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Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment

L.-C. HORN*, U. SCHNURRBUSCH*, K. BILEK†, B. HENTSCHEL‡ & J. EINENKEL†
Institute of Pathology (Gynecopathology); †Department of Obstetrics and Gynecology; and ‡Institute of Medical Informatics, Statistic and Epidemiology, University of Leipzig, Germany

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In most cases, the endometrioid adenocarcinoma of the endometrium is preceded by hyperplasia with different risk of progression into carcinoma. The original histologic slides from 560 consecutive cases with complex and atypical hyperplasia were re-examined to assess the interobserver-correlation. The hyperplasias were analyzed separately for their likelihood of progression to carcinoma in patients with and without progestogen hormonal therapy. In all cases, a fractional re-curreting was performed to establish the state of the disease.
The leading symptom was vaginal bleeding in 65.5% of the cases in the postmenopausal period. Eighty-six percent of the patients presented with obesity (BMI > 30 kg/m^2), 23% had had an exogeneous use of estrogens. Twenty-two cases were reclassified as simple hyperplasia and excluded from further analysis. The interobserver-correlation was 91% for complex, 92% for atypical hyperplasia, and 89% for endometrioid carcinoma, representing an overall correlation of 90%. Two percent of the cases with complex hyperplasia (8/390) progressed into carcinoma and 10.5% into atypical hyperplasia. Fifty-two percent of the atypical hyperplasias (58/112) progressed into carcinomas. In the case of progestogen treatment ($n = 208$; $P < 0.0001$) 61.5% showed remission confirmed by re-curetting, compared with 20.3% of the cases without hormonal treatment ($n = 182$; $P < 0.0001$).
Endometrial hyperplasia without atypia is likely to respond to hormonal treatment. Especially in postmenopausal situation, atypical hyperplasia should be treated with total hysterectomy.

KEYWORDS: endometrial cancer, endometrial hyperplasia, hormonal treatment, progression, interobserver-correlation.

Endometrial cancer (EC) is the most common invasive malignancy in the female genital tract with an estimated incidence of 40,100 new cases in the United States of America in the year 2003[1]. According to that statistic, it represents the fourth commonest cancer in women.

The endometrioid adenocarcinoma is the most frequent histologic variant, accounting for 57–80% of

Address correspondence and reprint requests to: Lars-Christian Horn, MD, PhD, Institute of Pathology, University of Leipzig, Liebigstrasse 26, Leipzig D-04103, Germany. Email: hornl@medizin.uni-leipzig.de

the cases[2]. Almost all cases of that histologic type are hormone-dependent and associated with obesity, exogeneous use of hormones, and elevated estrogen levels[3,4]. The lesion is known to arise from an endometrial hyperplasia[5–7]. The risk of progression of hyperplasia into endometrioid carcinoma is more closely related to the presence of cytologic atypia and to architectural crowding. The morphologic distinction between atypical hyperplasia and well-differentiated carcinoma in an endometrial biopsy or in curettings may be problematic[8,9] with a marked variation of interobserver correlation[10,11]. The present study was designed to assess interobserver agreement in the diagnosis of complex and atypical endometrial hyperplasia as well as to estimate the risk of EC in those lesions.

Materials and methods

About 602 consecutive cases were selected from the Gyn-Path Laboratory at the Department of Obstetrics and Gynecology, University of Leipzig, which represented complex or atypical endometrial hyperplasia on initial endometrial curettings. In 560 out of 602 women (93.0%), clinical data regarding the follow-up were available.

These patients were included in the study. The original hematoxylin and eosin stained slides of the 560 cases were re-evaluated for endometrial hyperplasia, using the histopathologic criteria of the WHO-classification to establish the diagnosis of simple, complex, and atypical hyperplasia as well as of well-differentiated endometrioid carcinoma[12]. The slide-review was performed without the knowledge of previous histologic diagnosis and of the behavior of the lesion (regression, persistence, progression). Initial histologic diagnosis (K.B.) was compared within the reviewed one (L.-C.H.) performing interobserver correlation. In cases with discrepancy between initial and reviewed diagnosis, the slides were discussed at a multihead microscope (K.B. and L.-C.H.) to establish the final diagnosis which was then stated in the further analysis. Intraobserver-correlation was not performed.

The results of the histologic re-evaluation were compared to the clinical data, hormonal treatment, and follow-up of the patients (J.E.), and statistical analysis (B.H.) using the Chi-square test (SPSS for windows®, version 10.0) was performed.

Clinical data were screened for a history of exogeneous use of estrogens, obesity (ie, BMI $> 30\,kg/m^2$[13]); arterial hypertension (diastolic pressure > 95 mmHg and systolic pressure > 160 mmHg), and diabetes mellitus.

Thirty-six patients with atypical hyperplasia were treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) because of additional symptoms. Hysterectomy and BSO were performed in 22 patients in whom complex hyperplasia was accompanied by uterine fibroids and/or descensus.

Two hundred and fifteen patients were treated with progestogens for 3 months. The other patients were asymptomatic after their curettage and consequently had no further treatment. Re-curetting was performed in all these cases after a median time of 4.8 months (range: 3–22 months) to control the endometrial status.

Endometrioid carcinomas associated with endometrial hyperplasia on re-examination of the curetting specimen or in patients who had been treated with hysterectomy without progestogen therapy were stated as synchronous. A metachroneous carcinoma was defined as an EC diagnosed histologically in re-curetting in cases with and without progestogeneous therapy.

Results

The majority of the patients (540/560 = 96.4%) presented with vaginal bleeding as the leading symptom; two-thirds of them in the postmenopausal period (354/540 = 65.5%). About one-fourth (23.5%) of the patients had had exogeneous use of estrogens, the majority of the cases represented with obesity (86.3% with BMI of more than $30\,kg/m^2$). There was no difference in the frequency of obesity between cases of complex and atypical endometrial hyperplasia (81.1% versus 90.7%; $P > 0.05$). About two-thirds (63.6%) of the patients suffered from arterial hypertension, and 21.2% were diabetics.

On histologic re-examination twenty-two of all cases were reclassified from complex hyperplasia into simple hyperplasia (3.9% of all 560 cases) and were excluded from further analysis. Therefore, the initial interobserver correlation was 96.1%.

In complex and atypical hyperplasias the agreement was 91.2% (458/502), the percentages of correlation and the cases which were under- or overdiagnosed are summarized in Table 1. Six out of the 102 endometrioid carcinomas were underdiagnosed initally. All of them were well-differentiated (G1) tumors.

Of all patients, 38.4% (215/560) received hormonal therapy according to their symptoms. Most of the patients, especially those with atypical hyperplasia, refused hormonal treatment.

Therefore, only 215 patients received hormonal treatment with norethistheroneacetat or medroxyprogesteroneacetat (MPA) over a period of 3–5

Table 1. Interobserver correlation in cases of endometrial hyperplasia (cases which were re-evaluated as simple hyperplasia are excluded)

	Interobserver correlation (%)	Disagreement	Cases with overestimation	Cases with underestimation
Complex hyperlasia ($n=390$)	91.0	35	26	9
Atypical hyperlasia ($n=112$)	92.0	9	3	6
Endometrial carcinoma				
Synchronous ($n=66$)	88.9	4	3	1
Metachronous ($n=36$)	90.4	7	2	5
All carcinomas ($n=102$)	89.2	11	5	6
All cases ($n=538$)	89.8	55	34	21

months. Pre- and perimenopausal patients were treated with norethistheroneacetat 5 mg/die and MPA 10 mg/die, respectively. Postmenopausal women received 20–50 mg/die MPA.

About three-fifth (59.5%) of the cases showed remission of the endometrial hyperplasia on re-curetting, 77 cases showed persistence of the lesion; in five cases the lesion progressed from complex to atypical hyperplasia and in another five cases from hyperplasia to endometrioid carcinoma (for details see Table 2).

In 36 patients, the atypical hyperplasia was accompanied by an endometrioid adenocarcinoma, representing a synchronous carcinoma. All cases were treated with total abdominal hysterectomy and bilateral BSO. In six of the patients who received hysterectomy as a treatment of the endometrial carcinoma, which had been diagnosed at fractional curetting, no cancer could be detected in the hysterectomy specimen regardless of the extensive or complete embedding of the endometrium that has been described recently[14]. The majority of the synchronous cancers (29/36=80.5%) were well-differentiated carcinomas, five were moderately and two poorly differentiated.

Six patients with complex hyperplasia who were initially treated by hysterectomy with BSO because of uterine fibroids/descensus suffered from an endometrioid carcinoma, staged pT1a/pT1b in hysterectomy specimen.

Discussion

Noninvasive endometrial proliferations (endometrial hyperplasias) constitute a group of heterogeneous lesions displaying a variety of cytologic and architectural alterations. The simple hyperplasia (syn. glandular-cystic hyperplasia) is a benign proliferation with the reported risk 0–1% of progression into carcinoma[5,6]. The WHO-classification includes a lesion termed 'simple atypical hyperplasia'[12]. The risk of a carcinoma resulting from that kind of endometrial hyperplasia has been described as ranging from 3 to 17%[5,6]. No case of simple atypical hyperplasia has been found in our retrospective screened material. In accordance with others, we assume that this category, if it does exist, is extremely rare and should be withdrawn form the classification systems and it is doubtful if it represents a reproducible histologic category[10,11,15].

Progestogens are the treatment of choice of endometrial hyperplasia because of their inhibitory effect

Table 2. Behavior of complex and atypical hyperplasia in cases with and without progestogeneous therapy*

	Remission	Persistence	Progression to Atypical hyperlasia	Progression to Endometrial carcinoma
Complex hyperlasia				
With progestogens† ($n=208$)	128 (61.5%)	73 (35.1%)	5 (2.4%)	2 (1.0%)
Without progestogens† ($n=182$)	37 (20.3%)	103 (56.6%)	36 (19.8%)	6 (3.3%)
All complex progestogens‡ ($n=390$)	165 (42.3%)	176 (45.1%)	41 (10.5%)	8 (2.0%)
Atypical hyperlasia				
With progestogens† ($n=7$)	–	4		3
Without progestogens† ($n=105$)	–	50 (47.6%)		55 (52.4%)
All complex progestogens‡ ($n=112$)		54 (48.2%)		58 (51.8%)
All cases ($n=502$)	165 (32.9%)	230 (45.8%)	41 (8.2%)	66 (13.1%)

*Cases with synchronous carcinomas are not included.

†,‡The differences regarding the progression of complex versus atypical hyperlasia were statistically significant ($P<0.0001$), the same statistical level was seen in a separate analysis of patients who received progestogens.

on epithelial proliferation. They act by reducing estrogenic receptors and increasing their catabolism, stimulating the 17-β-hydroxyesteroid dehydrogenase and sulfotransferase enzymes and thereby diminishing the estrogenic dominant conditions that lead to endometrial abnormalities which occur in hyperestrogenism[16]. In the case of a simple or complex hyperplasia, hormonal treatment can preserve the fertility in young women and can also be used in older patients with significant surgical risk.

In the present study, nearly two-thirds of the patients with complex hyperplasia, treated with progestogens, showed a regression of the lesion in fractional recurreting after 3 months (see Table 2). In 35.1% out of 208 patients, the lesions persisted. In five patients, a progression into atypical hyperplasia and in two patients into endometriod carcinoma occurred, representing an overall rate of progression of 2.4%. The rate of persistence of complex hyperplasia is higher than reported in literature. Unfortunately, the patients' compliance to treatment has not been controlled. Additionally, the high number of persistent lesions might have partly been caused by the duration of the progestin-therapy (3–5 months), and could probably be reduced by a prolongation of the hormonal therapy.

Three out of seven women with atypical hyperplasia who were treated primarily with progestogens, because of a high anesthetic risk, progressed into malignancy. About 20% of complex hyperplasias which received no hormonal treatment progressed into atypical hyperplasia, and six developed a carcinoma. In the group of the atypical hyperplasia without hormonal treatment, one half showed persistence and the other half progressed into carcinomas. In agreement with our results, most previous studies have found that an endometrial hyperplasia without atypia is likely to respond to hormonal therapy[17–20].

In atypical hyperplasias, the risk of consecutive EC ranges between 25 and 45%[5,6,17]. In the study of Ferenczy and Gelfand[17] it is stated that 10 out of 20 patients treated with progestogens for 'endometrial hyperplasia with cytologic atypia' had a persistence and five of them recurred. Additionally, five patients developed an adenocarcinoma during a mean follow-up time 5.5 years. The mean follow-up time in the study of Kurman *et al*.[6] has been reported as 17.8 years. Unfortunately, the regressive nature of the lesions was not confirmed histologically by recuretting in 34 cases. Baak *et al*.[5] reported a mean follow-up time between 17 and 32 months. The fact that the cancer risks in these two studies are as similar as they are (see Table 3), in spite of the dif- ferences in follow-up time and case numbers, indicates that most of the progression into cancer occurs in the first few years after the original endometrial biopsy/ curetting on which the diagnosis is based and is in accordance with our study.

This is supported by the fact that in hysterectomy specimen taken immediately after the biopsy/curretage diagnosis of atypical hyperplasia, the hyperplasia was associated with an endometrioid carcinoma in 17–43% of the cases[8,21–23]. Mecke *et al*.[24] reported three cancers in 56 resected uteri for complex hyperplasia (5.3%) within 4 weeks. Eight cancers were detected after an initial diagnosis of atypical hyperplasia (57.1%). Again, these data support the fact that the atypical hyperplasia is a directly precancerous lesion of the endometrioid adenocarcinoma.

The material obtained by endometrial scraping or hysteroscopically guided biopsy may not always have been entirely representative of the whole endometrium. Small foci of transformation into cancer left *in situ* at the first curretage might have already been present in the endometrium and have coexisted with the endometrial hyperplasia. For those cases, the term 'progression into cancer' is less adequate than 'association with cancer'. In the present study, we used metachronous ($n=66$) for the first and synchronous cancer ($n=36$) for the latter cases.

Therapeutically, the atypical hyperplasia in postmenopausal women and in perimenopausal patients who does not want to preserve their fertility should be treated with simple total hysterectomy. In older women with high surgical risk as well as in premenopausal women, the atypical hyperplasia can be treated with progestogens[19,25]. In cases of atypical hyperplasia, Randall and Kurman[19] reported regression in 16 out of 17 patients treated with progestogens. In endometroid cancer, a cure rate of about 66% has been reported[19,25]. The success of hormonal treatment in those cases probably could be improved by a combination of progestogens and GnRH-analogs[7]. This therapeutical decision may be supported by the fact that endometrial carcinomas associated with hyperplasia have a better prognosis than cancers without hyperlasia on resected uteri[26].

Due to the inconsistency of diagnoses and to the problems of reproducibility of the histopathlogic diagnosis; standardized clinical management of women with proliferative endometrial lesions is complicated. Several attempts have been made to distinguish atypical hyperplasia from well-differentiated endometroid adenocarcinomas[8,9,22]. However, difficulties still persisted[27]. In the present study, the interobserver correlation was 91% for complex and 92% for atypical hyperplasia, and 89.2% for endometrioid carcinomas. These percentages represent

Table 3. Risk of endometrial cancer in endometrial hyperplasia

	Kurman *et al.*[6]		Ferenczy and Gelfand[17]*		Baak *et al.*[5]		Horn *et al.* (present study)		overall risk	
	Total	With cancer	Total	With cancer	Total	With cancer	Total	With cancer	Total	With cancer
Simple hyperplasia	93	1 (1.1%)			8	0 (0%)	Not done		101	1 (1.0%)
Complex hyperplasia	29	1 (3.4%)			6	1 (16.7%)	390	8 (2.0%)	425	15 (3.5%)
Atypical hyperplasia	35	10 (28.6%)	20	5 (20%)	11	5 (45.4%)	112	58 (51.8%)	178	78 (43.8%)
Total	157	12 (7.6%)	20	5 (20%)	25	6 (24%)	502	66 (13.3%)	704	89 (12.6%)

*In the cases without cellular atypia, it was not started if cases with simple hyperplasia or only cases with complex hyperplasia were included in the study. Therefore, only cases with atypical hyperplasia were included in this study.

a surprisingly high agreement. Another one institutional study reported 60% interobserver agreement for complex, 47% for atypical hyperplasia, and 83% for endometrioid carcinoma[11]. A European multicenter study reported 46% for complex, 25% for atypical and 49% for well-differentiated endometrioid carcinomas[10]. Skov *et al.*[27] described an overall interobserver agreement for simple, complex, and atypical hyperplasia ranging from 42 to 59%. The reasons for the differences in interobserver correlation are quite unclear and may be partly attributable to the training background of the participants. In the American study, all five pathologists were from the same institution and had varying levels of training and experience[11] (minimum of 2-year fellowship). The European study was multicentric, including five pathologists from different countries with a special interest in gynecologic pathology[10]. The training background of the six pathologists in the study of Skov *et al.*[27] was not specified. Finally, the slides were screened by two pathologists from one institution with a minimum of experience in gynecologic pathology of 9 years in the present study (L.-C.H. and K.B.).

This might be a disadvantage of the present study, because in a one-institutional approach both observers may be proned to the same classification errors (due to their similar training background). Thus, the high degree of correlation of the diagnosis is not surprising but represents one aspect of quality management. One additional aspect should also be kept in mind: contrary to the other studies, the present one included only cases with unequivocal endometrial pathologies and no cyclic endometrium.

Because of the mentioned diagnostic dilemma, Bergeron *et al.*[10] have proposed a simplified 'Working Classification' for hysteroscopic biopsies and curettage specimens of the endometrium using only three diagnostic categories to improve diagnostic accuracy consisting of hyperplasia (complex), endometrioid neoplasia (previously atypical hyperplasia and well-differentiated carcinoma), and cyclical endometrium. This provoked strong diversities[28–30] which will not be discussed in detail here. On the basis of molecular data, Mutter and the 'Endometrial Collaborative Group' proposed the terms endometrial hyperplasia (previously simple and complex hyperplasia) and endometrial intraepithelial neoplasia for simple and complex atypical hyperplasia as endometrial intraepithelial neoplasia-concept[31]. However, recent cytogenetic studies[32] have shown that some chromosomal changes, detected by comparative genomic hybridization analysis, might be present in cases without cellular atypia.

At the moment, we recommend to use the diagnostic criteria and entities proposed by the last edition of the WHO-classification[12] until further molecular data are available which could possibly change classification system[15]. This potential change should be accepted internationally and has to be agreed on by the different research groups.

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