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ORIGINAL RESEARCH

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Hysteroscopic-view of endometrial atypical hyperplasia. A helpful diagnostic tool in the care and treatment process?

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Abstract

This present study was conducted over a 10-year period to investigate the hysteroscopic-view features of Endometrial Atypical Hyperplasia (EAH) and evaluate the accuracy of hysteroscopy imaging in detecting concurrent Endometrial Carcinoma (EC). A total of 69 patients diagnosed with EAH *via* hysteroscopy-guided biopsy and subsequently undergoing hysterectomy were eligible for analysis, and the uterine specimen histology was used as a reference for comparison. Of the included patients, EAH was confirmed in 40 women based on the hysterectomy specimens, while EC was identified in 29 cases (42.0% underestimation). Among the 40 patients with EAH, hysteroscopic-view reports of 37 cases (92.5%) indicated benign conditions, mostly diagnosed as polyps or hyperplasia. In the group of 29 women with underestimated EC, hysteroscopic-view agreed with the definitive diagnosis in 20 cases (68.9%), while in 9 patients, non-neoplastic patterns were observed. Overall, hysteroscopic imaging reported a benign endometrial overgrowth in 46 patients, and among them, EAH was identified in 37 cases based on the hysterectomy specimen (80.4%). Hysteroscopic-view demonstrated a sensitivity, specificity, negative predictive value, and positive predictive value of 76.3%, 93.0%, 81.6% and 90.6%, respectively, in predicting EC among patients who underwent hysteroscopic biopsy and received a diagnosis of EAH. However, no specific hysteroscopic features were associated with EAH diagnosis. Overall, despite hysteroscopic-view showing suboptimal sensitivity in detecting a concurrent EC, it can still exclude the presence of underlying EC in approximately 80% of patients when hysteroscopic imaging indicates a non-neoplastic growth.

Keywords

Atypical endometrial hyperplasia; Endometrial cancer; Endometrial biopsy; Hysteroscopy

1. Introduction

Over the past three decades, hysteroscopy has emerged as the gold standard for diagnosing endometrial pathology, surpassing the limitations associated with blind transcervical sampling techniques [1, 2]. Advancements in technology, coupled with a better understanding of endometrial imaging and its correlation with pathology, have elevated the importance of hysteroscopy in the diagnosis of endometrial diseases [3, 4]. Endometrial Atypical Hyperplasia (EAH) is considered the precursor to type 1 Endometrial Cancer (EC) that constitutes approximately 80% of all uterine corpus cancers. Therefore, distinguishing between EC and EAH before intervention is crucial for tailoring treatment approaches, which may involve surgical staging, less invasive surgery, or even medical therapy [5]. However, the pre-operative endometrial biopsies (EB) used to diagnose EAH are often prone to underestimating EC in 30% to 55% of cases [6, 7], which primarily arises due to the poorly defined histologic criteria of the World Health Organization's classification, leading to variability in individual interpretations and poor inter-observer reproducibility of pathological results [8, 9]. Moreover, the varying quality and quantity of endometrial tissue obtained through different biopsy techniques further hinder the diagnostic reliability of EAH [10, 11].

Comparatively, hysteroscopic-view, with its easily interpretable imaging, demonstrates high predictive value in diagnosing EC, exhibiting sensitivities ranging from 80% to 95% [3, 4, 12–14]. However, due to the limited imaging criteria for identifying endometrial hyperplasia, hysteroscopic-view can be less accurate in confirming such a diagnosis, with sensitivities ranging from 50% to 75% [4, 12]. Till now, only a few controlled trials have been conducted to explore the relationship between hysteroscopic imaging and the diagnosis

of EAH [13, 15–17]. Thus, the present study is aimed to examine hysteroscopic images of patients with EAH and to determine the accuracy of hysteroscopic-view in predicting concurrent EC following a targeted EB reporting EAH.

2. Patients and methods

2.1 Study design

This single-institution observational trial was conducted between January 2012 and December 2022. The study adhered to the principles of the 1964 Declaration of Helsinki and its subsequent amendments. We identified all patients from the institutional pathology database who had an EB report of EAH and underwent hysteroscopic assessment prior to undergoing hysterectomy. Hysteroscopic-view diagnoses were based on written reports and were compared to the pathological findings obtained from the hysterectomy specimens, which served as the reference. A team of resident pathologists conducted the pathology assessment of both the EB and hysterectomy specimens, and the reports were adjusted to comply with the current World Health Organization guidelines [9]. The hysterectomy was performed within 60 days after the biopsy, and the choice of surgical technique (vaginal, laparotomic or laparoscopic) was at the discretion of the primary surgeon. Lymphadenectomy was not performed in any of the included cases.

2.2 Patient selection

We included both premenopausal and postmenopausal women. Based on transvaginal ultrasound findings, in postmenopausal women hysteroscopy was indicated when abnormal uterine bleeding record was associated with an endometrial thickness greater than 3 mm, or when an endometrial lining greater than 5 mm was found in asymptomatic patients. In premenopausal women, hysteroscopy was indicated when abnormal uterine bleeding was unresponsive to medical therapy or when a non-homogeneous endometrial echo-texture during the early to middle proliferative phase of their menstrual cycle was detected. We selected all patients who underwent hysteroscopy-guided endometrial biopsy and received a diagnosis of EAH. Patients who had EAH diagnosed after hysteroscopic polypectomy and had normal findings on hysterectomy pathology were also included.

2.3 Hysteroscopic-view diagnosis

A team of nine gynecologists with different levels of technical expertise and surgical skills in hysteroscopy performed the diagnostic procedures. The hysteroscopy-view diagnosis was based on previously established guidelines and did not involve the use of a scoring system. Instead, the diagnosis was dependent on the subjective impression of the individual surgeon, as previously described [3, 4].

2.3.1 Normal endometrium

The hysteroscopy-view diagnosis included an evenly lined atrophic or functional mucosa with a regular distribution of gland openings, indicating no architectural distortion of the endometrial shape. The presence of focal subepithelial gland cysts in an atrophic endometrium was considered a normal feature.

2.3.2 Endometrial polyp

Focal luminal projections, whether single or multiple, and either sessile or pedunculated in nature, were identified during the hysteroscopic examination. These projections exhibited a soft or mildly fibrous consistency and were covered by an evenly lined functional or atrophic mucosa. They frequently displayed cyst-gland formations and were supplied by a thin vascular network. In cases where hyperplastic features were present within the polyp texture, a diagnosis of “hyperplastic polyp” was assigned.

2.3.3 Endometritis

Focal or diffuse micropapillary (less than 2–3 mm) projections associated with mucosal hyperemia and edema.

2.3.4 Endometrial hyperplasia

The diagnosis of endometrial hyperplasia was considered based on the presence of one or more of the following features: (i) Focal or diffuse polypoid or papillary mucosal endometrial thickening without necrosis; (ii) Abnormalities in the architecture of endometrial glands, including gland cysts with a button-like whitish appearance (referred to as psammoma bodies), gland crowding, and irregularly spaced gland openings; (iii) Presence of an enhanced and irregular, yet not overtly atypical, vascular network.

2.3.5 Endometrial cancer

The characteristics comprised focal or extended polypoid, papillary, nodular or mixed patterns of mucosal overgrowth showing friable/cerebroid consistency, surface necrosis, and an overt atypical vascular network.

The hysteroscopic-view diagnosis was based on the reports written at the end of interventions. Video clips of good quality were available for 20 patients, but they were solely used as supplementary imaging material for the manuscript (Figs. 2,3,4,5,6). The review of these videos did not influence or alter the results of the initial hysteroscopic-view written reports.

2.4 Hysteroscopic biopsy technique

Hysteroscopy was performed using two different approaches: as an outpatient clinical intervention without anesthesia or as an inpatient procedure with sedation. All interventions were conducted with the assistance of video technology and utilized saline as the uterine distending medium. The hysteroscopes used had a diameter of 16–18 Fr and included a 5 Fr operative channel, or a 27 Fr resectoscope equipped with a bipolar loop electrode. The vaginoscopic technique was primarily used to access the uterus, except in cases where cervical dilatation was necessary for patients treated with a resectoscope. The instrumentation used for endometrial sampling included 5 Fr mechanical tools such as scissors for biopsy formation and grasping forceps for tissue retrieval and electrosurgical devices such as 5 Fr bipolar electrodes and 2–4 mm resec-

toscopic loops. When the hysteroscopic-view indicated the possibility of endometrial cancer, one or more biopsies were performed by targeting viable tissues displaying overt signs of malignancy. In cases where the hysteroscopic-view suggested normal endometrium, endometritis, hyperplasia or polyps, random biopsies, biopsies targeted at the most significant mucosal abnormality, and visual-guided electrosurgical or mechanical polypectomy were conducted, respectively.

3. Statistical analysis

Quantitative variables are presented as means and standard deviation (SD), while absolute numbers and percentages are used for categorical variables. Statistical analysis was conducted using appropriate tests such as *t*-tests (mean ± SD), chi-square tests (χ^2; n (%)), or Fisher's exact test (n (%)) when the cell counts were less than 5, as appropriate. A *p*-value below 0.05 was considered statistically significant. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of hysteroscopic imaging for predicting the diagnosis of endometrial cancer were also calculated.

4. Results

Fig. 1 provides a flowchart summarizing the participants and the main results of this study. During the study period, 69 patients were found eligible for analysis, among whom 10 women underwent resectoscopic procedures for large polyps, while in 59 cases, a 16–18 Fr hysteroscope was used for polypectomies or biopsy sampling under visualization. Uterine pathologic assessment confirmed EAH following EB in 40 patients, while in 29 women, biopsy pathology underreported a concurrent infiltrating EC (42.0%). All EC cases showed endometrioid histology. Based on hysterectomy pathology, 21 patients were staged as IA, 4 as IB and 4 as more advanced stages.

Table 1 presents a comparison of clinical variables between the two groups of patients, and the results show no significant differences in age, menopausal status, bleeding symptoms, and body mass index. Table 2 summarizes the findings of hysteroscopic imaging compared to the pathologic reports obtained from hysterectomy specimens. Of the 40 patients with confirmed EAH, hysteroscopic-view reported benign disease in 37 cases (92.5%). Among the patients with large polyps (average size, 22.2 mm), 14 cases were described as having "hyperplastic" features (Fig. 2). Additionally, a hysteroscopic-view report of hyperplasia without further characterization was provided for 12 women (Fig. 3). Chronic endometritis was identified in 1 patient, while normal proliferative endometrium was described in one woman and focal cystic atrophy in another. In 3 patients (7.5%), hysteroscopic imaging upgraded the diagnosis from EAH to EC (Fig. 4).

Among the 29 women with underestimated coexisting EC, hysteroscopic-view indicated overt neoplastic growth in 20 cases (68.9%, Fig. 5), while 9 patients (31.0%) were reported to have benign conditions such as polyps (3 cases), hyperplasia (5 cases), and endometritis (1 case) (Fig. 6). According to Fisher's exact test, the hysteroscopic diagnosis of EC was significantly predictive of the final diagnosis obtained from the uterine specimen ($p < 0.001$). Overall, hysteroscopic-view indicated a non-neoplastic growth in 46 patients, and among them, 37 patients (80.4%) were confirmed to have EAH based on the pathology from the hysterectomy specimens, consistent with the initial biopsy diagnosis. Based on these results, the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of hysteroscopic-view in predicting underlying EC among patients with a hysteroscopic biopsy diagnosis of EAH were 76.3%, 93.0%, 81.6% and 90.6%, respectively.

5. Discussion

The findings of this study support the notion that when a pre-operative EB is diagnosed as EAH, there is a high likelihood of underlying EC. Despite using hysteroscopic guidance for endometrial sampling, we observed a significant underestimation of EC in 42% of patients. This underestimation rate is consistent with the results from Trimble *et al.*'s [18] Gynecologic Oncology Group-167 study, which utilized blind EB and aligns with existing literature reporting underestimation rates ranging from 30% to 55% [6, 7, 11, 19]. Our study, consistent with the review by Bourdel *et al.* [10], did not find a diagnostic advantage of hysteroscopic-driven biopsy over blind sampling methods in distinguishing between EAH and EC. Among blind procedures, Dilatation and Curettage (D&C) exhibited improved accuracy, with a reduced underestimation rate of concurrent EC to approximately 30% [10, 11, 17].

It is widely acknowledged that D&C allows retrieving a larger sample of hyperplastic endometrium, providing the pathologist with more material for accurate pathological interpretation. D&C is a basic technique that is accessible to all gynecologists. On the contrary, hysteroscopic sampling in cases of EC requires expertise due to various challenges, including the potential for bleeding that can obstruct visualization, the sometime difficult identification of a representative biopsy target, and the retrieval of sufficient neoplastic tissue from the endometrial cavity. These challenges are further compounded by the friable and cerebroid consistency often associated with EC [13, 20]. Nonetheless, hysteroscopic imaging can provide valuable information for predicting endometrial pathology, although a learning curve is necessary to ensure a reliable interpretation of endoscopic findings with pathology [20].

In recent years, two risk-scoring systems have been proposed to improve and standardize the hysteroscopic-view diagnosis of EC among practitioners. These scoring systems have demonstrated sensitivities ranging from 89% to 95% and specificities ranging from 92% to 98% in predicting EC [3, 4]. The assumption is that endometrial inspection alone should provide a high level of accuracy in confirming or excluding malignant proliferation. Over 15 years ago, we reported a good level of accuracy (sensitivity of 85% and specificity of 100%) in hysteroscopic-view diagnosis for predicting infiltrating EC in a small group of 25 patients with a pre-operative biopsy diagnosis of EAH [13]. However, our present study, which included a larger number of patients with EAH on EB, revealed that hysteroscopic-view could predict a diagnosis of infiltrating

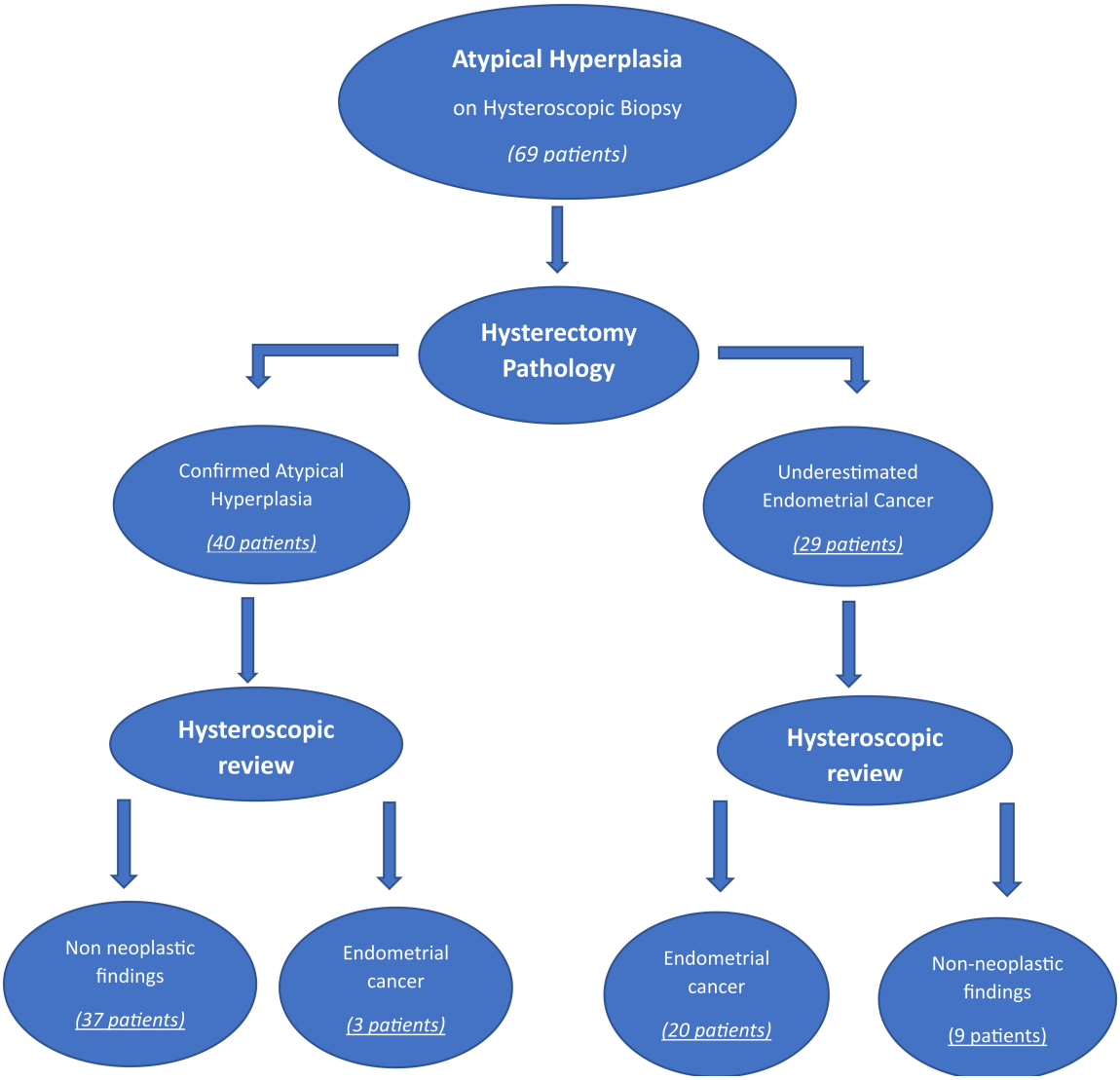

FIGURE 1. Flow-chart diagram of patients included in the study and summarized results.

TABLE 1. Clinical variable retrieved from 69 patients undergoing hysterectomy for a preoperative biopsy diagnosis of atypical hyperplasia. A comparison between women with a confirmed diagnosis of atypical hyperplasia and in which we underestimated an endometrial cancer is showed.

	Atypical Hyperplasia (N = 40)	Endometrial Carcinoma (N = 29)	*p* value
Age: mean (±SD)	58.1 (±8.45)	59.7 (±12.10)	0.511*
Menopausal status: n (%)			
	Pre-menopausal = 8 (20.0%) Post-menopausal = 32 (80.0%)	Pre-menopausal = 7 (24.1%) Post-menopausal = 22 (75.9%)	0.908^
Abnormal Uterine Bleeding (%)			
	Yes = 31 (77.5%) No = 9 (22.5%)	Yes = 27 (93.1%) No = 2 (6.9%)	0.104°
Body Mass Index; mean (±SD)	25.7 (±4.9)	25.6 (±4.5)	0.942*

*SD: Standard Deviation; *t-test; ^chi-square test; °Fisher's exact test.*

TABLE 2. Hysteroscopic-view findings displayed in 69 patients undergoing hysteroscopic-guided biopsy with diagnosis of atypical hyperplasia are related to definitive pathology on uterine specimen.

	Confirmed Atypical Hyperplasia (N = 40)	Concurrent Endometrial Carcinoma (N = 29)	*p* value
Hysteroscopic view			
Normal (%)	2 (5.0%)	0 (0.0%)	
Polyp (%) (size: mm, M ± SD)	22 (55.0%) (22.2 ± 11.5)	3 (10.3%) (20.6 ± 7.3)	
Hyperplasia (%)	12 (30.0%)	5 (17.2%)	
Endometritis (%)	1 (2.5%)	1 (3.4%)	
Carcinoma (%)	3 (7.5%)	20 (68.9%)	<0.001°

SD: Standard Deviation; °Fisher's exact test.

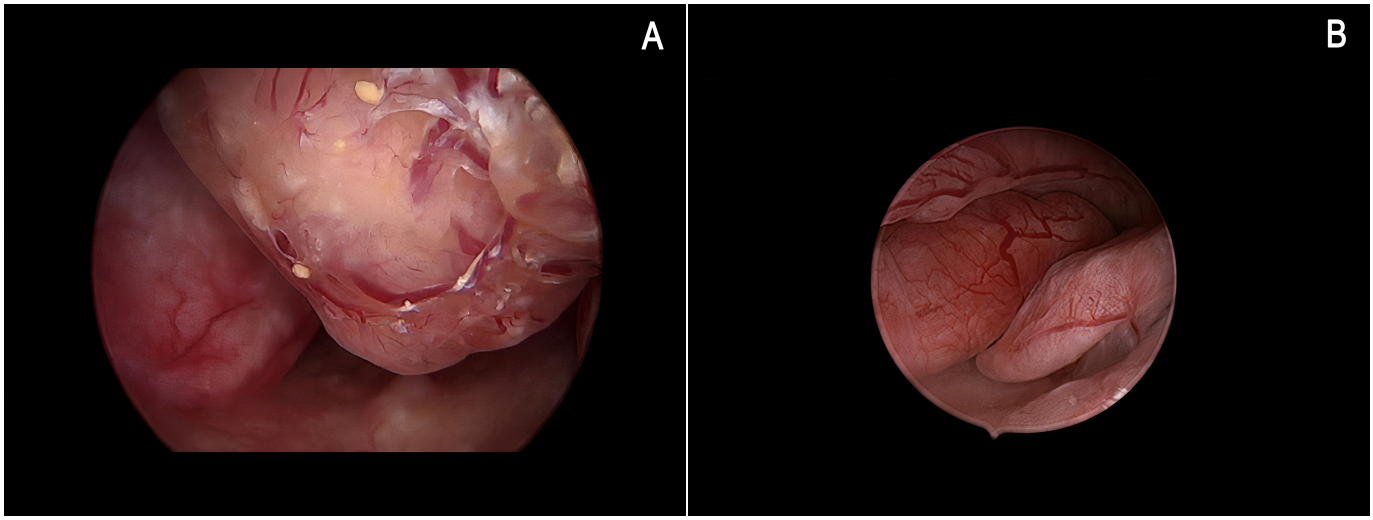

FIGURE 2. Endometrial polyps harboring hyperplastic features. Atypical hyperplasia was found both in hysteroscopic-sliced chips following polypectomy and in non-polypoid endometrium of hysterectomy specimen. In both patients hysteroscopic imaging was unsuspected for endometrial cancer. (A) Caudal pole of polyp showing a quite smooth surface, gland cysts, scattered psammoma bodies and markedly enhanced, but not overtly atypical vascular network. (B) Multiple polyps harboring gland crowding and enhanced vascular network.

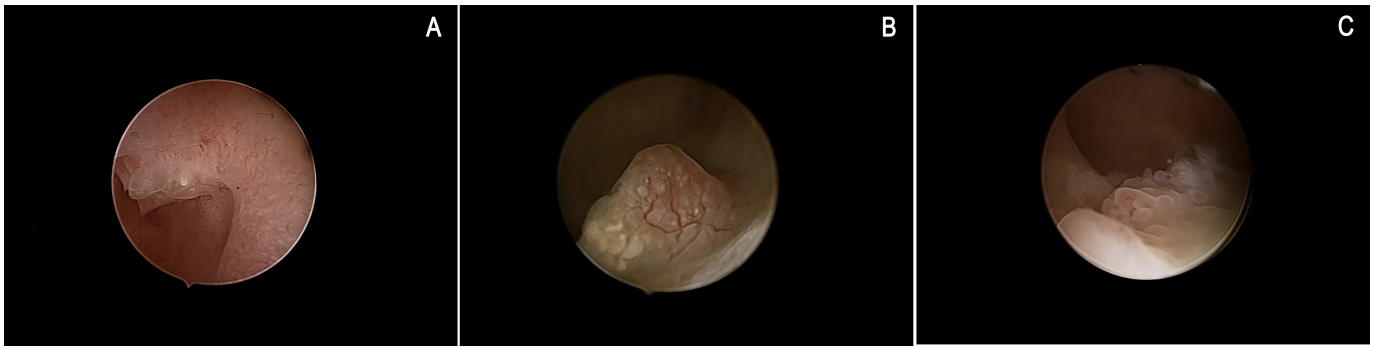

FIGURE 3. Endometrial overgrowths diagnosed as hyperplasia by hysteroscopic-view. In these patients no hysteroscopic feature led to endometrial cancer suspicion. Atypical hyperplasia was found both in biopsy pathology and hysterectomy specimen. (A) Polypoid projection showing irregular surface with psammoma bodies. (B) Focal polypoid growth with irregular surface, enhanced vascular network and crowding psammoma bodies. (C) Focal papillary overgrowth without overt gland and vascular network distortion.

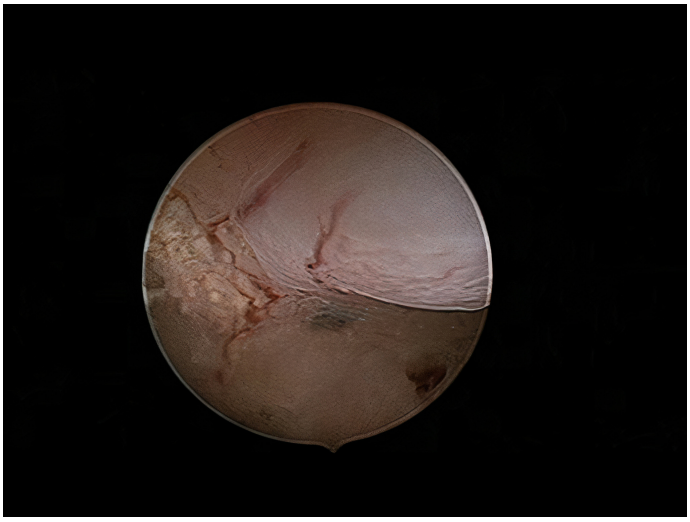

FIGURE 4. Atypical hyperplasia overestimated as endometrial cancer by hysteroscopic imaging. Focal polypoid overgrowth harboring gland crowding with psammoma bodies associated with vascular network judged as atypical was reported as endometrial cancer by hysteroscopic-view. Atypical hyperplasia was found in both biopsy and hysterectomy specimen.

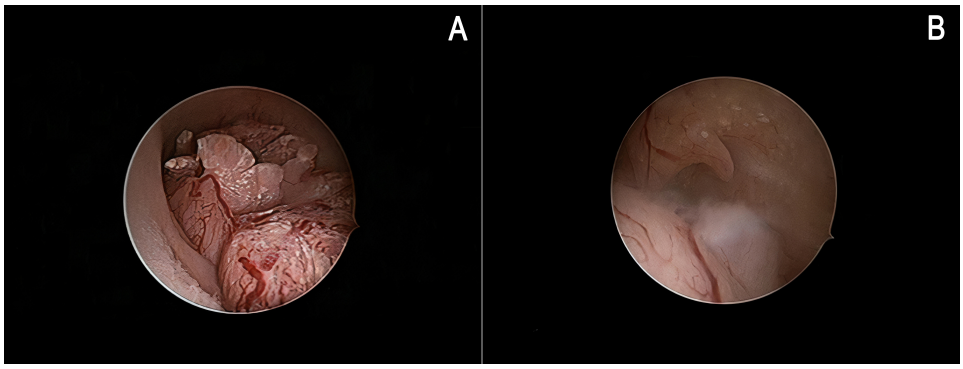

FIGURE 5. Endometrial cancers underestimated as atypical hyperplasia on biopsy pathology. Overt endometrial cancers diagnosed by hysteroscopic-view were reported as atypical hyperplasia on endometrial biopsy, underestimating an endometrial adenocarcinoma confirmed on hysterectomy pathology. (A) Overt neoplastic growth showing polypoid and papillary features, atypical vascular network and psammoma bodies. (B) Overt neoplastic growth defined by polypoid surface, cerebroid consistency and atypical vascular network.

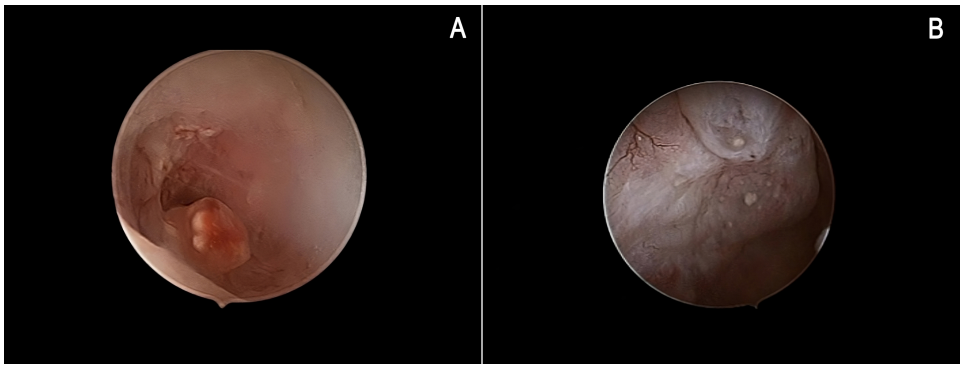

FIGURE 6. Endometrial cancers underestimated as non-neoplastic growth by hysteroscopic-view and atypical hyperplasia on biopsy pathology. In these women atypical hyperplasia was found on biopsy pathology whereas a final diagnosis of endometrial carcinoma was obtained on hysterectomy specimens. (A) Focal polypoid mucosal growth with irregular surface, psammoma bodies and an enhanced vascular network with somewhere atypical branching was diagnosed as hyperplasia on hysteroscopic imaging. (B) A large sessile mucosal overgrowth harboring psammoma bodies and gland crowding without an obvious atypical vascular network was described as hyperplastic polyp in the hysteroscopic-view report.

carcinoma in only 68.9% of cases, demonstrating a sensitivity of 76.3% that falls below the desired level of accuracy. This finding is disappointing when compared to other studies that have reported higher accuracy rates for hysteroscopy imaging in the diagnosis of EC, and it is challenging to provide a definitive explanation [3, 4, 13]. We hypothesized that this could be likely due to the involvement of multiple physicians in the diagnostic process, who had varied expertise in hysteroscopy, which resulted in these suboptimal results.

Our findings demonstrate that when hysteroscopic-view indicates a non-neoplastic endometrial growth, it aligns with EAH confirmation in 80.4% of patients based on the hysterectomy specimens, resulting in a specificity of 93.0% for excluding EC. These results are consistent with existing literature [3, 4]. However, they are different from the finding in a study conducted by Kurosawa *et al*. [15], who concluded that no hysteroscopic feature could predict concurrent EC in patients with EAH found on biopsy specimens. Conversely, a controlled series by Pace *et al*. [16], involving 80 women who underwent hysteroscopic biopsy with EAH, showed that hysteroscopic-view correctly predicted underlying EC in 80.0% of cases and excluded it in 77.8% of women with confirmed EAH on hysterectomy pathology. These findings support our results and suggest that reviewing hysteroscopic imaging following an EB report of EAH can be valuable in excluding or, to a lesser extent, predicting an underlying EC. However, it should be noted that before making therapeutic decisions, expert assessment of endoscopic imaging could be sought to help pathologists review uncertain histological diagnoses and guide gynecologists in considering further biopsies based on hysteroscopic-view suggestive of EC [2]. Therefore, endometrial imaging plays a significant role in supporting the diagnostic process and guiding the selection of appropriate radical or conservative therapeutic measures.

Currently, the hysteroscopic-view diagnosis of endometrial hyperplasia is based on single or concurrent imaging criteria widely accepted by the scientific community [12]. However, there is a lack of controlled studies confirming the true reliability of each morphologic pattern in predicting endometrial hyperplasia. The inspective diagnosis based on hysteroscopic imaging is highly dependent on the subjective interpretation and expertise of the surgeon. Additionally, no previous reports have specifically addressed whether hysteroscopic imaging can predict EAH. Our study analyzed the hysteroscopic-view reports of 40 patients who were confirmed to have EAH on hysterectomy. Among the 37 cases without any suspicion of neoplastic growth on imaging, we mostly found large polyps that were often reported to have hyperplastic features and endoscopic pictures consistent with endometrial hyperplasia not otherwise specified. Psammoma bodies, which represent focal subepithelial endometrial gland cyst necrosis, were frequently observed in cases of EAH. However, psammoma bodies have been found to have limited value in predicting specific endometrial diseases [3]. Therefore, our study suggests that no additional inspective finding can reliably predict a diagnosis of EAH beyond the currently accepted predictors of endometrial polyps or hyperplasia.

The main limitations of this present study are its retrospective design, the reliance on written reports for the hysteroscopic-view diagnosis, and the availability of video clips for review in only one-third of the patients. Furthermore, the varying skill levels of the surgeons involved might have impacted the study results to a certain extent.

6. Conclusions

Our study did not identify any specific hysteroscopic pattern that could be exclusively associated with a diagnosis of EAH. However, when a biopsy confirms EAH and the hysteroscopic imaging shows features consistent with endometrial polyp or hyperplasia, it was found to reliably confirm an EAH diagnosis in approximately 80% of patients. Hysteroscopic-view detected concurrent EC in approximately 69% of cases with a biopsy report confirming EAH.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are not publicly available due to the rules of patient's privacy but are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

GG—conceptualization and design, analysis and interpretation of data, writing original draft, wrote the manuscript; PFS—reviewing the manuscript, analysis and interpretation of data; MM—investigation, analysis and interpretation of data; OF—analysis and interpretation of data; GC—acquisition of data; AF—acquisition of data, conceptualization; MS—final approval of the version to be published. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed in line with the principle of the Declaration of Helsinky. This is an observational and retrospective study based or routinely delivered care. The Research Ethics Committee of the Public Sanitary Utility of Lodi (Italy) has confirmed that no ethical approval is required. All subjects involved in the study approved the final version of manuscript and consent to participate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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