Uterus Resected for Complex Atypical Hyperplasia of the Endometrium and Co-existing Endometrial Cancer: Ten-year Experience in a Regional Hospital

TN YAU MBChB, MRCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Kowloon, Hong Kong
WM PONG MBChB, FRCPA, FHKAM (Pathology)
Department of Pathology, Queen Elizabeth Hospital, Kowloon, Hong Kong
WH LI MBBS, MRCOG, FHKAM (O&G)
MYM CHAN MBBS, FRCOG, FHKAM (O&G)
Department of Obstetrics & Gynaecology, Queen Elizabeth Hospital, Kowloon, Hong Kong

***Objective*:**
To investigate the probability, the diagnostic accuracy of endometrial biopsy and curettage and the value of pathologists' comments in predicting co-existing endometrial cancer for uterus resected for complex atypical hyperplasia of the endometrium.

***Methods*:**
This was a retrospective analysis using data from the operative database of Queen Elizabeth Hospital from 1 July 1998 to 30 June 2008. Sixty-two patients who underwent hysterectomy for complex atypical hyperplasia were recruited for analysis. Patients with prolonged time interval from diagnosis of complex atypical hyperplasia to hysterectomy and those with indeterminate final histology were excluded.

***Results*:**
Final histopathological evaluation of hysterectomy specimens revealed endometrial cancer in 28 (45%) of 62 patients. Advanced age and being menopausal were significantly associated with cancer (p=0.027 and 0.002, respectively). A preoperative diagnosis of complex atypical hyperplasia was established by endometrial biopsy in 31 patients and curettage in 31 others. Among them, 16 (52%) and 12 (39%) respectively had endometrial cancer. The diagnostic accuracy of endometrial biopsies and curettage was similar (p=0.307). The chance of co-existing endometrial cancer was significantly associated with the severity of complex atypical hyperplasia revealed by microscopy (p<0.001). When the complex atypical hyperplasia was focal and / or there was mild nuclear atypia, the chance of co-existing cancer was low (1/13, 8%). For specimens reported as 'cancer could not be excluded', the chance of such a cancer was 70% (21/30). For specimens with complex atypical hyperplasia for which there was no further comment, the chance of co-existing cancer was 32% (6/19).

***Conclusion*:**
A relatively high incidence of co-existing endometrial cancer was found (45%). Older age and being menopausal increased the likelihood of co-existing endometrial cancer. The diagnostic accuracy of endometrial biopsy and curettage was comparable. Pathologists' comment on the microscopic appearance of specimens was an important predictor in co-existing endometrial cancer.

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Correspondence to: Dr TN Yau
Email: karentnyau@yahoo.com.hk

Introduction

Endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an increase in the gland / stroma ratio compared to the proliferative endometrium. The histopathological assessment of endometrial hyperplasia should include examination for nuclear, architectural, and cytological abnormalities. Based on the complexity of endometrial glands and any cytological atypia, it provides a basis for a classification into simple or complex forms of hyperplasia, with or without atypia[1,2]. The current classification proposed by the World Health Organization in 1994 and revised in 2003, entails a spectrum of diseases and takes into account both cytological and architectural abnormalities.

Endometrial complex atypical hyperplasia (CAH) is characterised by an increased glandular complexity with irregular growths and cytological atypia. It was first reported to be a precursor lesion of endometrial cancer (EC) by Cullen in 1900[3]. Almost half a century later, Gusberg[4] found that oestrogenic stimulation could cause endometrial hyperplasia and carcinoma. The natural history of the hyperplasia and its progression to cancer was described by Kurman et al[5]. Only 1% of simple hyperplasias and 3% of complex hyperplasias without cytological atypia progress to carcinoma, whereas 8% of simple hyperplasias and 29% of complex hyperplasias with cytological atypia do so. Increasing degrees of glandular complexity and crowding appear to increase the likelihood of such progression, but not to the extent that cytological atypia does.

In addition to the high risk of progression to overt EC, EC may already co-exist with CAH at the time of diagnosis but be missed due to sampling errors. In the literature, the prevalence of co-existing EC in uteri resected for CAH was reported to be 15 to 52%. Table 1 summarises findings from frequently cited studies[6-19].

This raises a concern about treating CAH in younger patients with progestogen, or when ovaries are preserved at the time of hysterectomy. Missing the co-existing EC may result in under-treatment and patients finally diagnosed to have EC after hysterectomy may need a second operation to remove the preserved ovaries to enable proper staging by gynae-oncologists. Therefore, predicting the chance of co-existing EC in CAH is important for patient management and counselling.

We reviewed patients who had hysterectomies for CAH during a 10-year period to investigate whether we could predict the chance of co-existing EC. We also tried to analyse whether a formal curettage is associated with a higher accuracy rate for diagnosing EC in the presence of

Table 1. Literature search on prevalence of co-existing endometrial cancer in patients with a preoperative diagnosis of atypical endometrial hyperplasia[6-19]

Authors	Atypical endometrial hyperplasia	Co-existing endometrial cancer
Gusberg and Kaplan[6], 1953	90	20 (22%)
Tavassoli and Kraus[7], 1978	48	12 (25%)
Kurman and Norris[8], 1982	89	15 (17%)
King et al[9], 1984	119	18 (15%)
Lambert et al[10], 1994	29	6 (21%)
Liapis et al[11], 1994	73	26 (36%)
Hunter et al[12], 1994	54	19 (35%)
Janicek and Rosenshein[13], 1994	44	19 (43%)
Dunton et al[14], 1996	23	12 (52%)
Widra et al[15], 1995	24	12 (50%)
Xie et al[16], 2002	86	33 (38%)
Bilgin et al[17], 2004	46	11 (24%)
Shutter and Wright[18], 2005	60	29 (48%)
Trimble et al[19], 2006	289	123 (43%)
Total	**1074**	**355 (33%)**

CAH. We also wanted to determine whether interpretation by pathologists (based on specimen microscopy) could assist in prediction of EC. The results of this study could aid both gynaecologists and pathologists in the general understanding and management of CAH.

Methods

The operative database in Queen Elizabeth Hospital covering a 10-year period (1 July 1998 to 30 June 2008) was searched. 'Complex atypical hyperplasia' recorded as a preoperative or operative diagnosis, 'total abdominal hysterectomy with or without bilateral salpingo-oophorectomy (BSO)', 'laparoscopic-assisted vaginal hysterectomy with or without BSO', and 'vaginal hysterectomy' were used as the key words for the search. A total of 73 patients with a diagnosis of CAH who underwent hysterectomy were identified.

Ideally, the interval from diagnosis of CAH to hysterectomy should be short, so as to minimise the chance of progression to EC. We therefore arbitrarily used 6 months as the cutoff point, and patients having a hysterectomy more than 6 months after the initial diagnosis of CAH were excluded. In our series there were 10 such patients, having their hysterectomy 8 to 36 months after endometrial sampling. Another patient was excluded because the final histological diagnosis of the hysterectomy specimen was uncertain, there being CAH bordering on early endometrioid adenocarcinoma.

Finally, 62 patients who had hysterectomies performed within a mean of 7 (range, 2-20) weeks after endometrial sampling were analysed. All the data including the demographic and clinical characteristics, method of diagnosis, surgical and pathological details were extracted from patient records. The patients were categorised into two groups according to the results of pathology of the hysterectomy specimens: the non-EC group (non-cancer group) and the EC group (cancer group). The microscopic description of CAH of pathologists in each case was further analysed and categorised according to comments about severity of CAH, as follows:

- Group A: CAH was focal and / or mild nuclear atypia was present (Fig 1);
- Group B: CAH, no other comment (Fig 2);
- Group C: CAH and cancer could not be excluded (Fig 3).

Chi-square tests were applied to categorical data, with Fisher's exact test used for expected values of less than 5 in any category. Continuous data were compared using standard *t* tests (one-tailed). A p value of less than 0.05 was accepted as statistically significant.

Results

Histopathological evaluation of hysterectomy specimens revealed endometrial adenocarcinoma in 28 (45%) patients. This formed the 'cancer group' and the 34 remaining patients formed the 'non-cancer group'.

The demographic and clinical characteristics of the patients are summarised in Table 2. The mean age of all the patients was 49 (range, 33-87; standard deviation, 10) years.

The prevalence of co-existing EC in menopausal and pre-menopausal women, and pre-menopausal women aged 45 years or below and older than 45 years is shown in Table 3.

Subgroup analysis based on comments about the microscopy of biopsy specimens by pathologists is shown in Table 4. When the CAH was commented to be focal or the nuclear atypia was mild, only 1 (8%) out of 13 patients had EC. When the pathologists commented that EC could not be excluded, 21 (70%) out of 30 patients turned out to have EC, but if there were no other comments, the figure was 31%. The most significant association was with the comment on the original endometrial biopsy / curettage by the pathologists ($p<0.001$), irrespective of whether the biopsy was performed in our hospital or elsewhere.

Analysis of known risks / predisposing factors, including parity, family history, hormonal exposure (e.g. tamoxifen), diabetes mellitus, and hypertension showed no significant difference between the cancer and non-cancer groups. The duration of presenting symptoms and the time interval from the diagnosis of CAH to hysterectomy were similar in both groups. The type of uterine sampling (biopsy vs curettage) was also not associated with any significant difference in EC prevalence ($p=0.307$).

Table 5 summarises the stage and histological grade distribution in patients with co-existing EC. Twenty-six

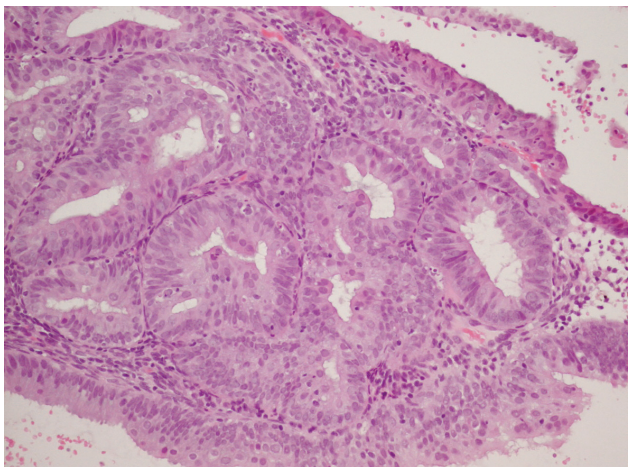

Figure 1. This is a case of complex atypical hyperplasia (CAH). The degree of atypia is mild with slight enlargement and rounding of nuclei (x 200). The final pathology (hysterectomy specimen) showed CAH

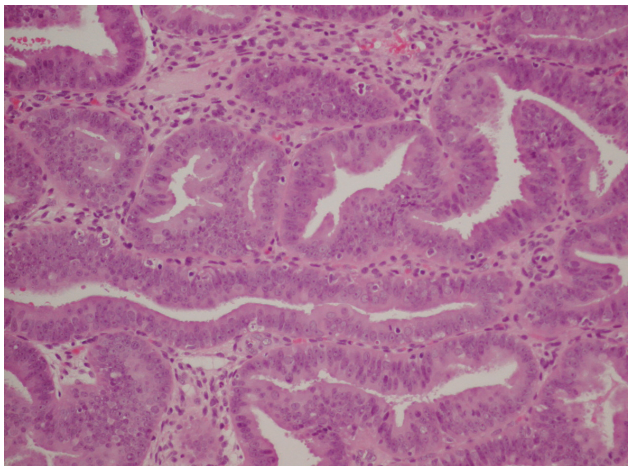

Figure 2. This is a case of complex atypical hyperplasia (CAH), with no other comments. The endometrial glands are back-to-back and branched. The lining cells feature obvious atypia with large round nuclei and prominent nucleoli (x 200). The final pathology of hysterectomy specimen also showed CAH

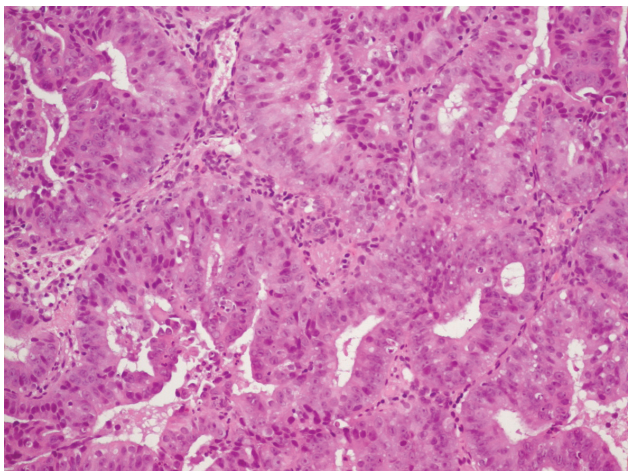

Figure 3. In this case of complex atypical hyperplasia, there is a beginning of confluence of the atypical glands (in the left lower field) in rare foci. This is worrisome for invasive tumour (x 200). This case turned out to be endometrial cancer

Table 2. Clinical characteristics of patients with preoperative diagnosis of endometrial complex atypical hyperplasia (CAH)

	Non-cancer group* (n=34)	Cancer group* (n=28)	p Value
Age (years)	46 ± 7	52 ± 12	0.027
Parity	1.7 ± 1.0	1.4 ± 1.7	0.476
Postmenopausal	2 (6%)	11 (39%)	0.002
Co-existing hypertension / diabetes mellitus / both	6 (18%)	11 (39%)	0.057
Positive family history	3 (9%)	1 (4%)	0.620
Hormonal exposure before presenting symptoms	1 (3%)	2 (7%)	0.585
Duration of presenting symptoms (months)	11 ± 14	9 ± 12	0.617
Diagnosis			
Endometrial sampling	15 (44%)	16 (57%)	0.307
Curettage	19 (56%)	12 (43%)	
In our hospital	29 (85%)	20 (71%)	0.220
Outside (referrals)	5 (15%)	8 (29%)	
Progestogen after diagnosis of CAH	7 (21%)	3 (11%)	0.490
Time to hysterectomy (weeks)	8 ± 5	5 ± 4	0.053

* Data are shown as mean ± standard deviation, or No. (%)

Table 3. Incidence of co-existing endometrial cancer according to menopausal status and age in pre-menopausal patients

	Non-cancer group	Cancer group	p Value
Pre-menopausal	32 (65%)	17 (35%)	0.002
Menopausal	2 (15%)	11 (85%)	
Pre-menopausal			
≤45 years	18 (75%)	6 (25%)	0.232
>45 years	14 (56%)	11 (44%)	

(93%) of the patients had endometrioid adenocarcinoma while two had mucinous adenocarcinoma. Sixteen (57%) of them had EC localised to the endometrium only (stage IA). While in the other 12 patients it was invading the myometrium (7 patients into the inner half, 2 into the outer half), the endocervical glands (1 patient), the endocervical stroma (1 patient), and the peritoneum (peritoneal cytology being positive in 1 patient).

Table 4. Sub-group analysis of comments by pathologists

	Non-cancer group (n=34)	Cancer group (n=28)	p Value
Group A CAH* was focal and / or mild nuclear atypia was present	12 (35%)	1 (4%)	-
Group B CAH, no other comment	13 (38%)	6 (21%)	-
Group C CAH and cancer could not be excluded	9 (26%)	21 (75%)	<0.001

* CAH denotes complex atypical hyperplasia

Discussion

Our results show that the prevalence of EC in uteri removed for CAH was 45%, which was greater than the 33% reported in historical data (Table 1) but comparable to that reported in the Gynecologic Oncology Group study by Trimble et al[19], which was the only prospective cohort investigation. Trimble et al[19] has commented that several factors may have contributed to the high prevalence, including its prospective design, multi-institutional recruitment of a large sample, and independent review by a panel of gynaecological pathologists. Besides, the threshold for the diagnosis of carcinoma may have been lowered in recent years, particularly in hysterectomy specimens. Conversely, the threshold for the diagnosis of carcinoma may be higher in biopsy specimens, because ordinarily such a diagnosis prompts major surgery.

Atypical hyperplasia is diagnosed by the presence of nuclear atypia, which is characterised by rounding of nuclei, coarsening of chromatin and prominent nucleoli, in the hyperplastic endometrial glands. However, making such a diagnosis is problematic, due to significant inter- and intra-observer variation[20-22], which is sometimes further complicated by the presence of metaplastic changes and fixation artifacts. Theoretically, review of slides by a single pathologist should reduce inter-observer variation, but may not be practicable in many settings. Our results indicated that additional comment on the diagnosis of atypical hyperplasia related to the extent and the degree of severity of atypia in the pathology report, was the most significant predictor of co-existing EC (p<0.001), although the slides were not reviewed by a single pathologist. Atypia can be arbitrarily stratified into three groups—mild, moderate and severe—depending on the degree of nuclear enlargement, variation of nuclear sizes / shapes and coarsening of the chromatin. Actually, it is not our standard practice to sub-classify the degree of atypia in atypical hyperplasia. It is only performed when the degree of atypia or architecture are 'unusual' (i.e. too focal, too mild, too complex, or too atypical) such that the reporting pathologist makes a further comment. There were no objective criteria for this sub-classification and the comments themselves were quite subjective. Nevertheless, our results indicated that such comments were predictive of a co-existing EC. Based on the pathologists' comments, we could further stratify patients into different groups with different risks of co-existing EC and for counselling purpose. When the pathologist commented that EC could not excluded, serious consideration was given to offering surgery rather than progestogens as the definitive treatment. Even if progestogens are highly desirable in younger patients who want to preserve fertility, cautious counselling is advised to ensure that the inherent risk of co-existing EC and the need for repeated endometrial assessment is fully understood. For pre-menopausal patients undergoing hysterectomies, they should be strongly advised to have

Table 5. Stage and grade distribution of patients with co-existing endometrial cancer*

	Stage						Total
	IA	IB	IC	IIA	IIB	IIIA	
Grade I	15	5	2	1	-	-	**23**
Grade II	1	2	-	-	1	1	**5**
Grade III	-	-	-	-	-	-	**-**
Total	**16**	**7**	**2**	**1**	**1**	**1**	**28**

* The patients were staged and graded according to FIGO (International Federation of Gynecology and Obstetrics) stage 1988

bilateral oophorectomy at the same time, so as to avoid a second operation (for staging) if the hysterectomy specimen shows co-existing carcinoma. On the other hand, if the atypia is mild or only focal, it may be quite safe to be conservative and allows the patient to retain her uterus and her ovaries.

Besides the overwhelming predictive value of additional comments by pathologists, our results show that advanced age and menopausal status are also associated with a higher probability of co-existing EC (p=0.027 and 0.002, respectively). Menopausal patients usually undergo hysterectomy and BSO if they are diagnosed to have CAH. For those who are pre-menopausal, age may be an important consideration for prophylactic BSO. Women approaching or older than 45 years appear to be more suitable for prophylactic BSO and vice versa, although the basis of such a recommendation is not supported by a statistically significant difference in risk (p=0.232). Therefore, age alone cannot be used to predict EC in pre-menopausal women with CAH, with any confidence.

Our results indicate that a diagnosis of CAH after endometrial biopsy and curettage confer the same risk of co-existing EC, which is also consistent with previous studies[23]. Endometrial biopsy offers the advantage of being performed in an office setting, without the need for anaesthesia. However, as we did not include patients with preoperative diagnosis of EC in this study, further studies are needed to evaluate endometrial biopsy versus curettage.

Among our 28 patients with EC, 12 (43%) had disease outside the endometrium, which amounts to 19% (12/62) of the patients with CAH. According to our management protocol, if only hysterectomy and BSO are performed, adjuvant therapy (irradiation or chemotherapy) is offered to patients with stage II or higher disease, as well as stage I disease with deep myometrial invasion and / or poorly differentiated tumours. Hence, among our patients, five (2 with stage IC, 1 with stage IIA, 1 with stage IIB, and 1 with stage IIIA) would have been treated differently had there been a preoperative diagnosis of EC.

In the literature, various non-invasive or non-surgical methods to determine the presence of co-existing EC have been reported. Altintas et al[24] had reported that deep myometrial invasion could be accurately predicted in approximately 90% of patients with EC by gross examination of the uterus and frozen sections. However, Bilgin et al[17] reported that frozen sections missed 50% of ECs, especially in those patients without myometrial invasion. Therefore, the value of frozen sections appears limited in patients suspected to have EC without deep myometrial invasion. Although the risk of lymphadenopathy is low in patients with no or superficial myometrial invasion, preservation of the ovaries remains a contentious issue, if frozen sections cannot differentiate between pure CAH and EC. Moreover, the workload to obtain an intra-operative diagnosis for all CAH patients may become overwhelming in service hospital settings.

Immediate preoperative hysteroscopic examination of the endometrial cavity is another possible approach to differentiate hyperplasia from carcinoma. Ceci et al[25] reported hysteroscopy with targeted biopsy or dilatation and curettage to have excellent sensitivity and specificity for detecting endometrial pathology. However, Ben-Yehuda et al[26] failed to show improvement in the sensitivity for the detection of endometrial hyperplasia or carcinoma with curettage.

Evidence of myometrial invasion is an indicator of EC and if detected before surgery, confirms the diagnosis of EC, though once again disease limited to the endometrium will be missed. Imaging techniques such as transvaginal ultrasound examination and magnetic resonance imaging (MRI) to assess the depth of myometrial invasion have been widely studied. The results are conflicting and both techniques are operator dependent[27-31]. In general, MRI is superior to transvaginal ultrasound for evaluating myometrial invasion. However, MRI is expensive, time-consuming, and thus would not be suitable as a screening test. On the other hand, transvaginal ultrasound examination is a relatively low-cost technique, which can be easily performed and repeated, although it requires more operator experience than MRI to achieve high accuracy.

In the future, development of new molecular markers by immuno-histochemical studies is a possible way out in predicting the presence of co-existing EC in CAH.

Conclusion

Co-existing EC is commonly found in uteri resected for CAH (45%). During the counselling for patients with a preoperative diagnosis of CAH, the possibility of co-existing EC should be carefully discussed before proceeding to any modalities of treatment, especially when conservative treatment with progestogens or conservation of the ovaries are opted for.

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