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ORIGINAL ARTICLE

The diagnosis of endometrial atypia by hysteroscopy with guided biopsy in postmenopausal patients with hyperplasia: a reliable practice?

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Abstract Atypical endometrial hyperplasia shows a high propensity to progress to endometrioid adenocarcinoma. Hysteroscopic biopsy represents a valid method for detection of this pre-neoplastic disease. This study assesses the accuracy of histological diagnosis of endometrial atypia in hysteroscopy with blind biopsy, in postmenopausal women with an endometrial thickness (ET) greater than 5 mm. In order, to determine the relationship between ET and atypia more precisely, ET was subdivided in three categories of 5–7 mm, ≥7–9 mm and >9 mm. Ninety-nine postmenopausal patients, aged 51–79 years, with abnormal uterine bleeding and an endometrial thickness >5 mm in whom a diagnosis of endometrial hyperplasia, with or without atypia, was established with hysteroscopy with biopsy, underwent subsequent hysterectomy. Hysteroscopy and biopsy were carried out using a blind endometrial biopsy guided by hysteroscopic findings. The results of biopsies and hysterectomy histology, for the presence of atypia, were compared. Sensitivity and likelihood ratio of hysteroscopic biopsy, as a diagnostic tool for detecting atypia, were calculated. The sensitivity in detecting atypia was 93.3 % corresponding to a negative likelihood ratio equal to 0.06. Univariate analysis did not show a significant association between atypia, age and/or endometrial thickness. The high sensitivity of hysteroscopic biopsy, corresponding to a strong negative likelihood ratio, made it a valid diagnostic tool for detecting atypia in postmenopausal women with abnormal uterine bleeding, hyperplasia and endometrial thickness >5 mm. There was no association between atypia and increase of endometrial thickness from 5 to >9 mm.

Keywords Hysteroscopy · Endometrium · Atypia · Biopsy · Menopause

Introduction

Abnormal uterine bleeding is a common gynaecological symptom and when it occurs in postmenopausal women, endometrial carcinoma must be excluded. Transvaginal ultrasound (TVU) is a diagnostic tool commonly used to evaluate uterine bleeding and includes a measurement of endometrial thickness (ET). Endometrial malignancy is uncommon in women with an ET measurement less than 5 mm [1, 2]. When an increased ET is detected with TVU, hysteroscopy and biopsy should be performed [3–6]. Outpatient hysteroscopic biopsy is a feasible and highly acceptable technique, giving a high detection rate for intrauterine pathology including endometrial hyperplasia [7, 8].

Endometrial glandular hyperplasia is, by definition, the presence of architectural (glandular) irregularity and disarray. The term “atypical” indicates cytological atypia, mainly nuclear abnormality. Regardless of the type of hyperplasia,

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simple or complex (architectural abnormality), the most important feature which determines the outcome of patients is nuclear atypia. Endometrial hyperplasia with atypia most likely progresses to type 1 (endometrioid) endometrial adenocarcinoma [9–11] and can also occur in combination with endometrial carcinoma [12, 13]. Despite publications regarding the relationship between endometrial glandular hyperplasia and the development of endometrial cancer, to the best of our knowledge, there are no reports on the accuracy of diagnostic hysteroscopy in detecting atypia.

The aim of this study was to determine the accuracy of histological diagnosis of endometrial atypia through hysteroscopy with blind biopsy (HBB) in postmenopausal women with an ET greater than 5 mm.

The hysteroscopic biopsy was not under direct visualization of the endometrial cavity but consisted in preliminary inspection of suspicious areas of endometrium which were sampled.

Materials and methods

Six hundred thirty-five postmenopausal patients with abnormal uterine bleeding presented to the Gynaecology Division of San Carlo di Nancy Hospital, Rome, Italy, from January 2010 through December 2012. Exclusion criteria were anatomical abnormality, polyps, adenomyosis, leiomyoma, coagulopathy or iatrogenic causes of abnormal uterine bleeding. Only patients who were diagnosed after the biopsy with endometrial hyperplasia, with or without atypia, were included in the study. None of the patients were taking hormone replacement therapy. The average age was 61.4 years (σ = 6.8, median = 60, range 51–79 years). All patients underwent TVU for ET measurement and hysteroscopic-guided biopsy.

In order, to determine the relationship between ET and atypia more precisely, ET was subdivided in three categories of 5–7 mm, ≥7–9 mm and >9 mm.

Two pathologists (CM&MEN) with experience in the field of gynaecological pathology observed the slides. All cases were reviewed by an expert in endometrial pathology (SR). Only cases where complete agreement for atypia was reached among all pathologists (CM, MEN and SR) were included in the study. Twenty-six patients were excluded due to disagreement between pathologists on diagnosis of atypia. The histological diagnosis of atypia was assigned according to the published criteria [14].

HBB and hysterectomy were performed on all patients. Hysteroscopy and biopsy were carried out using a blind endometrial biopsy guided by hysteroscopic findings. Briefly, under direct vision, a 4 mm diameter Hamou Microhysteroscope (Karl Storz, Tuttlingen, Germany) was passed through the cervix into the endometrial cavity. This was distended with carbon dioxide via a hysteroflator (Karl Storz) set at a maximum pressure of 75 mmHg and flow rate of 200 ml/min. The cavity was illuminated with a Coldlight Fountain (Karl Storz), and the images were displayed on a Sony Trinitron monitor using a Telecam Pal single chip camera system (Karl Storz). The endometrium was serially inspected for pathology. Then the gas and scope were removed from the uterus. Finally, a 3-mm forcep endometrial sampler was used to obtain a biopsy of the endometrium with no more than two attempts.

All specimens were formalin fixed paraffin embedded. Routine haematoxylin and eosin stain sections were performed and sent for histopathological analysis. Neither analgesia nor anaesthesia was routinely used or required by any patient in this series.

Patients with a histological diagnosis of atypia were offered total hysterectomy. Patients with a diagnosis of endometrial hyperplasia without atypia were offered medical therapy clarifying the advantages and disadvantages of this therapy. In particular, the possibility that the small amount of tissue on endometrial biopsy may not be representative of the whole endometrium and the presence of atypia could not be entirely ruled out was highlighted. Hysterectomy as an alternative therapy was suggested. All patients opted for hysterectomy. In the hysterectomy specimens, the entire endometrium was submitted, as described above, for tissue processing and histological diagnosis.

The referral test to confirm the atypia was hysterectomy. However, since the presence of atypia could not be ignored, those cases in which atypia was identified in biopsy, and not in hysterectomy specimens, were calculated as positive for the presence of atypia. The specificity would be a priori 100 % and, therefore, is not reported.

Statistical analysis

Statistical analysis was performed with SPSS software package V.22 (SPSS, Inc., Chicago, Illinois, USA). Clinical characteristics were summarised by standard descriptive summaries. The patients were divided in two groups by age (<60 and ≥60 years, respectively). The association between the final diagnosis of atypia on hysterectomy specimens and age, ET and atypia diagnosed on biopsy were compared using Fisher's exact test for categorical variables or a test for trend if appropriate. Sensitivity and likelihood ratios of HBB as a diagnostic tool for detecting atypia were calculated.

Results

Ninety-nine patients were enrolled for this prospective study.

Endometrial thickness (ET) in 60 patients (61 %) was between 5 and 7 mm, 55 (92 %) of whom showed atypia. Thirty-

two cases (58 %) of atypia occurred in complex and 23 (42 %) in simple hyperplasia.

Thirty-seven patients (37 %) presented ET between 7 and 9 mm. Thirty-two (86 %) had atypia. Twenty cases (62.5 %) of atypia occurred in complex and 12 (37.5 %) in simple hyperplasia.

Two (2 %) patients had ET >9 mm. Both had atypia, one with complex and one with simple hyperplasia (Table 1).

The association between atypia on biopsy and age, ET and atypia diagnosed on hysterectomy specimens (including adenocarcinomas) are described in Table 2.

Univariate analysis did not show a significant association between atypia on biopsy and age (divided in two subgroups, <60 or ≥60 years, $p = 0.62$) and ET (test for trend $p = 0.64$).

The proportion of atypia diagnosed on hysterectomy specimens was significantly higher than that detected on biopsy (96 vs 90 %; Fisher's exact text, $p < 0.001$).

In 89 patients, who showed atypia on biopsy samples, diagnosis was confirmed by hysterectomy in 83 cases while 6 patients did not show atypia. The opposite was found in 10 patients without atypia on biopsy as 4 did not show atypia on hysterectomy while 6 did (Table 3).

Six women bearing atypia on biopsy showed endometrioid adenocarcinoma in hysterectomy. Three were FIGO stage 1A and three stage 1B.

The sensitivity of HBB as a diagnostic tool for detecting atypia was 93.3 %. The negative likelihood ratio was 0.06, while the positive likelihood ratio could not be calculated since the specificity was a priori 100 %.

Discussion

Endometrial hyperplasia is a non-invasive proliferation of the epithelial component of the endometrium and, based on architectural complexity and nuclear abnormality, according to the WHO classification of 1994, is classified as simple or complex, with or without atypia. The simple subtype is generally recognised as a non-neoplastic disorder and complex hyperplasia sometimes behaves as pre-neoplastic disease [9].

Table 1 Clinical and histopathological characteristics of patients. Results are presented as frequency (row percentage)

Diagnosis of hyperplasia on biopsy			Endometrial thickness		
			5 to 7 mm ($N = 60$)	≥7 to 9 mm ($N = 37$)	>9 mm ($N = 2$)
Simple	Atypia	No	4 (6.7)	5 (13.5)	0
		Yes	23 (38.3)	12 (32.4)	1 (50)
Complex	Atypia	No	1 (1.7)	0	0
		Yes	32 (53.3)	20 (54.1)	1 (50)

Table 2 Association between atypia (including adenocarcinomas) on biopsy, age, endometrial thickness and atypia in hysterectomy specimens

	Atypia on biopsy		
	Yes ($N = 89$)	No ($N = 10$)	p value*
Age			
<60	41 (46.1)	6 (60)	0.62
≥60	48 (53.9)	4 (40)	
Endometrial thickness			
5 to 7 mm	55 (61.8)	5 (50)	0.64**
≥7 to 9 mm	32 (36)	5 (50)	
>9 mm	2 (2.2)	0	
Atypia on hysterectomy			
Yes	83 (93.3)	6 (60)	<0.001
No	6	4 (40)	

*Refers to Fisher's exact test

**Test for linear trend

This classification system led to confusion among clinicians and pathologists and in most instances the diagnosis was inadequate, with surgery carried out for hyperplasia with no atypia or the administration of pharmacological progestin based therapy for atypical hyperplasia [15]. The latest WHO classification of 2014 clarified the matter dividing the endometrial hyperplasia in hyperplasia without atypia and atypical hyperplasia/endometrioid intraepithelial neoplasia (EIN) [16].

Atypical endometrial hyperplasia (AEH) is a well-known precursor of endometrial cancer and 15–30 % of patients with AEH will progress to endometrial adenocarcinoma type I [9, 17, 18].

The histological diagnosis of endometrial glandular hyperplasia on biopsy is relatively simple due to architectural disarray and irregularity. However, the diagnosis of atypia, even in abundant material obtained from dilatation and curettage (D&C), is not always simple or straightforward and there is a substantial lack of interobserver reproducibility among pathologists in the histological diagnosis of endometrial atypia [11, 19–24].

In addition, endometrial atypia could occur in the absence of architectural disorder and disarray [25].

Our data show that the high sensitivity of HBB, corresponding to a strong negative likelihood ratio, together with

Table 3 The rate of atypia on biopsy and hysterectomy

Atypia on biopsy	Atypia on hysterectomy		
	Yes	No	Total
Yes	83	6	89
No	6	4	10
Total	89	10	99

its low invasiveness, makes it a valid diagnostic tool in the detection of endometrial atypia in postmenopausal women with abnormal uterine bleeding.

Furthermore, we found that an increase of ET from 5 to >9 mm was not directly proportional to increased atypia.

It is worth mentioning that a recent study revealed that in pre-menopausal women ET is of little value in prediction of intracavitary pathology. In this study, the prevalence of hyperplasia, with and without atypia, in postmenopausal women with abnormal uterine bleeding was 2.2 % [26].

In six cases, atypia was diagnosed on biopsy but not on hysterectomy. The more reasonable explanation for women who present atypia on biopsy but not on hysterectomy is that the tiny foci regress spontaneously or are entirely removed by biopsy.

Conversely, six patients without atypia on biopsy showed atypia on hysterectomy specimens. This might be due to a sampling artefact during biopsy because the limit of the present study was the use of an "old-fashioned" hysteroscopic technique with no targeted biopsy under direct visualisation of the suspected endometrial area. Indeed, at present, new devices for diagnostic outpatient hysteroscopy allow targeted endometrial biopsy with no significant pain and discomfort for women [27].

In summary, the present study shows that hysteroscopic biopsy is a valid diagnostic tool for detecting atypia in postmenopausal women with abnormal uterine bleeding, hyperplasia and endometrial thickness >5 mm. However, there is no association between atypia and increase of endometrial thickness from 5 to >9 mm.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. No identifying information about patients is included in this article.

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