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Presence of endometrial adenocarcinoma *in situ* in complex atypical endometrial hyperplasia is associated with increased incidence of endometrial carcinoma in subsequent hysterectomy

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The distinction of complex atypical endometrial hyperplasia from endometrial adenocarcinoma is often problematic. Foci of back-to-back arrangement of glands or foci of cribriform arrangement of glands smaller than 2.1 mm in diameter are considered insufficient for the diagnosis of endometrial adenocarcinoma by some authors, and sufficient to be diagnosed as endometrial adenocarcinoma by other authors. We refer to these foci as endometrial adenocarcinoma *in situ*. In this study, we evaluated findings in subsequent hysterectomy in complex atypical endometrial hyperplasia patients with and without adenocarcinoma *in situ*. Follow-up findings, including the presence or absence of endometrial adenocarcinoma in the hysterectomy specimen, the grade of the carcinoma and the depth of myometrial invasion were analyzed. Of the total 87 patients with complex atypical endometrial hyperplasia, 33 patients had adenocarcinoma *in situ* and 54 lacked adenocarcinoma *in situ*. Of 33 patients 22 (66%) with adenocarcinoma *in situ* had endometrial adenocarcinoma on subsequent hysterectomy *vs* 13 of 54 (24%) patients without adenocarcinoma *in situ* ($P=0.0001$). Myoinvasive endometrial adenocarcinoma was present in 20 of 33 (61%) patients with adenocarcinoma *in situ* *vs* 8 of the 54 (15%) patients without adenocarcinoma *in situ* ($P\leq0.0001$). The depth of myometrial invasion in cases with myoinvasion was $24.5+19.4\%$ in patients with adenocarcinoma *in situ* and$12.8+8.5\%$ in patients without adenocarcinoma *in situ* ($P=0.05$). Among patients younger than age of 50, 5 of the 7 (71%) with adenocarcinoma *in situ* had myoinvasive carcinoma *vs* 2 of the 13 (15%) without adenocarcinoma *in situ* ($P=0.02$). The likelihood of finding endometrial adenocarcinoma in subsequent hysterectomy in patients with complex atypical endometrial hyperplasia is significantly increased if adenocarcinoma *in situ* is present in prior endometrial sampling. Endometrial adenocarcinomas in patients with adenocarcinoma *in situ* are far more frequently myoinvasive, and invade to a greater depth than endometrial adenocarcinomas seen in patients without adenocarcinoma *in situ*. Use of adenocarcinoma *in situ* terminology could lead to improved management of patients with complex atypical endometrial hyperplasia.
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Keywords: endometrial adenocarcinoma *in situ*; endometrial hyperplasia; endometrial carcinoma

The distinction of complex atypical endometrial hyperplasia from endometrial adenocarcinoma is frequently problematic.[1–11] Foci of back-to-back arrangement of glands or foci of cribriform arrangement of glands smaller than 2.1 mm in diameter are considered insufficient for the diagnosis of endometrial adenocarcinoma by some authors,[11] and sufficient to be diagnosed as endometrial adenocarcinoma by other authors.[10] We have referred to these foci as endometrial adenocarcinoma *in situ* (AIS) in the past. We have previously shown that the presence of such foci in complex atypical endometrial hyperplasia is associated with increased risk of finding endometrial carcinoma in subsequent hysterectomy.[12] In the current study we have used a larger number of cases of complex atypical

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endometrial hyperplasia from three different centers to further evaluate this association.

Materials and methods

Cases with the diagnosis of complex atypical endometrial hyperplasia on endometrial curettage/biopsy and subsequent hysterectomy were examined for the presence of AIS. The cases were seen at New York University Medical Center, New York; North Broward Medical Center, Deerfield Beach, FL, and at Thomas Jefferson University Hospital, Philadelphia, PA. The cases were retrieved by searching for cases with the diagnosis of complex endometrial hyperplasia in the computerized records in each facility. The cases were sequential and seen from 2003 to 2006. Scant or otherwise suboptimal specimens were excluded from the study. The presence or absence of AIS was diagnosed at each facility based on review of the case by individual pathologists. Cytologic features were not included as a criteria for exclusion of a case, but none of the cases had grade III nuclei. The review of biopsies was done blindly without knowledge of the hysterectomy findings. Hysterectomy diagnosis of record was used. AIS was defined as foci of back-to-back arrangement of glands or foci of cribriform arrangement of glands composed of at least four glands and smaller than 2.1 mm in diameter (Figures 1–3). Foci with marked glandular crowding, where stromal cells were readily identified between adjacent glands, were not considered AIS. Artifactual cribriform arrangement of glands such as appearance can be seen when there is squamous metaplasia or morule formation in endometrial glands, and these were also not included as AIS (Figure 4). The size of the largest AIS focus was noted in each case. Follow-up findings in the two groups of patients with and without AIS were analyzed, including the presence or absence of carcinoma in the hysterectomy specimen, the grade of the carcinoma and the depth of myometrial invasion.

Results

There were a total of 87 patients with complex atypical endometrial hyperplasia. The incidence of endometrial adenocarcinoma was 40% (35 of 87) and of myoinvasive carcinoma 32% (28 of 87) in subsequent hysterectomy in the entire group. All carcinomas were of endometrioid histology, and either grades I or II. Thirty-three patients (38%) had AIS and fifty-four (62%) lacked AIS. Twenty two of 33 (66%) patients with AIS had endometrial adenocarcinoma on subsequent hysterectomy *vs* 13 of 54 (24%) patients without AIS ($P=0.0001$). Myoinvasive adenocarcinoma was present in 20 of 33 (61%) patients with AIS *vs* 8 of the 54 (15%) patients without AIS ($P<0.0001$). Myoinvasive carcinoma to a depth of 2 mm or more was present

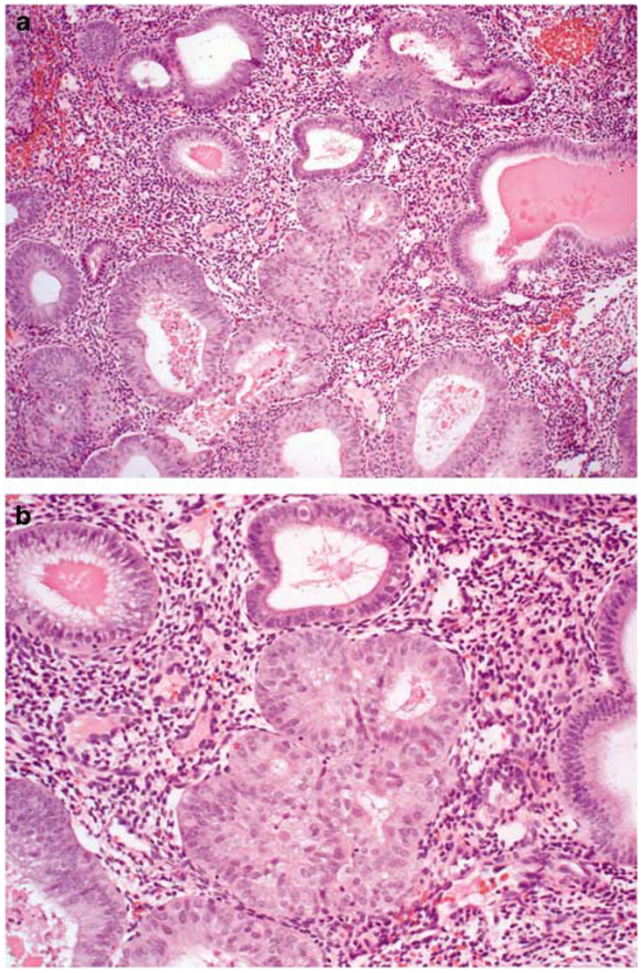

Figure 1 An example of adenocarcinoma *in situ* in case of complex atypical endometrial hyperplasia. (**a**) Lower power view (H&E, ×40). (**b**) The corresponding higher power (H&E, ×200).

in 20 of the 33 (61%) patients with AIS *vs* 6 of the 54 (11%) patients without AIS ($P<0.0001$). Myoinvasive carcinoma to a depth of 3 mm or more was present in 15 of the 33 (45%) patients with AIS *vs* 2 of the 54 (4%) patients without AIS ($P<0.0001$). The depth of myometrial invasion in cases with myoinvasion was $24.5\pm19.4\%$ in patients with AIS and $12.8\pm8.5\%$ in patients without AIS ($P=0.05$). The absolute depth of invasion in myoinvasive cases was 4.8 ± 3.5 mm in patients with AIS and 2.1 ± 1 mm in patients without AIS ($P=0.01$). A depth of invasion of greater than 50% was seen in 3 of the 33 patients with AIS, but in none of the 54 patients without AIS ($P=0.05$). None of the carcinomas in either group were FIGO grade III. The larger size of the AIS focus (>1 to <2.1 mm *vs* 1 mm or smaller) was not predictive of subsequent carcinoma ($P=0.68$). The results are summarized in Table 1.

Patients Younger than Age of 50

Among patients younger than age of 50, 5 of the 7 (71%) with AIS had myoinvasive carcinoma *vs* 2 of

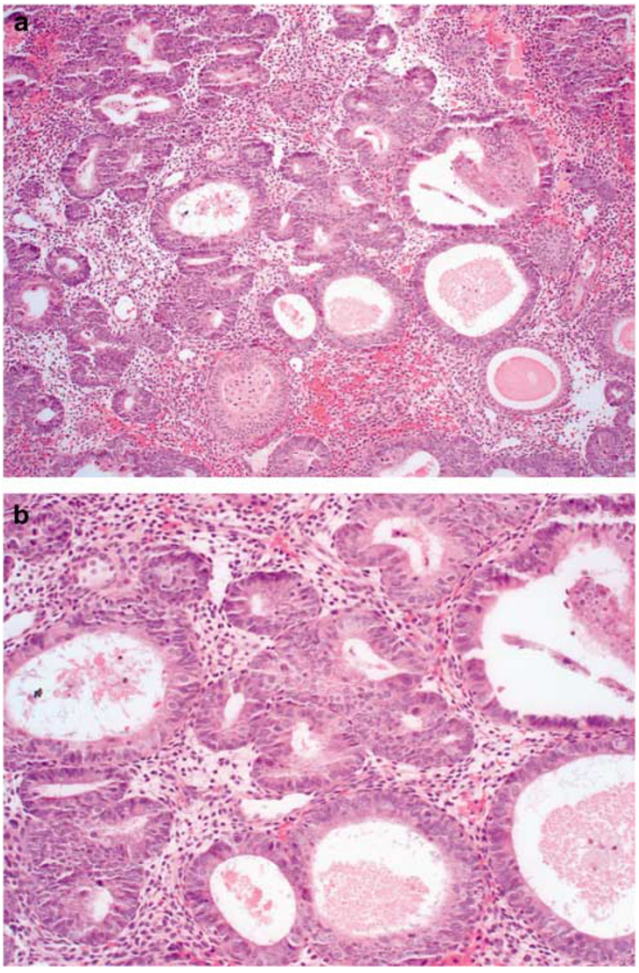

Figure 2 An example of adenocarcinoma *in situ* in case of complex atypical endometrial hyperplasia. (**a**) Lower power view (H&E, ×40). (**b**) The corresponding higher power (H&E, ×200).

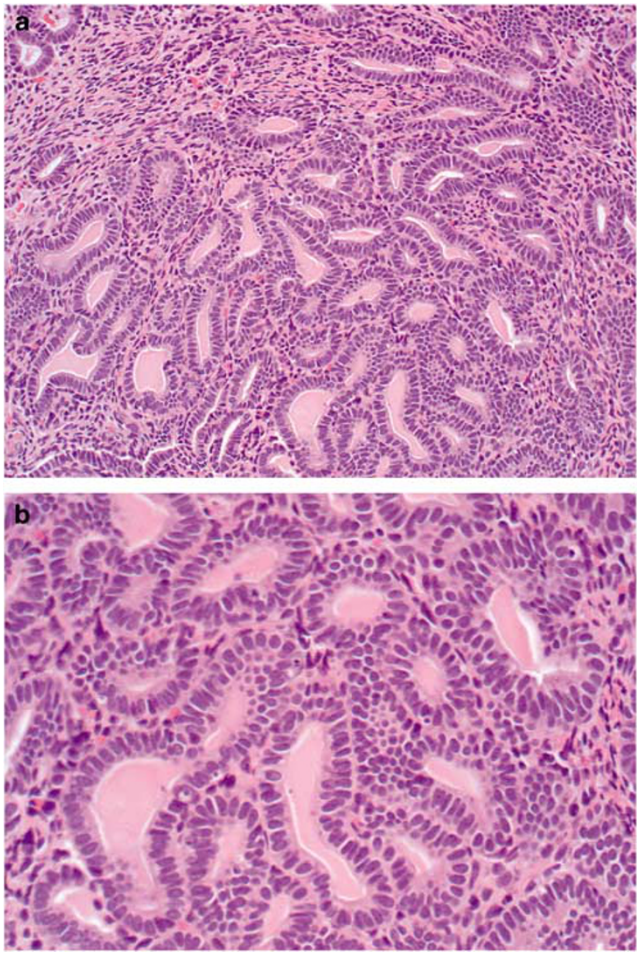

Figure 3 An example of adenocarcinoma *in situ* in case of complex atypical endometrial hyperplasia. (**a**) Lower power view (H&E, ×40). (**b**) The corresponding higher power (H&E, ×200).

the 14 (14%) without AIS ($P=0.02$). In all five patients that had myoinvasive carcinoma in the AIS group, the depth of invasion was 3 mm or greater. One of these patients had myoinvasion of 1 cm, equal to 58% of myometrial thickness. The two patients in the group without AIS had 1 and 2 mm depth of invasion, respectively. The results are summarized in Table 2.

Discussion

The overall incidence of endometrial adenocarcinoma and myoinvasive endometrial adenocarcinoma on follow-up hysterectomy in the group of complex atypical endometrial hyperplasia patients reported here was similar to what has been reported in the literature.[6,7,11,13,14] We found that the presence of AIS in complex atypical endometrial hyperplasia patients was associated with significantly greater likelihood of finding endometrial adenocarcinoma and myoinvasive endometrial adenocarcinoma on subsequent hysterectomy. Approximately two-thirds of patients with AIS in endometrial curettage/biopsy

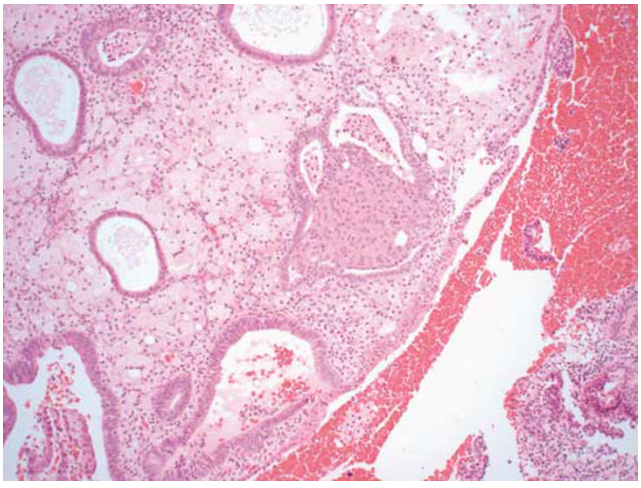

Figure 4 A cribriform like appearance can be seen due to squamous morule formation in endometrial glands. This should not be confused with adenocarcinoma *in situ* (H&E, ×200).

have endometrial adenocarcinoma on subsequent hysterectomy *vs* about a quarter of those that lack AIS. Endometrial adenocarcinomas in patients with

Table 1 Endometrial adenocarcinoma and myoinvasion was much more likely to be found in subsequent hysterectomy in cases with complex atypical endometrial hyperplasia on endometrial biopsy if adenocarcinoma-*in situ* was present in prior endometrial biopsy

Feature	*CAH with AIS (%)*	*CAH without AIS (%)*
Carcinoma in hysterectomy	22/33 (66)	13/54 (24)
Myoinvasive carcinoma	20/33 (61)	8/54 (15)
Myoinvasive carcinoma $\geq$2 mm deep	20/33 (61)	6/54 (11)
Myoinvasive carcinoma $\geq$3 mm deep	15/33 (45)	2/54 (4)
Myoinvasive carcinoma >50% deep	3/33 (9)	0/54 (0)

Abbreviations: CAH, complex atypical hyperplasia; AIS, adenocarcinoma *in situ*.

Table 2 In a subgroup of patients younger than 50 years of age, Endometrial adenocarcinoma and myoinvasion was much more likely to be found in subsequent hysterectomy in cases with adenocarcinoma-*in situ* in complex atypical endometrial hyperplasia on endometrial biopsy

Feature	*CAH with AIS (%)*	*CAH without AIS (%)*
Carcinoma in hysterectomy	5/7 (71)	2/14 (14)
Myoinvasive carcinoma	5/7 (71)	2/14 (14)
Myoinvasive carcinoma $\geq$2 mm deep	5/7 (71)	1/14 (7)
Myoinvasive carcinoma $\geq$3 mm deep	5/7 (71)	0/14 (0)
Myoinvasive carcinoma >50% deep	1/7 (15)	0/14 (0)

Abbreviations: CAH, complex atypical hyperplasia; AIS, adenocarcinoma *in situ*.

AIS are far more frequently myoinvasive, and invade to a greater depth than carcinomas seen in patients that have complex atypical endometrial hyperplasia without AIS.

There is considerable confusion in the literature as to where complex atypical endometrial hyperplasia ends and endometrial adenocarcinoma starts. The distinction of endometrial carcinoma from complex endometrial hyperplasia has generally been based on the criteria proposed by Kurman and Norris nearly 25 years ago.[11,15,16] In these studies, the cut off for endometrial carcinoma was arbitrarily set at 2.1 mm lesional size showing features of 'stromal invasion'. However, 7 of the 89 patients that lacked 'stromal invasion' also showed myoinvasive carcinoma in that study. It is unclear if any of these seven patients with myoinvasive carcinoma had AIS. This group without 'stromal invasion' included cases with complex atypical endometrial hyperplasia and 'carcinoma-*in situ*', but separate follow-up data for patients in complex atypical endometrial hyperplasia and 'carcinoma-*in situ*' groups was not provided.[11] In other words, no data were presented regarding the outcome of patients that showed smaller foci of what was called 'stromal invasion'. Such lesions are diagnosed as complex atypical endometrial hyperplasia by some pathologists,[11] as endometrial adenocarcinoma by others,[10] and as endometrial adenocarcinoma cannot be ruled out by yet others. King *et al*[17] examined a group of patients that they called 'adenocarcinoma without stromal invasion' and found endometrial carcinoma in 28% (12 of 43) and myoinvasive carcinoma in 16% (7 of 43) of these patients on follow-up hysterectomy. Longacre *at al*[18] have shown that glandular complexity captured by a pictorial architectural index, along with nuclear pleomorphism and prominence of the nucleoli are features most predictive for the presence of myoinvasive carcinoma in complex atypical endometrial hyperplasia. They also reported that extensive squamous differentiation and fibroblastic stroma do not contribute to prediction of myoinvasive endometrial carcinoma in subsequent hysterectomy. Hendrickson *et al*[19] did not find fibrous stroma in curettings from most patients with subsequent myoinvasive endometrial carcinoma.

We propose that foci of back-to-back glands or cribriform arrangement of glands smaller than 2.1 mm across be classified as AIS. The term 'carcinoma-*in situ*' was mistakenly applied to eosinophilic metaplasia of the endometrium many years ago[20] is no longer used in that context. The concept of designating small foci of cribriform arrangement of glands in endometrium as 'carcinoma-*in situ*' is not entirely new, and has been used in the past by Welch and Scully,[21] by Vellios[22] and by Buehl *et al*.[23] This concept, however, was not strictly defined previously, its definition varied from author to author, and follow-up data on these cases was not published. World Health Organization did not include any form of carcinoma-*in situ* of endometrium in its classification[24] because of lack of agreement on its definition.[21] In the current study, we have provided a strict definition for AIS of the endometrium, and documented its prognostic significance.

The relationship between AIS diagnosed preoperatively and endometrial adenocarcinoma found in hysterectomy specimens is unclear. Some lesions might represent smaller foci of the same neoplasm whereas others might represent independent and incompletely developed, incipient invasive carcinomas or risk lesions. The following observations support the latter possibility in some cases. Multiple foci of AIS can be seen without associated endometrial adenocarcinoma. Foci of AIS are often fairly widely distributed, with intervening areas of complex atypical endometrial hyperplasia. We have also seen cases where the histomorphologic appearance of these foci varies, suggesting their independent origin from each other (Figure 5).

Although we prefer to use the term AIS, a number of alternative terms could be potentially used for this lesion. These would include terms such as CAH types I and II, CAH type A and B, endometrial adenocarcinoma without stromal invasion, minimal

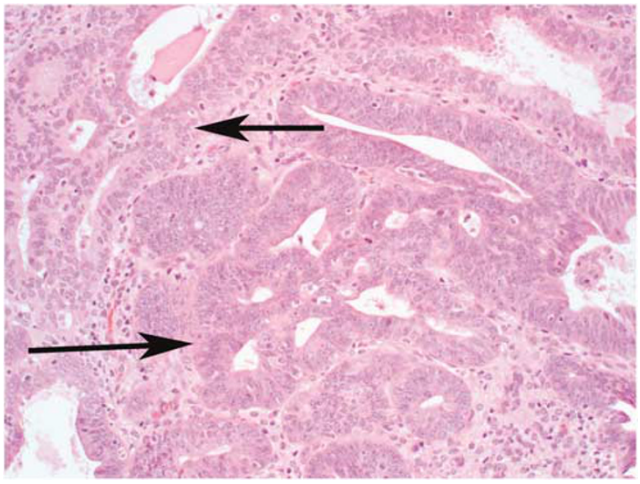

Figure 5 Occasionally, different foci of adenocarcinoma *in situ* on the same slide have different morphologic features in the cells, suggesting their independent origin (H&E, ×200).

carcinoma, microcarcinoma, microinvasive carcinoma, CAH with focal glandular confluence and 'microscopic focus of adenocarcinoma'.

AIS of endometrium should not be confused with endometrial intraepithelial carcinoma (EIC),[25] which is an early form of uterine serous carcinoma characterized by growth of cells with high-grade nuclei on the endometrial surface and in glands. These cells usually overexpress p53. Cribriform arrangement of glands or back-to-back arrangement of glands is not seen in EIC. EIC usually arises in the background of an atrophic endometrium.

Recognition of the substantial risk of myometrial invasion following a diagnosis of AIS should allow gynecologists and patients to make better informed decisions when conservative, nonsurgical management is considered. In the current study, only 2 of the 14 patients with complex atypical endometrial hyperplasia without AIS age 50 or under had myoinvasion, which was 1 and 2 mm, respectively. Two had carcinoma confined to the endometrium, whereas 10 had no carcinoma. Thus these patients can be managed conservatively. In contrast 5 of the 7 patients, 50 or under with complex atypical endometrial hyperplasia with AIS had myoinvasive carcinoma, and the depth of invasion in each of the five patients was 3 mm or more. One patient had 58% depth of invasion. Patients with complex atypical endometrial hyperplasia with AIS may also be considered for lymph node sampling at hysterectomy if these lymph nodes are enlarged.

In Summary, presence of AIS should be looked for and reported by pathologists in endometrial biopsies showing complex atypical endometrial hyperplasia because of a significantly greater likelihood of finding endometrial adenocarcinoma and myoinvasive endometrial adenocarcinoma in subsequent hysterectomy if AIS is present.

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