sonuçları açısından karşılaştırıldığında istatistiksel olarak anlamlı fark görülmedi (p=0.252). Postoperatif patolojik değerlendirmede malignite tespit edilen hastaların grade ve evre açısından iki grup arasında karşılaştırma yapıldığında da istatistiksel olarak anlamlı fark saptanmadı (p=0.603 ve p= 0.552).*

Sonuç: *Farklı kurumlarda alınan endometrial biyopsi sonucunda AEH tanısı alan hastaların parafin bloklarının tekrar jinekolog patologlar tarafından yapılan incelemesinde (blok konsültasyon) sonucunda farklı sonuçlar çıkmakla birlikte; postoperatif patoloji sonuçları açısından değerlendirme yapıldığında anlamlı fark bulunmamıştır. İş yükü ve zaman kaybını artırmamak adına endometrial biyopsi sonucunda AEH tanısı konan hastaların tanıyı doğrulamak adına parafin blokları yeniden incelenmeden opere edilmesinde sakınca yoktur.*

INTRODUCTION

Endometrial hyperplasia (EH) is an increase in the ratio of gland/stroma and irregular proliferation of endometrial glands. In 1994, the World Health Organization (WHO) determined four types of EH: hyperplasia with simple atypia, hyperplasia with complex atypia, simple hyperplasia without atypia, and complex hyperplasia without atypia. In particular, atypical EH (AEH) is strongly associated with endometrial cancer (EC) (1). However, WHO's 1994 criteria are highly subjective and can lead to inconsistency, especially in the distinction between EH and AEH. Therefore, studies on EC risk associated with EH are warranted (2).

EH usually develops as a result of estrogen excess that is not counter-acted by progesterone. The difference between simple hyperplasia without atypia and complex atypical hyperplasia is that the former resembles normal proliferative endometrium, and the latter resembles well-differentiated endometrioid adenocarcinoma. Many studies reported the rate of cancer accompanying EH between 15% and 54% (3). However, the progression risk for carcinoma is the highest among patients with AEH and there is a high risk of persistence despite hormonal treatment (4).

Previous studies that diagnostically reassessed the WHO system reported kappa values of 0.2-0.7 for overall inter-observer agreement in EH diagnosis. With kappa values ranging from 0.28 to 0.65 or less than 25% agreement, the diagnosis of AEH was the least reproducible classification. Characteristics, such as inadequate specimens, metaplasia or polyps, have been suggested as factors responsible for the variability of the diagnosis of atypia (5-8).

This study aimed to investigate the need to re-evaluate paraffin block pathology preparations of samples from patients diagnosed with AEH based on endometrial biopsy at different institutions by gynaecologic pathologists at a tertiary hospital. In this way, it is aimed to determine the risks that may occur due to the increase in comorbidity due to unnecessary operation of the patients or the inability to provide curative treatment due to incomplete treatment.

MATERIALS AND METHODS

The present study included 116 patients with AEH diagnosis based on endometrial biopsy of samples taken at different institutions between January 2017 and January 2021 and operated on at our clinic. The hospital ethics committee approved the study (2021/03-37) and the study was conducted following the Declaration of Helsinki. This was a retrospective study and medical data were obtained from patient records.

Patients data, including body mass index (BMI), age, menopausal status, parity, comorbidities (diabetes and hypertension), smoking, Ca-125, results of endometrial biopsy conducted at an external centre, results of paraffin block re-evaluation at our hospital, results of intraoperative frozen pathology and post-operative pathology, were examined. Patients were classified into two groups: those diagnosed with AEH according to endometrial biopsy at an external centre and those diagnosed with AEH according to paraffin block examination. The post-operative pathology results of the two groups were compared.

The prepared paraffin blocks of the samples from patients diagnosed with AEH based on endometrial biopsy performed at different institutions were collected and examined at the pathology laboratory of our hospital. A 5-µ-thick section was taken from each block of each patient sample and a single preparation was made. The preparations were stained with haematoxylin–eosin and re-examined through light microscopy by gynaecologic pathologists.

Of 116 patients with AEH as a result of endometrial biopsy performed in an external center; As a result of the second examination, the decision of operation was made for patients who were diagnosed with malignancy or AEH. The patients who were diagnosed as benign in the second examination consisted of patients who wanted to be operated after they were informed about the results of both the first and second pathological examinations and the risks were explained.

All patients underwent hysterectomy ± bilateral salpingoophorectomy/bilateral salpingectomy procedure with intraoperative frozen pathology at our hospital. The operation of patients with benign frozen section results was terminated. For patients with EC, hysterectomy samples were evaluated for grade, myometrial invasion, LVSI and tumour size. Based on the results of these evaluations, surgical staging was performed for samples from patients with high-grade, non-endometrioid histological type, deep myometrial invasion (≥1/2), tumour diameter >2 cm and cervical involvement. After the frozen sections were examined, the samples was fixed i formalin and paraffin blocks were prepard. Patients diagnosed with EC based on post-operative pathology results were subjected to surgical staging according to FIGO 2009.

SPSS (SPSS Statistics version 22.0, SPSS Inc.) statistical software was used for statistical analyses. A t-test was used for parametric variables comparison, and Pearson's chi-square and Fisher's exact tests were used for categorical variables comparison. Categorical variables are expressed as numbers and percentages (n; %), whereas numerical variables are presented as mean ± standard deviation (SD) and median [quartile]. A P value of <0.05 was considered statistically significant.

RESULTS

The study included 116 patients with AEH diagnosed based on an endometrial biopsy performed at an external centre. The patients' mean age was 52.6 ± 9.2 years, and the mean BMI was 32.5 ± 6.3. Of all the patients, 31 (26.7%) had diabetes, 51 (44.0%) had hypertension and 62 (53.4%) had a history of smoking (Table 1). After re-examination of all 116 patients diagnosed with AEH at the external centre by gynaecological pathologists at our hospital, 77 (66.4%) patients were diagnosed with AEH, 8 (6.9%) with benign and 31 (26.7%) with malignant (Table 1).

On analysing the post-operative pathology results of all 116 patients, 15 (12.9%) patients were diagnosed with benign, 42 (36.2%) with AEH and 59 (50.9%) with malignant. On analysing the post-operative pathology results of 77 patients re-diagnosed with AEH based on paraffin block examination, 9 (11.7%) patients were diagnosed with benign, 37 (48.1%) with AEH and 31 (40.3%) with malignant. No significant difference was found between the two groups regarding post-operative pathology results ($p = 0.252$; Table 2).

Table 1. Demographic characteristics and pathology results of patients

Characteristics	Patients (n)	% or ± SD
Age	52.6	±9.2
BMI	32.5	±6.3
Nulliparity	2	1.7
Diabetes	31	26.7
Hypertension	51	44.0
Smoking	62	53.4
Block consultation result: Benign	8	6.9
Block consultation result: AEH	77	66.4
Block consultation result: Malignant	31	26.7
Post-operative pathology result: malignant, grade 1	35	59.3
Post-operative pathology result: malignant, grade 2	23	39.0
Post-operative pathology result: malignant, grade 3	1	1.7
Post-operative pathology result: malignant, stage 1A	51	86.4
Post-operative pathology result: malignant, stage 1B	6	10.2
Post-operative pathology result: malignant, stage 2	2	3.4

BMI, body mass index; AEH, atypical endometrial hyperplasia
Results are presented as mean ± standard deviation (SD) for parametric values and n (%) for nonparametric values.

Table 2. Comparison of post-operative pathology results of patients diagnosed with AEH at an external centre and those diagnosed with AEH based on paraffin block examination

	External Centre (n = 116)		PB (n = 77)		P value
	n	%	n	%	
Benign	15	12.9	9	11.7	0.252
AEH	42	36.2	37	48.1	0.252
Malignant	59	50.9	31	40.3	0.252
Grade 1	35	59.3	21	67.7	0.603
Grade 2	23	39.0	9	29.9	0.603
Grade 3	1	1.7	1	3.2	0.603
Stage 1A	51	86.4	27	87.1	0.552
Stage 1B	6	10.2	4	12.9	0.552
Stage 2	2	3.4	0	0	0.552

AEH, atypical endometrial hyperplasia; PB, paraffin block
Results are presented as mean ± standard deviation (SD) for parametric values and n (%) for nonparametric values.

The results of post-operative pathologic examination of 116 patients with AEH diagnosed at an external centre revealed that 59 patients had malignancy (endometrioid adenocarcinoma). Of these, 35 (59.3%) patients had grade 1, 23 (39%) had grade 2 and 1 (1.7%) had grade 3 malignancy; moreover, 51 (86.4%) patients were at stage 1A, 6 (10.2%) were at stage 1B and 2 (3.4%) were at stage 2. Of the 77 patients whose data were re-evaluated by gynaecological pathologists at our hospital and diagnosed with AEH based on paraffin block examination, the grade and stage of 31 patients diagnosed with malignancy on post-operative pathological examination were analysed. Of these, 21 (67.7%) patients had grade 1, 9 (29%) had grade 2 and 1 (3.2%) had grade 3; moreover, 27 (87.1%) were at stage 1A, 4 (12.9%) were at stage 1B and none were at stage 2. No significant difference wasfound between the two groups regarding grade and stage ($p = 0.603$ and $p = 0.552$, respectively; Table 2).

DISCUSSION

In the present study, the results of approximately 66.4% of the patients with AEH diagnosis based on endometrial biopsy at an external centre were in agreement with the results of paraffin block examination conducted by gynaeco-pathologists in our hospital. Paraffin block examination is a pathology practice frequently used for the evaluation of several tissues. In general, agreement rates are around 50% (9,10).

Paraffin block examination is also frequently performed in gynaecological pathology practice. In a study on 34 patients with vulvar intraepithelial neoplasia, good inter-pathologist agreement was noted (kappa 0.75); however, it was moderate (kappa 0.50) in another study that evaluated lymphovascular invasion in early stage cervical cancer (11,12). Another study that conducted paraffin block examination of 66 patients with high-grade endometrial carcinoma showed good agreement (13).

According to Kurman's study; The presence of cytological atypia has been demonstrated to be a distinguishing factor for the probability of progression to carcinoma in proliferative lesions. It has been observed that it progresses to carcinoma at a rate of 1% in simple hyperplasia, 3% in complex hyperplasia, 8% in hyperplasia with simple atypia, and 29% in hyperplasia with complex atypia. Although the proportional difference between these four subgroups is not statistically significant; The presence of cytological atypia in endometrial hyperplasia has been identified as the most useful criterion for estimating the probability of progression to carcinoma (14). In other studies; showed that patients with atypical endometrial hyperplasia have a 20-52% risk of co-existing endometrial cancer (2,15-21).

In the present study, paraffin block examination of 116 patients diagnosed with AEH at an external centre revealed that 66.4% of the patients had the same diagnosis, whereas 6.9% of the patients were diagnosed with benign and 26% with malignancy. In a prospective study on 289 patients with AEH, 74 (25.6%) patients were diagnosed with benign, 115 (39.8%) with AEH, 84 (29.1%) with malignancy and no consensus could be reached for 16 (5.5%) patients based on re-evaluated biopsy results (2). The previous study findings are similar to those of the present study.

In addition to the agreement between initial diagnosis and paraffin block examination, an important aspect is the agreement between post-operative pathological evaluation and pre-operative pathologic diagnosis, especially in patients diagnosed with AEH. In the present study, no significant difference was found regarding results of post-operative pathology test at our hospital between the patients diagnosed with AEH based on endometrial biopsy at an external centre (116 patients) and those diagnosed with AEH based on paraffin block examination by gynaecological pathologists at our hospital (77 patients). In addition, no significant difference was found between the groups regarding both grade and stage of the disease in patients with post-operative malignancy.

Despite the 66.4% agreement between the results of paraffin block examination and endometrial biopsy of patients diagnosed with AEH at an external centre, no difference was observed on post-operative pathological evaluation. The post-operative pathology results of all patients and of those diagnosed with AEH based on block consultation were similar. Thus, no difference was found regarding diagnosis, disease stage or extra interventions required. This raises the question of why we used our hospital pathologists as the gold standard because when we made a comparison in terms of postoperative pathology results, there was no difference in terms of the pathology of the external center and our hospital. An editorial comment on this subject by Carr N. for the comparison study of pathological evaluation in prostate biopsy is also noteworthy (22).

This study has certain limitations: (a) this is a retrospective study and (b) patients initially diagnosed with AEH in our hospital were not included. The study's strengths are as follows: (a) the large sample size and (b) the comparison of the post-operative pathology results.

CONCLUSION

The results of paraffin block examination of the samples of patients diagnosed with AEH at an external centre were consistent with the initial diagnosis and there was no difference in the post-operative pathology results. As there is no difference in terms of malignancy rate, tumour grade and stage in the post-operative evaluation of patients diagnosed with AEH in an external centre, surgery can be performed on these patients without examining paraffin blocks to avoid unnecessary labour burden.

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