Evaluation of the histopathological diagnosis of patients preoperatively diagnosed with atypical endometrial hyperplasia after hysterectomy

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Summary

Objective: To evaluate the patients diagnosed with atypical endometrial hyperplasia preoperatively, and compare preoperative and postoperative results. *Materials and method:* We investigated the files of 58 patients diagnosed with atypical endometrial hyperplasia who were treated surgically after clinical evaluation. We compared sociodemographic diagnosis, preoperative and postoperative diagnosis. *Results:* Mean-age of patients was 51.7. Obesity, diabetes mellitus, hypertension and infertility were seen, respectively, in eight cases (13.7%), 12 cases (20.6%), 19 cases (32.7%) and four cases (6.8%). While endometrial cancer was not found postoperatively in patients preoperatively diagnosed with simple atypical endometrial hyperplasia, we determined well differentiated endometrial adenocarcinoma in 44.7% of the patients. *Conclusion:* In the literature the probability of developing well differentiated endometrial cancer from complex atypical endometrial hyperplasia is 40-50%. All patients diagnosed with complex atypical hyperplasia should be evaluated preoperatively for well differentiated adenocarcinoma and undergo an appropriate surgical technique and staging.

Key words: Atypia; Biopsy; Consensus diagnosis; Endometrial hyperplasia; Endometrioid adenocarcinoma; Hysterectomy.

Introduction

Endometrial hyperplasia (EH) is a non-physiological non-invasive proliferation of the endometrium. Histologically, the disease spectrum ranges from benign to precancerous lesions. Without considering age, EH is seen in 1.5% of all abnormal uterine hemorrhage although its exact incidence is unknown [1]. This figure is about 15% in women with postmenopausal hemorrhage [1, 2]. Although prevalence of EH increases after the ages of 45 to 55, EH has been reported in young adults with anovulatory cycles and even during the teenage period [1, 2]. The most important reason for ongoing discussions about diagnosis, treatment and classification of EH is the fact that 5-10% of the women diagnosed as having this pathology have concomitant genital cancers [1-5]. The primary risk factor for EH is unbalanced estrogen and/or hyperestrogenic milieu. This is frequently associated with such conditions as anovulatory cycles (adolescence period, polycystic ovaries, perimenopausal period), excessive endogenous estrogen release (granulosa cell tumor, thecoma, adrenocortical hyperplasia, obesity), and exogenous estrogen intake (tamoxifen). Furthermore, genetic predisposition exists in women with hereditary non-polyposis colorectal cancer. Excessive estrogen leads to hyperplastic lesions by acting via PTEN mutation or k-RAS activation, and to mutagenic and carcinogenic effects in the hyperplastic endometrial lesions depending on total dose and duration of action. The standard diagnostic method for diagnosis of endometrial hyperplasia is endometrial biopsy. Differing diagnostic success rates have been reported in studies on classical dilation and curettage, endometrial sampling with pipette, hysterescopic biopsy or office hysterescopic biopsies. Well differentiated adenocarcinoma is found in hysterectomy specimens in 17-62% of the patients with endometrial hyperplasia with complex atypia [2]. In the present study, we investigated the accordance between preoperative and postoperative diagnoses in 58 patients who were diagnosed as having atypical endometrial hyperplasia by means of dilation and curettage (D&C) and who underwent hysterectomy in three hospitals in Izmir. We discuss current therapeutic approaches in the patients with a diagnosis of atypical endometrial hyperplasia in accordance with the literature.

Materials and Methods

Hospital files of 58 patients who were diagnosed as having atypical endometrial hyperplasia by means of fractional curettage and who underwent surgical treatment upon clinical evaluation in three hospitals in Izmir were reviewed retrospectively. In the patient files diagnostic methods (D&C, office H/S) and accordance between preoperative and postoperative diagnoses were reviewed along with risk factors predisposing to endometrial cancer. All patients who were diagnosed as having postoperative carcinoma were evaluated for grade, depth of myometrial invasion, involvement of lymphovascular area (LVA), and tumor size. The patients for whom frozen-section (FS) investigation was performed during surgery and who were diagnosed as having endometrial cancer were staged surgically. The patients were classified according to FIGO criteria.

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Results

Mean age of the 58 patients meeting study criteria was 51.7 years. Eight (13.7%) of the patients were obese, 12 (20.6%) had diabetes mellitus, 19 (32.7%) had hypertension, and four (6.8%) had infertility. Three patients (5.17%) had been operated previously for breast cancer and had adjuvant chemotherapy. The most common complaint at the time of presentation was irregular vaginal bleeding in 48 (82.7%) of the patients with 31 (53.4%) patients being in the postmenopausal period and 27 (46.6%) patients being in the premenopausal period (Table 1). Forty-nine out of 58 patients underwent fractional curettage under general anesthesia and nine patients under local anesthesia. Evaluating the results of fractional curettage, we found that 38 patients had a diagnosis of complex atypical hyperplasia (CAH), and 20 had a diagnosis of simple atypical hyperplasia (SAH). Mean length of time between biopsy procedure and operation was 4.9 ± 1.7 weeks. In 58 patients with a preoperative diagnosis of atypical endometrial hyperplasia who were operated, no cancer was observed among any of the 20 patients with a preoperative diagnosis of SAH whereas endometrial cancer was found in 17 (44.7%) of the 38 patients with a preoperative diagnosis of CAH (Table 2). Grade 1 tumor was seen in 16 of these patients and grade 3 tumor in one. Fifteen patients had myometrial invasion; depth of invasion was more than one-half in three of them and involvement of lymphovascular area in two. In 14 patients who had a diagnosis of CAH, frozen-section pathologic examination was performed during surgey. Results of frozen-section procedure were reported as being malignant in six of 14 patients (42.8%) and these patients underwent surgical staging. No lymph node metastasis was observed in any patients undergoing surgical staging. Results of paraffin block examinations were reported as being cancer in all of six patients. In eight patients whose results of frozen-section examination were reported as being benign, results of paraffin block examination were benign in six patients and endometrial cancer in two patients. No lymph node metastasis in the pelvic region was observed in any of the patients with cancer found during hysterectomy. In terms of histological diagnosis, pathological diagnosis in the first biopsy was compatible with the results of examination of paraffin blocks in 25 out of 58 patients. Operative pathologies defined lower grade lesions in six patients whereas well differentiated adenocarcinoma was found in 17 patients. The compatibility rate was 43.1%.

Table 1. — *Characteristics of women with preoperative simple atypical endometrial hyperplasia*.

	Mean ± S.D. (range)
Age	51.7 ± 9.2
Parity	2.6 ± 1.5
Time passed from diagnosis to operation	4.9 ± 1.7
	n (%)
Hypertension	19 (32.7)
Diabetes mellitus	12 (20.6)
Obesity	8 (13.7)
Infertility	4 (6.8)
Menapousal status	31 (53.4)
Vaginal bleeding	48 (82.6)

Table 2. — *Preoperative and postoperative diagnosis compatibility*.

	Preoperative D&C diagnosis	Diagnosis of postoperative hysterectomy			
		CAH	SAH	Other	Endometrium cancer
Simple atypical hyperplasia	20		9 (45%)	11 (55%)	0
Complex atypical hyperplasia	38	16 (42.1%)	1 (2.6%)	4 (10.5%)	17 (44.7%)

Discussion

Associated with irregular glandular and stromal increase in the endometrium, endometrial hyperplasias take place between normal proliferative endometrium and well differentiated adenocarcinomas, and are important because of their associations with endometrial carcinomas [6]. The fact that carcinoma develops in some of the patients with untreated hyperplasia and hyperplasia is found in many areas in hysterectomy specimens which were diagnosed as having endometrial carcinoma raises the importance of diagnosing hyperplasia [2]. It has been shown in some retrospective studies where specimens were reevaluated that atypical hyperplasia existed in up to 45% of patients with endometrial cancer, and that concomitant cancers existed in 17-62% of specimens of patients with atypical hyperplasia [3]. Myometrial invasion may be found in 7.9-51% of these cancers [3-5, 7]. In our series, results of hysterectomy were reported as endometrial cancer in 44.7% of the operations being performed for complex atypical hyperplasia. Fifteen of 17 patients in whom we found endometrial cancer after hysterectomy had myometrial invasion. Depth of invasion was more than one-half in three of them. Evaluating risk factors (e.g., anovulation, obesity, estrogen replacement therapy, tamoxifen, diabetes mellitus, hypertension, estrogen-releasing ovarian tumors, and familial cancer syndrome) and symptoms are of importance [8]. Postmenopausal bleeding, thickness of postmenopausal endometrium > 5 mm on transvaginal ultrasound, endometrial fluid accumulation, endometrial irregularities, and presence of endometrial cells in postmenopausal smears are conditions warranting further investigation. The gold standard in the diagnosis is endometrial sampling. Sampling may be done with dilation and curettage (sensitivity > 90%), biopsy at the office with pipel (sensitivity 83-97%), and hysterescopic biopsy (sensitivity 98%). Hysteroscopy may detect structural pathologies (e.g., polyps, myomas) more precisely than D&C while the macroscopic view may be confused with benign polyps in hyperplasias and endometrial cancers [9, 10]. Biopsy under hysteroscopic guidance has the highest diagnostic value but we use classical D&C in patients with suspected malignancy. Although its prognostic role is controversial, hysteroscopy has the potential to spread

cytologically into the peritoneal cavity. Hysteroscopic biopsy at the office or low-pressure hysteroscopic biopsy for patients in whom malignancy is strongly suspected clinically (in the presence of inadequate material) is more successful in providing adequate material for diagnosis from focal lesions developing from structural pathology (polyps) [1, 3, 9, 10]. Diagnosis was made with D&C in our patients. Well differentiated adenocarcinoma was found at high rates (17-62%) in hysterectomy specimens of the patients with atypical endometrial hyperplasia. Thus, diagnostic methods with higher rates of preoperative sensitivity and specificity are required to plan optimal treatment for these patients.

Accurate defining and classifying hyperplasia is especially important in samples of endometrial biopsy and curettage because a correct diagnosis leads to clinical treatment modalities thay may vary substantially depending on the type of hyperplasia. Intra- and interobserver variations in the treatment of hyperplasia cause concern about reproducibility of a classification plan [11, 12]. Reasons for high risk of unknown cancer in women with a preoperative diagnosis of complex atypical endometrial hyperplasia originate from inconsistent and different interpretations of histological criteria used in distinguishing complex atypical endometrial hyperplasia from grade 1 adenocarcinoma. In concordance with this finding, well differentiated adenocarcinoma was found in surgical specimens of 17 (44.7%) of 38 patients with CAH in the present study. In a GOG study, 306 endometrial biopsy samples with diagnoses of atypical endometrial hyperplasia were evaluated. In the evaluation consisting of three separate pathological schools, a consensus was reached in 38% of diagnoses of atypical hyperplasia whereas diagnoses at later stage were reported in 29% and diagnoses at earlier stages in 25% [13]. Thus, many authors have recommended a modified classification system of WHO in order to make more standardized diagnoses and perform more appropriate treatments. Classification of endometrial intraepithelial hyperplasia (EIN) was developed to meet this requirement. EIN is a classification system developed to detect cancer precursors better than the WHO-94 and direct the treatment of patients with hyperplasia better.

In this classification system endometrial pathologies are divided in three main categories:

1) Benign hyperplasias (benign hyperplasias due to unbalanced estrogen);

2) EIN (a monoclonal and neoplastic occurrence which is first local and later diffuse);

3) Carcinoma.

Criteria determining this category have not been widely used clinically although they seem to be associated with cancer risk, and to be objective. Use of EIN in daily practice and its cost-effectiveness analysis is unknown. Its routine use is still controversial. At the current point, distinguishing atypical endometrial hyperplasia from well differentiated adenocarcinoma should be evaluated together with biological markers, age, obesity, and other known risk factors by considering the limitations of the interventional and diagnostic methods. Current studies have shown that biopsy material obtained with D&C is more adequate in terms of diagnostic evaluation compared to endometrial biopsy with pipel, and it distinguishes atypical hyperplasia better [10, 13-15]. Furthermore, the rate of unexpected cancer significantly increases in hysterectomy materials with advanced age [1, 3, 11, 13]. In a patient series of 824 patients in which sensitivity of preoperative D&C in risk of undefined adenocarcinoma and complex atypical endometrial hyperplasia was investigated, Burgman *et al*. found that age was an important risk factor in the diagnosis of unexpected cancer. According to the results of that study, mean age of women with cancer was 59 after hysterectomy while mean age of those without cancer was 55. Risk of cancer rises each decade after age of 50. Cancer rate is 40% in the women younger than 50 years while it hasw been reported to be higher than 78% in women older than 80 years [13]. In the present study, mean age was found to be 52.4 years for those patients whose result of hysterectomy was reported to be malignant and 51.7 years for those with benign hysterectomy results to be benign.

The fact that malignancy is found at high rates in patients with CAH, difficulty in defining it intraoperatively is a serious problem which may be encountered in the therapeutic process. Cancer found in the patients operated for CAH was usually well differentiated and showed superficial infiltration. The lesion in such cases is usually not observed. Thus, sections are made in this group of patients randomly through a frozen-section (FS) procedure. This implies that the tumor can not be found at high rates in FS studies. Looking at studies on intraoperative frozen-section procedures to avoid incomplete surgery in patients with CAH, the positive predictive rate of FS ranges between 39% and 75% [16-18]. Additionally, even in patients with known endometrial cancer obvious inconsistency is seen for diagnosis with FS among pathologists and upstaging diagnoses are found in the diagnosis [19]. While studies are still being continued on optimal diagnostic and therapeutic strategies of patients with atypical hyperplasia, performing surgical staging would not be an excessive option in patients with atypical hyperplasia as a consequence of a high rate of overlapping between atypical hyperplasia and well differentiated adenocarcinoma as potential advantages of surgical staging increases in early stages of endometrial adenocarcinoma [20, 21].

Conclusion

Our aim in carrying out the present study was to draw attention to the association between atypical endometrial hyperplasia and well differentiated adenocarcinoma, to mention diagnostic difficulties in that distinguishment, and to emphasize performing complete surgical staging by considering patients with a preoperative diagnosis of atypical endometrial hyperplasia as well differentiated endometrial carcinoma to plan optimal treatment of such patients.

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