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ORIGINAL ARTICLE

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Alteration of CD44 and cadherins expression: possible association with augmented aggressiveness and invasiveness of endometrial carcinoma

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Abstract Cadherins and CD44 isoforms are transmembrane glycoproteins with diverse functions in cell–cell and cell–matrix interactions and may be a determinant of invasive and metastatic behavior in carcinomas. The immunohistochemical expression of cadherins and CD44 in tissue samples from 15 normal endometrium and 33 endometrial adenocarcinomas were examined. The immunohistochemical analysis was performed using the monoclonal antibody HECD-1 against E-cadherin and the polyclonal antibody against N-cadherin. In addition, the monoclonal antibodies 2C5, which binds to CD44s and all of the variants encoded by exons 3–10; 3G5, which is specific for CD44v3; and 2F10, which is specific for CD44v6 were used. E-cadherin (P=0.0001) and N-cadherin (P<0.001) expressions were statistically lower in endometrial adenocarcinoma than in normal endometrium. In contrast, an overexpression of CD44 isoforms (P<0.01) and CD44v3 (P<0.01) expressions was found in endometrial adenocarcinomas compared with normal endometrium. No difference was noted for CD44v6. An association was found between a decrease in E-cadherin expression and the occurrence of local recurrent and nodal metastasis. An association was found between CD44 overexpression, lymph space involvement, and myometrial invasion. Our results suggest that cadherin and CD44 expressions in endometrial carcinomas may have a prognostic value. Alteration of CD44 seems to be related to local invasion, while alteration of E-cadherin seems to be associated with dissemination of the disease.

Keywords Cadherins · CD44 · Adhesion molecule · Immunohistochemistry · Endometrium · Endometrial carcinoma

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Introduction

Endometrial cancer is the leading gynecologic cancer and the fourth most frequent cancer in women [29]. Fifty percent of endometrial adenocarcinoma occur in women with risk factors, such as hyperplasia, with atypical cytologic features and obesity [15, 18, 25]. Endometrial carcinoma is a heterogeneous disease with five-year survival rates ranging from 36% to 95% for women with clinical stage I disease [19]. Preoperatively, only a few factors, such as patient age, histology, and tumor grade, are available to predict the extent of disease [15, 18, 19, 25, 29, 33]. Despite these prognostic factors, the prediction of patients at high risk of extrauterine disease remains difficult. Indeed, the prediction of nodal disease based on depth of myometrial invasion using an imaging technique [20] and on grade determination from curettage specimens is controversial. Therefore, in addition to histologic type and grade of the tumor, the identification of reliable [19] prognostic markers is particularly crucial in the case of endometrial carcinoma.

Cadherins and CD44 isoforms are transmembrane glycoproteins implicated in cell-cell and cell-matrix adhesion [32, 35, 36]. Impairment of cadherin and CD44-mediated adhesion is likely to constitute one of the main factors leading to the reduced cell-cell and cell-matrix adhesion characteristics of tumor cells and play a pivotal

role in the acquisition of invasive and metastatic properties by neoplastic epithelial cells [3, 27, 34, 37]. There are many examples of carcinomas in which the occurrence of altered cadherin expression has been correlated with low histological differentiation, increased risk of local invasion and metastatic disease, recurrence, and poor prognosis [9, 10, 14, 21]. In the same way, much interest has recently focused on the role of CD44 proteins, particularly CD44 variants v3 and v6 as diagnostic and prognostic markers in gynecologic pathology [7, 15], malignant tumors of the breast, [17] and premalignant and malignant tumors of the ovary [5, 6].

We were, therefore, prompted to analyze the immunohistochemical expression of E- and N-cadherins, CD44 isoforms, and variants v3 and v6 in a series of endometrial carcinoma. In order to verify the correct histological analysis of endometrial carcinomas, only formalin-fixed, paraffin-embedded tissue was used. Our aims were to evaluate: (1) the immunohistochemical expression of E- and N-cadherins and CD44 proteins in endometrial adenocarcinoma tissue samples, (2) to compare the expression with that found in normal endometrium, and (3) to correlate the expression in endometrial carcinomas with clinicopathological parameters.

Material and methods

Material

Tissue samples from endometrial adenocarcinoma (n=33) and normal endometrium (n=15) were obtained from 48 patients, treated at the Service de Gynécologie de l'hôpital Bichat-Claude Bernard. Histological typing was performed according to the International Federation of Gynecology and Obstetrics recommendations [24]. Patients with a disease other than endometrial adenocarcinoma were excluded.

The mean age of the patients with adenocarcinoma was 66 years (range 43–88 years). Twenty-three (70%), zero, eight (24.2%), and two (5.8%) patients had stage I, stage II, stage III, and stage IV disease, respectively, according to the system for surgical staging of endometrial carcinoma.

Normal endometrium tissue samples were obtained from 15 patients. Tissue samples were taken in the proliferative (n=7) and the secretory (n=8) phases. Patients with endometrial hyperplasia, adenomyosis, or endometriosis were excluded. The median clinical follow-up was 58 months (range 30–120 months).

Methods

Antibodies

The antibody against E-cadherin was the monoclonal mouse antibody HECD-1 (R&D Systems, Abingdon, UK). To detect N-cadherin we used a commercially available rabbit polyclonal antibody raised against the C-terminal amino acid sequence of chicken N-cadherin (Sigma, St Louis, Mo.). The monoclonal antibodies (R&D Systems, Abingdon, UK) 2C5, which binds to CD44s and all of the variants encoded by exons 3–10; 3G5, which is specific for CD44v3; and 2F10, which is specific for CD44v6 were used in this study.

Immunohistochemical technique

In all cases, 3-µm-thick paraffin-embedded sections of formalin-fixed tissue samples was used. Sections were deparaffinized and rehydrated through a graded ethanol series and were incubated in methanol containing 0.3% H_2O_2 to inhibit endogenous peroxidase. For antigen unmasking, sections were incubated in 10 mM citrate buffer, pH 6, in a microwave oven for three 5-min periods at 500 W. After washing, sections were incubated for 1 h at room temperature with the primary antibody in 1/100 dilution as previously reported [5, 6, 7]. The revelation was performed using the avidin–biotin technique (Vector Laboratories, Burlingame, UK). Peroxidase activity was detected according to the method of Graham and Karnovsky [12]. Negative controls were obtained by means of omitting the primary antibody, substituted by either phosphate-buffered saline (PBS) or isotopic immunoglobins. All controls were negative.

Analysis of immunohistochemical results

The percentage of positive cells was evaluated on ten consecutive high magnification power fields (×40) by two observers. Mean values were obtained by averaging ten counts per tissue section. Variations between the two observers were less than 5%. In addition, for cadherin expression, in accordance with previous studies [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32], tumors were considered homogeneously positive when more than 90% of tumor cells were labeled, heterogeneously positive when 10–90% of tumor cells were labeled, and negative when less than 10% of tumor cells were labeled.

Statistical analysis

For statistical evaluation, Fisher's exact test was used for comparison of the percentage of epithelial cells labeled in normal endometrium and endometrial carcinoma. Wilcoxon two-sample test was used to evaluate the association between CD44 or E-cadherin expression and clinicopathological parameters in endometrial carcinoma. A P value less than 0.05 was considered significant.

Results

Immunohistochemical detection of E- and N-cadherins in normal endometrium and endometrial carcinoma

At the cellular level, E- and N-cadherins were detected along the lateral membranes and in the cytoplasmic compartment of endometrial cells (Fig. 1a). In endometrial carcinoma cells, E-cadherin was detected over the whole surface of the cells (Fig. 1b). A similar distribution was observed for N-cadherin immunostaining.

In the normal endometrium, E-cadherin immunostaining was homogeneously positive in 13 cases (86.6%) and heterogeneously positive in two cases (13.4%). No difference in E-cadherin expression was found according to the phases of menstrual cycle. Furthermore, there was no detection of stromal E-cadherin immunostaining in any of the normal endometrium samples.

In endometrial carcinoma, E-cadherin was found negative in 9 of the 33 cases (27.3%) and heterogeneously positive in 24 of 33 cases (72.7%) (Fig. 1b). There was no case of E-cadherin homogeneously positive among the endometrial carcinoma samples. A statistically significant difference (P<0.02) in E-cadherin expression was found between normal endometrium and endometrial adenocarcinoma samples (Fig. 2a). No stromal staining was observed. A statistically significant difference

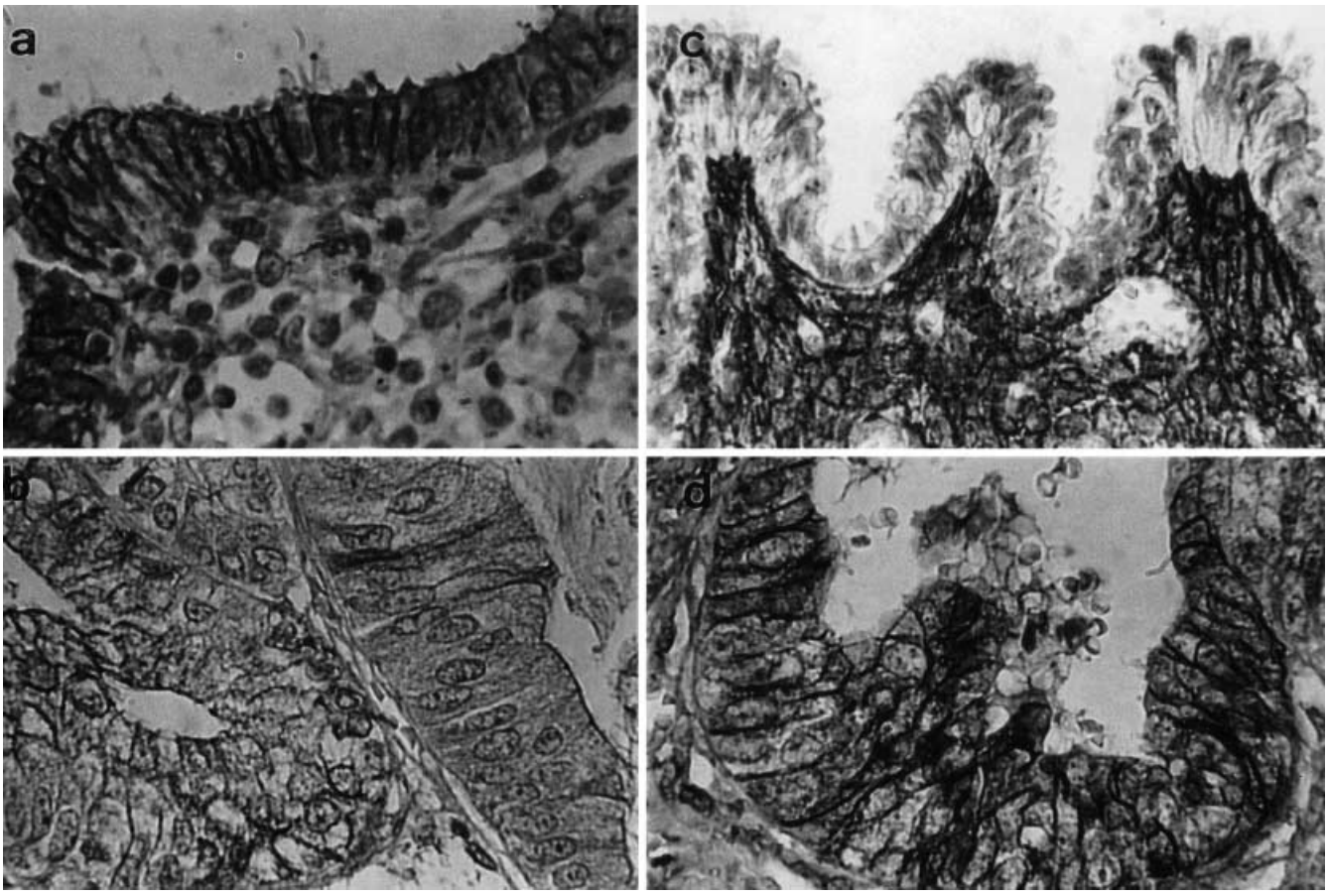

Fig. 1 Representative examples of E-cadherin and CD44 immunostaining in normal endometrium and endometrial carcinomas. In normal endometrium (**a**), E-cadherin was detected along the lateral membranes of cells. In endometrial carcinomas (**b**), E-cadherin was visible only on a few scattered cells. During the proliferative phase of the menstrual cycle (**c**), no CD44 isoforms staining was detected along laterobasal membranes of endometrial cells, whereas a strong CD44 immunostaining was homogeneously retained by stromal cells. In contrast, in endometrial carcinoma cells (**d**), CD44 isoforms were detected over the whole surface of the cells. (Immunoperoxidase with nuclear countercoloration with Harris' hematoxylin; original magnification ×80)

(P<0.0001) was noted in the percentage±SD of E-cadherin positive cells in normal endometrium (92%±17) and in endometrial carcinoma (33%±33).

In the normal endometrium, N-cadherin immunostaining was homogeneously positive in all 15 cases (100%). In addition, we noted that stromal N-cadherin immunostaining varied according to the phases of menstrual cycle. Indeed, stromal N-cadherin staining was positive in five of seven cases of proliferative endometrium and was negative in the eight cases of secretory endometrium.

In endometrial carcinomas, N-cadherin was considered negative in 1 of the 33 cases (3%) and heterogeneously positive in 32 of 33 cases (97%). Zero of 33 endometrial carcinomas were N-cadherin homogeneously positive. Stromal cells were N-cadherin negative. A statistically significant difference (P<0.001) was noted in the percentage ± SD of N-cadherin positive cells in normal endometrium (93%±3) and in endometrial carcinoma (62%±10) (Fig. 2b).

Immunohistochemical detection of CD44 isoforms in normal endometrium and endometrial carcinomas

At the cellular level, CD44 isoforms immunostaining were detected at the latero-basal membranes of endometrial cells. No cytoplasmic CD44 immunostaining was observed. In endometrial carcinoma cells, CD44 isoforms were detected over the whole surface of the cells. Similar distributions were found for CD44v3 and CD44v6 immunostaining.

In the normal endometrium, epithelial cells showed staining for the monoclonal antibody 2C5, which was directed to all CD44 isoforms, in five of eight cases of secretory endometrium. In contrast, for all seven cases of proliferative endometrium samples, CD44 staining was negative (Fig. 1c). Stromal cells were positive for CD44 isoforms irrespective of the phases of menstrual cycle.

In endometrial carcinomas, CD44 isoforms immunostaining was positive in 32 of 33 patients (97%; Fig. 1d). A statistically significant difference (P<0.01) was noted in the percentage ± SD of CD44 isoforms positive cells

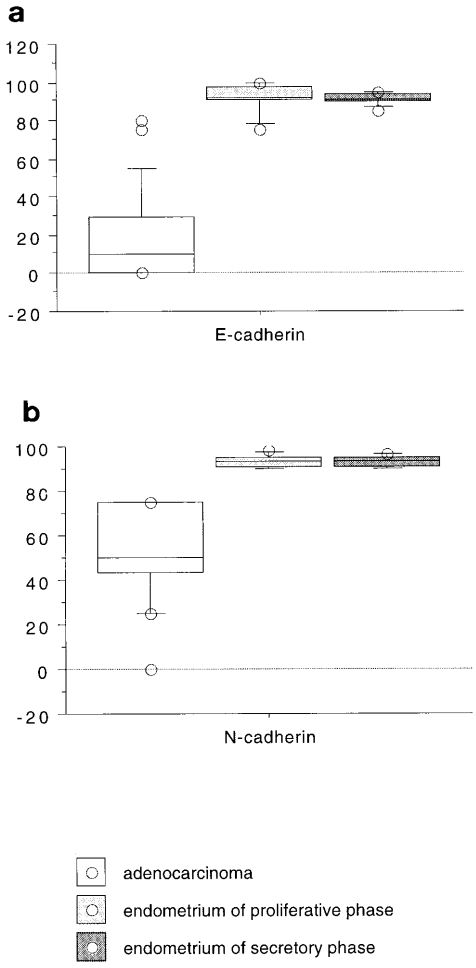

Fig. 2 **a** Distribution of an epithelial cell labeled for E-cadherin in normal endometrium and endometrial carcinoma (P<0.0001) (Fischer'exact test). **b** Distribution of an epithelial cell labeled for N-cadherin in normal endometrium and endometrial carcinoma (P<0.001) (Fischer'exact test)

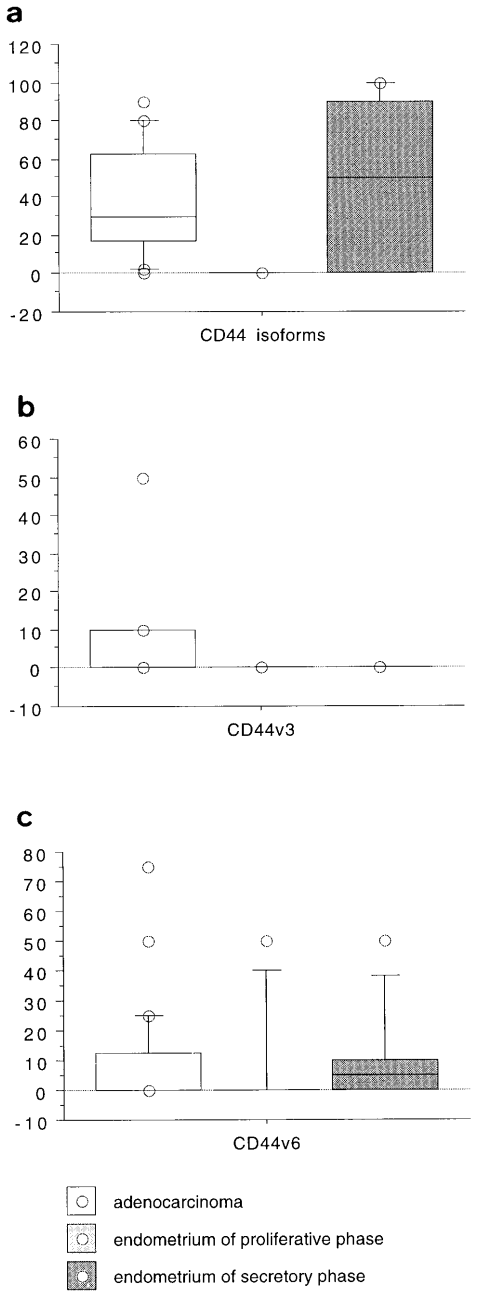

Fig. 3 **a** Distribution of an epithelial cell labeled for CD44 isoforms in normal endometrium and endometrial carcinoma (P<0.01) (Fischer'exact test). **b** Distribution of an epithelial cell labeled for CD44v3 in normal endometrium and endometrial carcinoma (P<0.01; Fischer'exact test). **c** Distribution of an epithelial cell labeled for CD44v6 in normal endometrium and endometrial carcinoma (not significant; Fischer'exact test)

in normal endometrium (25%±38) and in endometrial carcinoma (40%±27; Fig. 3a).

In the normal endometrium, neither epithelial nor stromal immunostaining for CD44v3 was noted. In endometrial carcinomas, CD44v3 immunostaining was positive in 11 of 33 patients (33.3%). A statistically significant difference (P<0.01) in CD44v3 expression was found between normal endometrium and endometrial carcinomas. A statistically significant difference (P<0.01) was noted in the percentage ± SD of CD44v3 positive cells in normal endometrium (0%) and in endometrial carcinoma (15%±19; Fig. 3b).

In the normal endometrium, CD44v6 immunostaining was observed in 5 of 15 cases (33.3%). Four of eight cases of secretory endometrium (50%) were CD44v6 positive. In contrast, only one of seven cases of proliferative endometrium (14.2%) were CD44v6 positive. No CD44v6 immunostaining was found in the stroma.

In endometrial carcinomas, 16 of 33 tumors were CD44v6 positive. No difference in CD44v6 expression was found between normal endometrium and endometrial carcinomas. No difference in the percentage ± SD of CD44v6 positive cells was found between normal endometrium (10±18) and endometrial carcinomas (27%±38; Fig. 3c).

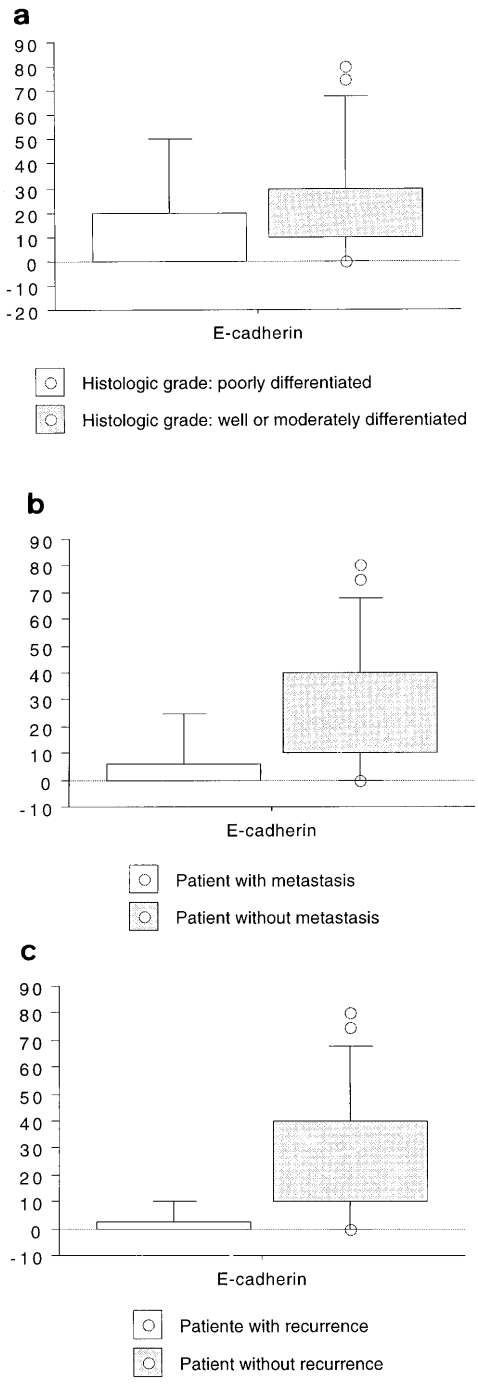

Fig. 4 **a** Distribution of patients according to histological differentiation and E-cadherin expression (P=0.02; Wilcoxon two sample test). **b** Distribution of patients with or without metastasis and E-cadherin expression (P=0.001; Wilcoxon two sample test). **c** Distribution of patients with or without pelvic recurrence and E-cadherin expression (P=0.001; Wilcoxon two sample test)

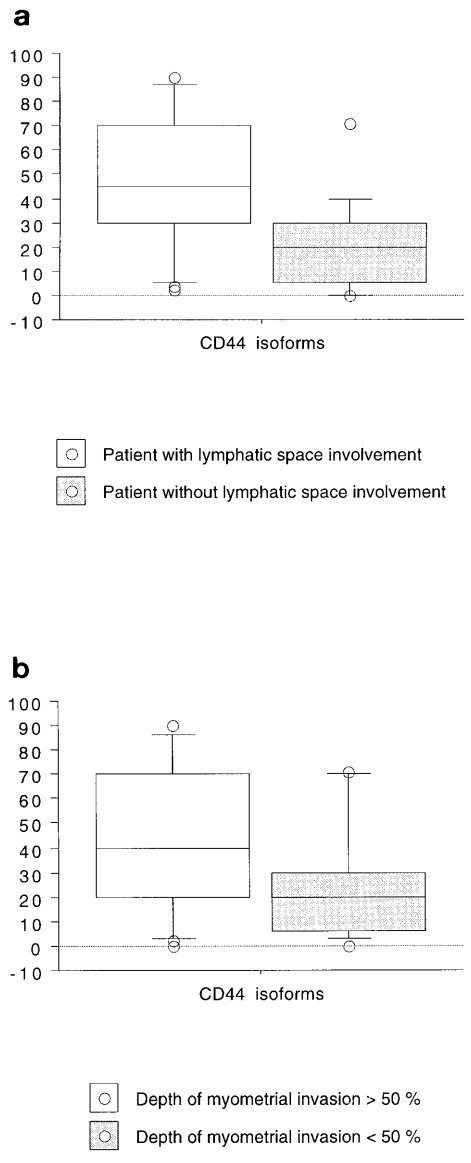

Fig. 5 **a** Distribution of patients with or without lymphatic space involvement and CD44 isoforms expression (P=0.03; Wilcoxon two sample test). **b** Distribution of patients with or without depth myometrial invasion >50% and CD44 isoforms expression (P=0.02; Wilcoxon two sample test)

Relationship between cadherins and CD44 isoform expressions and clinicopathological parameters in endometrial carcinomas

In endometrial carcinomas, a relationship was found between the loss of E-cadherin expression and clinicopathological parameters such as (1) the histological grade (P=0.02; Fig. 4a), (2) occurrence of recurrence (P=0.001; Fig. 4b), and (3) the presence of metastasis (P=0.001; Fig. 4c). No relation was observed between E-cadherin negative tumors and (1) the stage of the disease according to the International Federation of Gynecology and Obstetrics (FIGO) classification, (2) the age of patients, (3) the lymphatic space involvement, and (4) the depth of myometrial invasion greater than 50%. In a similar manner, no relationship was observed between N-cadherin expression and the clinicopathological parameters.

In endometrial carcinomas, a relationship was found between overexpression of CD44 isoforms and (1) the

occurrence of lymphatic space involvement (P=0.03; Fig. 5a) and (2) the depth of myometrial invasion greater than 50% (P=0.02; Fig. 5b). No relationship was found between CD44v3 and CD44v6 expressions and the clinicopathological parameters. The number of patients with E-cadherin negative and CD44 isoforms positive tumors was too small to evaluate the prognostic interest of this combination. Due to the sample size, multivariate analysis could not been performed.

Discussion

The present study shows that at least two cadherins are expressed in endometrium and endometrial carcinomas: E-cadherin and a cadherin related to N-cadherin. We observed that normal endometrium epithelial cells were constantly E-cadherin positive without variation according to the phase of the menstrual cycle. Similar results were found for epithelial N-cadherin expression. Furthermore, in the endometrial stroma, no immunostaining for E-cadherin was detected. In contrast, we found that the stromal cells during the proliferative phase do express N-cadherin. These results are similar to previous studies [40, 41], which reported a similar expression of E-cadherin during proliferative and secretory phases and the absence of a relationship between this expression and estradiol and progesterone serum levels.

In endometrial carcinomas, we found a decrease of E-cadherin expression relative to normal endometrium samples. Our results are in accordance with those found in various carcinomas, such as epithelial ovarian cancers [5], uterine cancer of the cervix [8, 14], and breast carcinomas [16]. Furthermore, our data are in line with those of experimental studies [23], which reported an enhancement of invasiveness in the presence of an anti-E-cadherin antibody, HECD-1, in three human endometrial carcinoma cell lines. In addition, several authors [27, 28] have identified mutations in the E-cadherin gene on chromosome 16q22 in endometrial cancers. This supports the classification of E-cadherin as a human tumor suppressor gene. Moreover, recently, a decrease in E-cadherin and β-catenin mRNA expressions were noted in endometrial cancer [10], suggesting that cadherin in association with catenins may have a pivotal role in endometrial carcinogenesis.

In endometrial carcinomas, no data was so far available about N-cadherin expression, which is usually regarded as characteristic of neural and muscular cells [26]. We observed a decrease of N-cadherin expression by endometrial carcinoma cells relative to normal endometrial cells. These data are in line with those of previous studies [5, 26], which reported a decrease of N-cadherin expression from benign to overt malignant tumors of the ovary.

In the present study, epithelial endometrial cells expressed CD44 isoforms only during the secretory phase of the menstrual cycle. Similar results were found for CD44v6 expression. In contrast, in the normal endometrium, no CD44v3 immunostaining was detected. Our data are in accordance with others [30, 38] who found CD44 expression in the secretory phase to be higher than in the proliferative phase. These results suggest a possible role of CD44 proteins in the implantation phase and a potential hormonal regulation of CD44 expression. This hypothesis is reinforced by experimental studies [1, 13], which postulated that CD44 expression appeared to be triggered by embryonic signaling. However, the variations of CD44 expression according to the phases of menstrual cycle may only coincide with the increase in motility required for cyclical re-epithelialization [2].

In endometrial carcinomas, compared with normal endometrium, we observed an overexpression of CD44 isoforms and CD44v3 but not of the CD44v6 splice variant. These results are partly in accordance with previous studies, which reported an overexpression of both CD44 isoforms and splice variants for tumors of other origins, such as those of the digestive tract [42], the breast [17], the ovary [5, 6], and the cervix [7]. In endometrial cancers, controversial results on CD44 expression have been published. Indeed, in uterine adenocarcinomas and human endometrial carcinoma cell lines, Fujita et al. [11] showed, using reverse transcriptase polymerase chain reaction (RT-PCR) and immunohistochemistry, a decrease in CD44 expression and splice variants. In contrast, as in our experience, Yorishima et al. [43] reported an overexpression of both CD44 isoforms and variant v6 in a series of 23 uterine carcinoma.

Few biologic markers, which are used to evaluate the prognosis, are available in endometrial carcinomas. High levels of estrogen and progesterone receptors have been correlated with tumor differentiation, myometrial invasion, nodal metastasis, and survival [4]. Furthermore, DNA aneuploidy, overexpression of HER-2/neu, and mutations of *P53* tumor-suppressor gene have been identified [29]. Nevertheless, their implications for treatment are not yet clear. In our experience, a loss of E-cadherin expression was associated with poorly differentiated endometrial cancer and the recurrence and metastatic spread. Our results are partly in accordance with those of previous studies [22, 31], which reported, in endometrial carcinomas, a relationship between E-cadherin expression and the tumor grade, and with myometrial invasion and lymph node metastasis. In addition, Nomura et al. [22], in multivariate analysis, revealed that among histologic grade, nuclear grade, and E-cadherin expression, E-cadherin was the better prognostic factor of myometrial invasion.

In our series, no relationship was found between N-cadherin expression and the clinicopathological parameters. In this report, in endometrial carcinomas, a relationship was noted between CD44 overexpression, the lymph space involvement, and the depth of myometrial invasion. Our data are in accordance with a previous study [11],which reported CD44 overexpression in endometrial carcinoma. However, these authors [11] did not find a relationship between CD44 expression and myometrial invasion that may be due to the low number of stage III and stage IV tumors included in their series.

As in our experience, previous studies [38, 39] have reported the absence of a relationship between CD44v6 expression and the clinicopathological parameters in endometrial carcinomas. Finally, our results suggest that overexpression of CD44 isoforms by endometrial carcinomas is related to local invasion. In contrast, the loss of E-cadherin expression seems to be related to the development of metastasis and the risk of recurrence. In consequence, the combination of E-cadherin and CD44 isoform expressions may help to identify patients presenting a high risk of poor evolution.

In summary, from the pathogenetic point of view, our results strongly suggest a differential involvement of cadherin and CD44 alterations in the process of endometrial carcinogenesis. Alterations of E-cadherin seem to be associated with the dissemination of the disease. In contrast, alterations of CD44 seem to occur during local invasion. Therefore, from the clinical point of view, in endometrial cancers, the analysis of cadherin and CD44 expressions may help to identify patients with poor prognosis who may benefit from adjuvant therapies.

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