with adenofibroma-associated carcinoma, 10 (71%) had stage I, 1 (7%) had stage II, 2 (14%) had stage III, and 1 (7%) had stage IV carcinoma. Twenty-two solitary endometrioses were also identified from salpingo-oophorectomy specimens. The research protocol was approved by the ethics committee of the National Defense Medical College, Tokorozawa, Japan.

On the basis of the previously described histological criteria for 'atypical endometriosis',[5,7,8] endometriotic lesions adjacent to clear-cell adenocarcinoma were classified into non-atypical and atypical forms. Of the 28 patients with endometriosis-associated carcinoma, 15 had both non-atypical and atypical endometriosis, 6 had only non-atypical endometriosis, and 7 had only atypical endometriosis. Therefore, 21 non-atypical and 22 atypical endometriotic lesions as well as 28 endometriosis-associated invasive carcinoma components were analyzed by immunohistochemistry.

With reference to the histopathological criteria of benign and borderline clear-cell adenofibroma described previously,[7,9] adenoma lesions in each adenofibroma were histologically subclassified into benign and borderline categories. Consequently, 9 of the 14 adenofibroma-associated patients had both the evaluable benign and borderline (clear-cell) adenofibroma components, 4 had the borderline adenofibroma component only, and 1 had the benign adenofibroma only. Therefore, 10 benign adenofibroma components, 13 borderline components, and 14 adenofibroma-associated invasive carcinoma components were analyzed by immunohistochemistry.

Immunohistochemistry for ARID1A Detection

All the selected formalin-fixed and paraffin-embedded specimens were cut into 4 μm thick serial sections and analyzed by immunohistochemistry. A commercially available polyclonal rabbit anti-ARID1A antibody (HPA005456; Sigma-Aldrich; diluted 1:50) was used as the primary antibody for ARID1A protein detection, as described previously.[28] Sections were deparaffinized and boiled in an autoclave at 121 °C for 15 min in 0.01 mol/l citrate buffer (pH 6.0) and then allowed to cool at room temperature. Endogenous peroxidase activity was blocked using 5% hydrogen peroxide. The slides were incubated at 4 °C overnight with primary antibodies and then reacted with a dextran polymer reagent combined with secondary antibodies and peroxidase for 1 h at room temperature. Specific antigen–antibody reactions were visualized with 0.2% diaminobenzidine tetrahydrochloride and hydrogen peroxide, and counterstaining was performed using Mayer's hematoxylin. Non-neoplastic cells, including endothelial cells, fibroblasts, and lymphocytes, normally show ARID1A nuclear immunoreactivity, and therefore, they served as positive internal controls. As negative controls, sections without the primary antibody were used.

Previous studies have shown that inactivating mutations of *ARID1A* are associated with the loss of protein expression.[12,27] Therefore, we focused our attention on the lesions with undetectable ARID1A immunoreactivity in the nucleus and used a scoring system to classify all lesions into ARID1A deficient (immunoreactions undetectable) and ARID1A intact (immunoreactions detectable); any level of ARID1A immunoreactivity was considered ARID1A intact. As the majority of the carcinomas showed an ARID1A immunoreaction that was diffusely (>80% of the cells of interest) immunoreactive or homogeneously undetectable, we did not consider the percentage of the immunoreactive cells in the examined lesions.

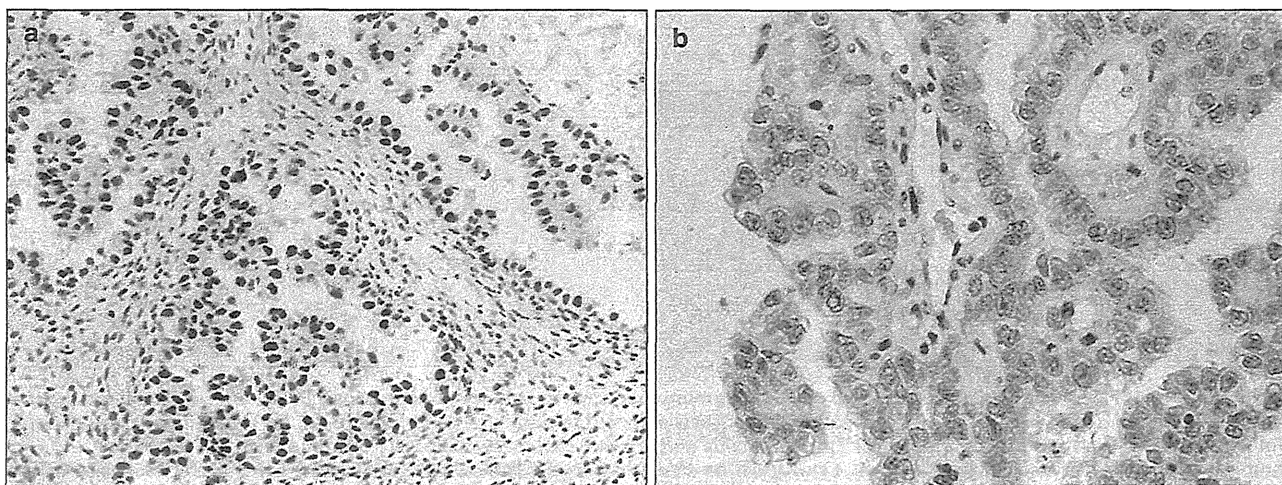

Figure 1 ARID1A immunoreactivity in two representative ovarian clear-cell carcinoma cases. (**a**) A clear-cell carcinoma showing diffuse and strong nuclear immunoreactivity for ARID1A. (**b**) A clear-cell carcinoma with undetectable ARID1A immunoreactivity. Stromal cells of both the samples show moderate to strong immunoreactivity and serve as internal positive controls. The carcinomas shown in panels **a** and **b** were defined as ARID1A-intact and ARID1A-deficient carcinomas, respectively. Immunoperoxidase stain, original magnification ×200 for (**a**) and ×400 for (**b**).

Mutation Assay of the *PIK3CA* Gene

Invasive carcinoma components from the enrolled 42 cases were analyzed for somatic mutations of the *PIK3CA* gene using direct genomic DNA sequencing. Details of these methods have been described in our previous study.[15] Briefly, exons 9 and 20 of the *PIK3CA* gene were amplified using PCR for genomic DNA. PCR was conducted using AmpliTaq Gold (Applied Biosystems, Foster City, CA). The primers for PCR and sequencing conditions have been described previously.[15] The PCR products were subsequently subjected to direct sequencing PCR with BigDye terminator V 3.1/1.1 cycle sequencing reagents (Applied Biosystems), and samples were analyzed on an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems) with DNA Sequencing Analysis Software v5.2 (Applied Biosystems). For 23 of the 28 patients with endometriosis-associated carcinomas, we used the required data from our previous study.[15] The remaining 5 patients with endometriosis-associated carcinomas and 14 with adenofibroma-associated carcinomas were analyzed for the first time in the present study.

Statistical Analysis

Statistical analyses were performed using StatMate III software (ATMS, Tokyo, Japan). Comparisons between parameters were computed using the χ^2 test or Student's *t*-test for unpaired data.

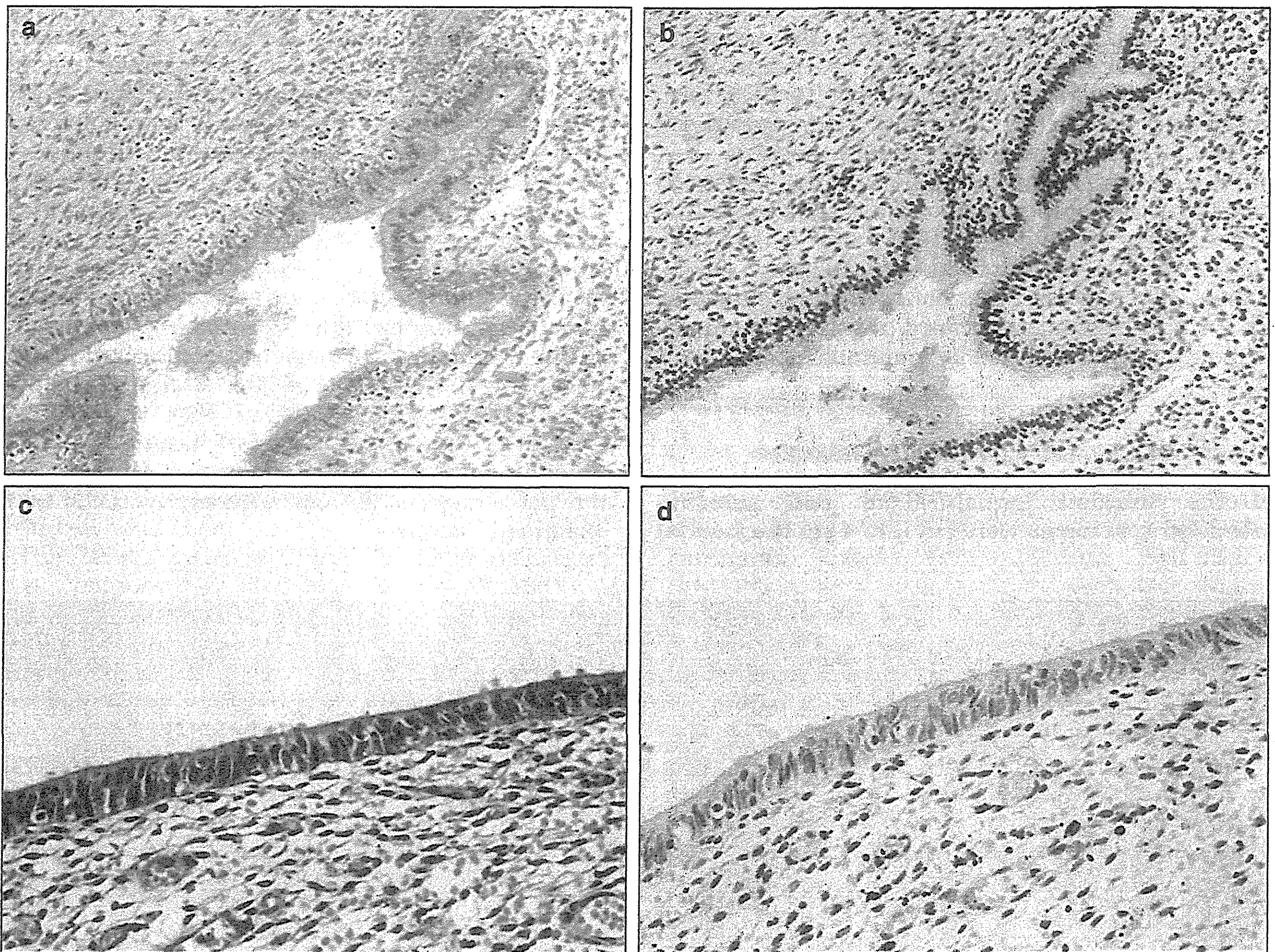

Figure 2 Representative histological features and ARID1A immunoreactions in solitary endometriosis (**a**, **b**), non-atypical endometriosis adjacent to clear-cell carcinoma (**c**, **d**), and atypical endometriosis adjacent to clear-cell carcinoma (**e**–**h**). (**a**) Hematoxylin and eosin (HE) staining of a solitary endometriosis sample. (**b**) Epithelial cells and stromal cells show diffusely immunoreactive for ARID1A. (**c**) A case of non-atypical endometriosis lacking evident cytological or structural atypia in the epithelial cells. (**d**) Stromal cells are diffusely immunoreactive for ARID1A, while the immunoreaction is undetectable in the endometriotic epithelia. (**e**) A case of atypical endometriosis showing moderate degrees of cytological atypia and cellular stratification. (**f**) Similar to panel **d**, the ARID1A immunoreaction is undetectable in epithelia. (**g**) HE staining of another case of atypical endometriosis. (**h**) ARID1A immunostaining of the samples shown in (**g**). Epithelial cells, as well as stromal cells, show diffuse immunoreactivity for ARID1A. (**a**, **c**, **e**, and **g**) HE stain, original magnification ×200 for (**a**, **e**, and **g**) and ×400 for (**c**). (**b**, **d**, **f**, and **h**) Immunoperoxidase stain, original magnification ×200 for (**b**, **f**, and **h**) and ×400 for (**d**).

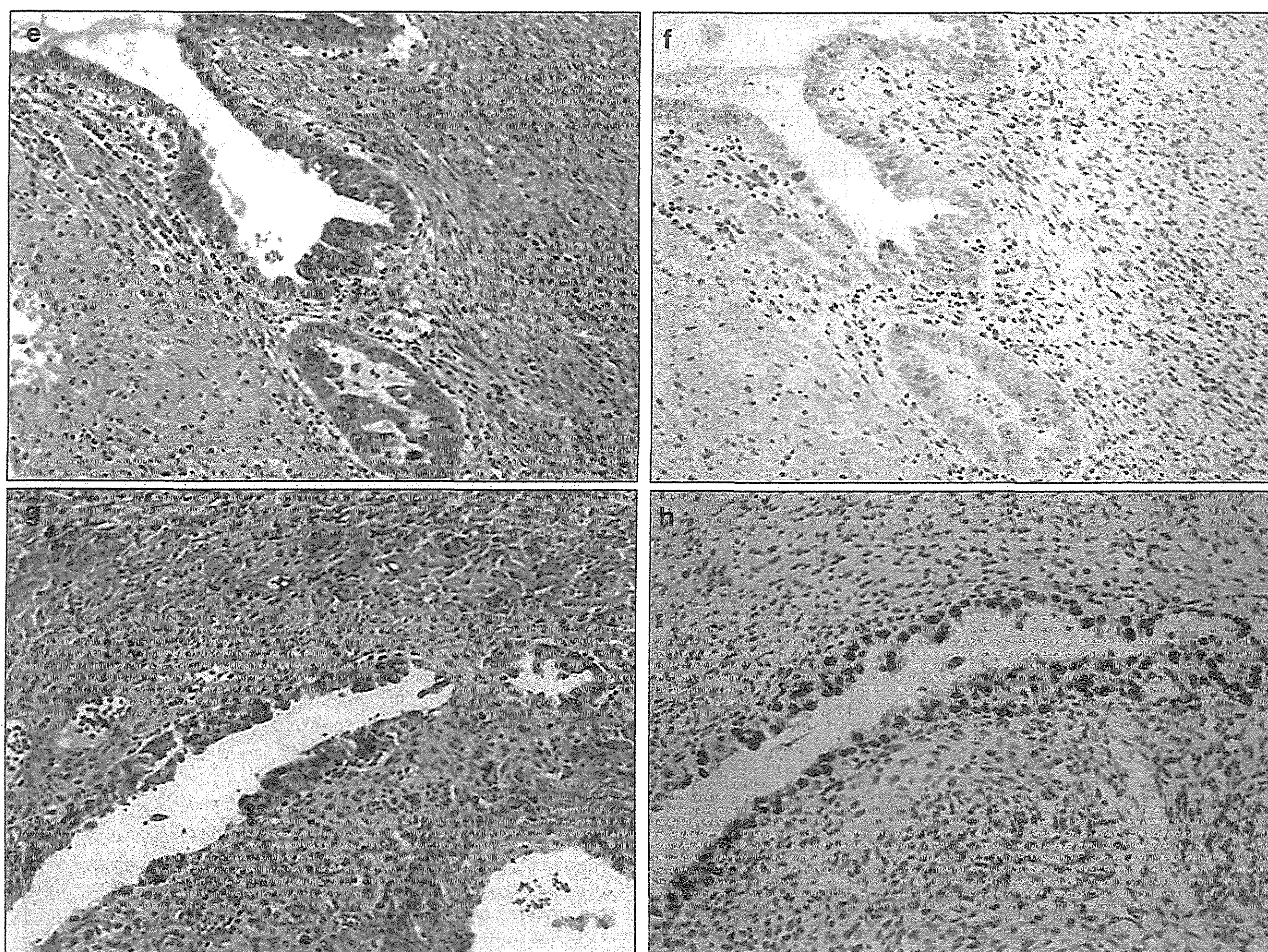

Figure 2 Continued.

Values of $P<0.05$ were considered to be statistically significant.

Results

ARID1A Expression in Invasive Carcinoma Components

Analysis of invasive carcinoma components showed that immunoreactivity was always in a diffusely (not heterogeneously) detectable or homogeneously undetectable pattern. Of the 28 endometriosis-associated carcinomas, 17 (61%) and 11 (39%) were judged as the ARID1A-deficient and the ARID1A-intact tumors, respectively (Figure 1). Of the 14 adenofibroma-associated carcinomas, 6 (43%) and 8 (57%) were judged as the ARID1A-deficient and the ARID1A-intact tumors, respectively. Overall, 23 (55%) of the 42 clear-cell carcinomas analyzed were determined as ARID1A deficient. Comparison between the endometriosis-associated carcinomas and adenofibroma-associated carcinomas showed no statistically significant differences in the frequency of deficiency of ARID1A immunoreaction ($P=0.273$).

ARID1A Expression in Endometriosis

All of the 22 solitary endometriosis samples showed diffuse and strong immunoreactions for ARID1A (Figures 2a and b; Table 1).

Among the 17 patients with endometriosis-associated carcinomas that were ARID1A-deficient tumors, 14 non-atypical endometrioses and 14 atypical endometrioses were histologically identified. Of the 14 non-atypical endometrioses, 12 (86%) and 2 (14%) endometrioses were judged as ARID1A deficient and ARID1A intact, respectively (Figures 2c and d), and all of the 14 atypical endometrioses were ARID1A deficient (Figures 2e and f). Three (25%) of the 12 ARID1A-deficient non-atypical endometrioses showed front formation during immunoreactivity, ie, the areas of ARID1A-deficient cells were adjacent to the ARID1A-intact areas, giving the impression of an 'abrupt loss' of ARID1A expression (Figure 3).

Among the 11 endometriosis-associated carcinoma cases with an ARID1A-intact carcinoma, 7 non-atypical and 8 atypical endometrioses lesions were identified, and all 15 lesions showed diffusely immunoreactivity for ARID1A (Figures 2g and h).

Table 1 The ARID1A immunoreactivity in the putative precursor lesions of ovarian clear-cell carcinomas

	Number of cases (%)	
	ARID1A	*ARID1A*
Type of precursor lesion	Deficient	Intact
In the endometriosis-associated carcinomas		
In the ARID1A-deficient carcinomas		
Non-atypical endometriosis (distant; $n=10$)	—0	10 (100)
Non-atypical endometriosis (adjacent; $n=14$)	12 (86)[a]	2 (14)
Atypical endometriosis (adjacent; $n=14$)	14 (100)	0
In the ARID1A-intact carcinomas		
Non-atypical endometriosis (adjacent; $n=7$)	0	7 (100)
Atypical endometriosis ($n=8$)	0	8 (100)
In the adenofibroma-associated carcinomas		
In the ARID1A-deficient carcinomas		
Benign clear-cell adenofibroma (adjacent; $n=3$)	3 (100)	0
Borderline clear-cell adenofibroma (adjacent; $n=6$)	6 (100)	0
In the ARID1A-intact carcinomas		
Benign clear-cell adenofibroma (adjacent; $n=10$)	0	7 (100)
Borderline clear-cell adenofibroma (adjacent; $n=14$)	0	7 (100)

[a]Three of these 12 lesions exhibited a pattern of immunoreactivity in which areas of ARID1A-deficient cells were adjacent to the ARID1A-intact areas.

Of the 23 patients with endometriosis-associated carcinomas that were ARID1A deficient, 10 lesions of non-atypical endometriosis distant from carcinoma components were also identified, and all 10 lesions were diffusely immunoreactive for ARID1A.

Consequently, with the exception of three ARID1A-deficient non-atypical endometrioses showing heterogeneous immunoreaction (area of ARID1A-deficient cells was adjacent to the area of ARID1A-intact cells), all of the endometriotic lesions analyzed showed diffusely detectable or homogeneously undetectable immunoreaction patterns for ARID1A.

ARID1A Expression in Clear-Cell Adenofibroma

Among the six cases of adenofibroma-associated carcinomas that were ARID1A-deficient tumors, three benign clear-cell adenofibroma and six clear-cell borderline adenofibroma components were histologically identified (Table 1). All three benign adenofibromas and six borderline adenofibroma components were judged as ARID1A deficient (Figures 4a–d).

Among the eight cases of adenofibroma-associated carcinomas that were ARID1A-intact tumors, seven benign adenofibromas and seven borderline adenofibroma components were histologically identified, and all 14 lesions were diffusely immunoreactive for ARID1A (Figures 4e and f).

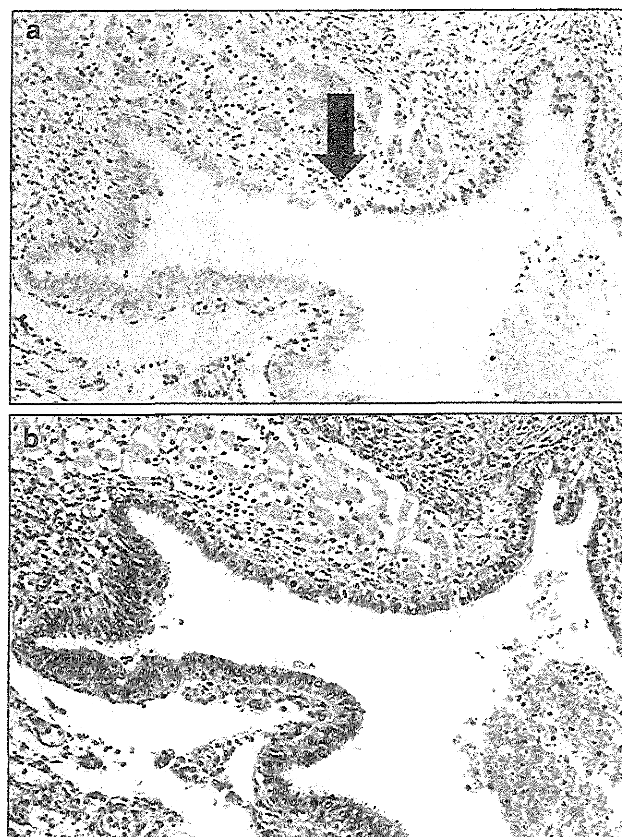

Figure 3 Representative case of a non-atypical endometriosis lesion adjacent to clear-cell carcinoma, showing a pattern of heterogeneous immunoreactions for ARID1A. (**a**) The area of ARID1A-deficient cells is adjacent to the ARID1A-intact area and shows front formation, namely the 'abrupt loss of ARID1A expression' (arrow), suggesting that mutations arose in clones within this lesion. (**b**) Hematoxylin and eosin (HE) staining corresponding to the samples shown in panel **a**. Regarding the histomorphology or the extent of cellular atypia, the ARID1A-intact and ARID1A-deficient epithelia show similar appearance. Original magnification, ×200 each.

Consequently, all the clear-cell adenofibroma components analyzed showed a diffusely detectable or homogeneously undetectable immunoreaction pattern for ARID1A.

Relationship Between ARID1A Immunoreactivity and PIK3CA Mutations

Sequencing chromatograms for *PIK3CA* exons 9 and 20 were obtained for all the 42 carcinomas analyzed. Direct sequencing showed mutations in 17 (40%) carcinomas: 14 (83%) were found in exon 20 (all of these were H1047R substitutions); and the remaining 3 (17%) were in exon 9 (two were E545K substitutions and one was an E545V substitution). Of the 17 *PIK3CA*-mutation-positive carcinomas, 12 (71%) tumors were ARID1A-deficient carcinomas;

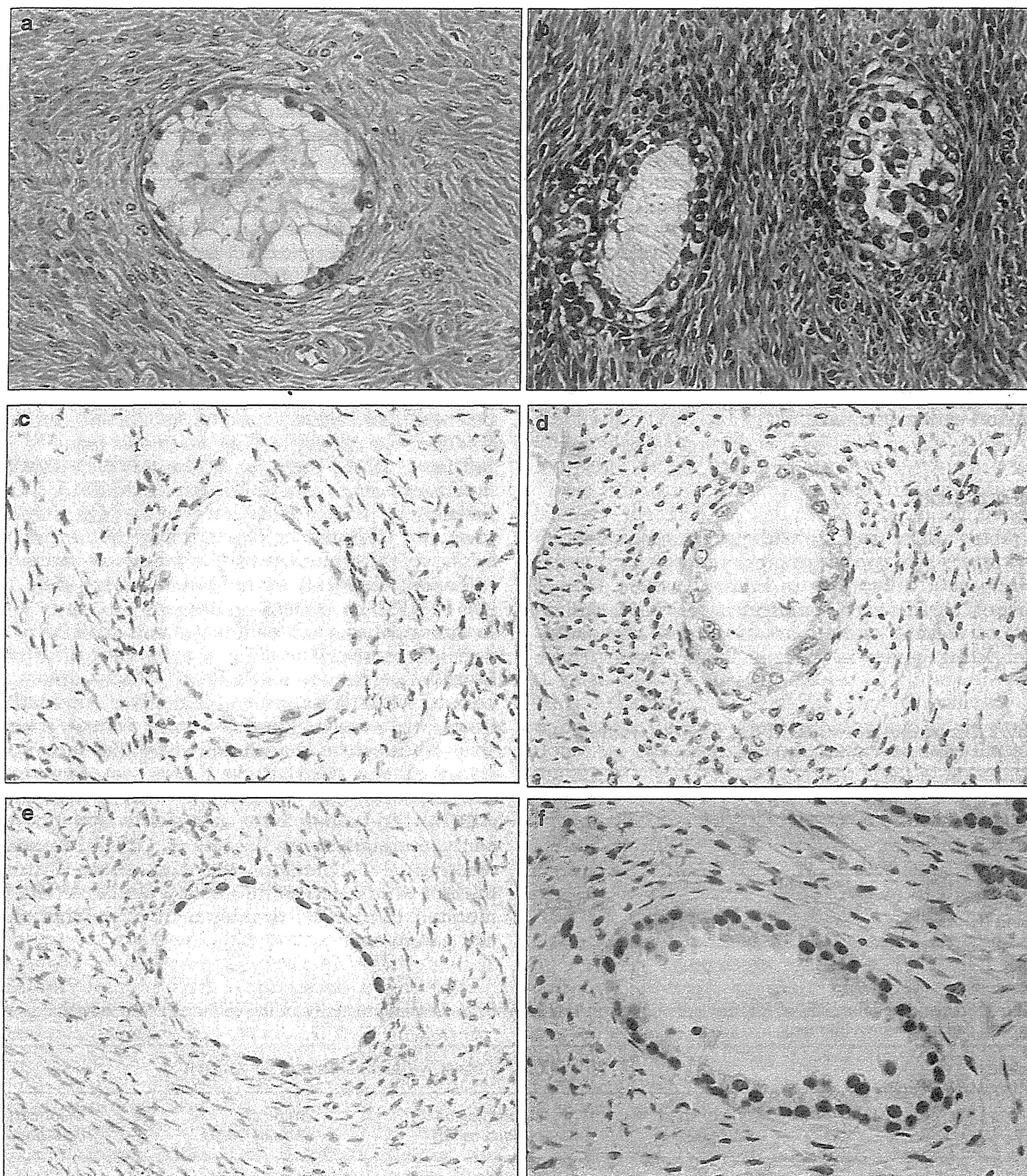

Figure 4 Representative histological features and ARID1A immunoreactions in benign clear-cell adenofibroma (**a**, **c**, and **e**) and borderline clear-cell adenofibroma (**b**, **d**, and **f**). (**a**) A case of benign clear-cell adenofibroma lacking cytological or structural atypia. (**b**) A case of borderline clear-cell adenofibroma. Epithelial cells show a moderate degree of cytological atypia. (**c**, **d**) Stromal cells are diffusely immunoreactive for ARID1A, while the immunoreaction is undetectable in epithelial cells. (**e**, **f**) Epithelial cells, as well as stromal cells, show diffuse immunoreactivity for ARID1A. (**a**, **b**) Hematoxylin and eosin (HE) staining, original magnification ×400 each. (**c–f**) Immunoperoxidase stain, original magnification ×400 each.

of the 19 ARID1A-intact carcinomas, *PIK3CA* mutations were detected in only 5 (26%) tumors (Table 2). The frequency of *PIK3CA* mutations in the ARID1A-deficient carcinomas was higher than that in the ARID1A-intact carcinomas, but not significantly different ($P=0.083$).

The ten endometriosis-associated carcinoma cases, in which our previous study analyzed the status of *PIK3CA* mutations both in clear-cell carcinoma and coexisting endometriotic lesions,[15] were combined with the data obtained from the present study (Table 3). Of these 10 carcinoma components harboring *PIK3CA* mutations, all but one carcinomas (case no. 12) were ARID1A deficient. All of the six *PIK3CA*-mutation-positive non-atypical endometrioses (case no. 5, 8, 14, 17, 18, and 20) were immunohistochemically ARID1A deficient. Moreover, except for case no. 12, all of the six atypical endometrioses harboring *PIK3CA* mutations were of ARID1A deficient. In case no. 6, *PIK3CA* mutation was firstly documented in the invasive carcinoma component, but ARID1A immunoreactions was already deficient in the adjacent atypical endometriosis.

Discussion

In recent years, genome-wide sequencing analyses have made substantial progress in cataloging molecular genetic alterations in human cancers. One of the most significant recent findings is the identification of somatic mutations of several chromatin-remodeling genes in certain tumor types. These genes include the *JARID1C* gene in renal cell carcinomas,[29] *SMARCA4/BRG1* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4) in lung carcinomas,[30,31] and most recently, *ARID1A* in ovarian and endometrial cancers.[12,13,28] The mutations in *ARID1A* were widely distributed throughout the coding region and all were predicted to truncate the protein through a base substitution, resulting in a stop codon or an out-of-frame insertion or deletion. These alterations resulted in the loss of ARID1A protein expression, suggesting that somatic mutations inactivate the gene product as a tumor suppressor.[12,13]

The main findings of our investigation can be summarized as follows: (a) loss of ARID1A expression in the putative precursor lesions of ovarian clear-cell carcinoma occurred specifically in cases in which the corresponding carcinoma was ARID1A deficient. (b) In majority of the ARID1A-deficient carcinoma cases, the deficiency of ARID1A immunoreaction was already evident at the stage of precursor lesions lacking cytological atypia (ie, non-atypical endometriosis adjacent to carcinoma or benign clear-cell adenofibroma), suggesting that loss of ARID1A protein occurs as a very early event in tumorigenesis. (c) Even in patients with ARID1A-deficient clear-cell carcinoma, endometriosis distant from the carcinoma was always ARID1A intact. (d) Loss of ARID1A expression and *PIK3CA* mutations frequently coexisted and were not mutually exclusive. Although in the current study the mutational status of the *ARID1A* gene was not known, in ovarian clear-cell carcinomas, the presence of *ARID1A* mutations were adequately, but not perfectly, correlated with the loss of ARIDA1 immunoreactivity.[12,27] Therefore, the data obtained in the present study may indicate how early *ARID1A* is mutated during the development of ovarian clear-cell carcinoma.

Table 2 Comparison between the ARID1A immunoreactivity and *PIK3CA* mutations in ovarian clear-cell carcinomas

PIK3CA mutations	*Number of cases (%)*		*P-value*
	ARID1A	*ARID1A*	
In exon 9 or 20	Deficient	Intact	
Present ($n=17$)	12 (71)	5 (29)	0.083
Absent ($n=25$)	11 (44)	14 (56)	

Table 3 Frequent concurrence of *PIK3CA* mutations and loss of ARID1A immunoreactivity in the endometriosis-associated ovarian clear-cell carcinoma development

Case no. (patient's age (years))	*Status of* PIK3CA/*immunoreaction for ARID1A*			
	Clinical stage of disease[a]	*Non-atypical endometriosis*	*Atypical endometriosis*	*Clear-cell carcinoma*
5 (49)	I	Mut/deficient	Mut/deficient	Mut/deficient
6 (48)	I	Wt/intact	Wt/deficient	Mut/deficient
8 (56)	IV	Mut/deficient	–/–	Mut/deficient
12 (53)	I	Wt/intact	Mut/intact	Mut/intact
13 (41)	IV	–/–	Mut/deficient	Mut/deficient
14 (51)	I	Mut/deficient	Mut/deficient	Mut/deficient
15 (58)	II	–/–	Mut/deficient	Mut/deficient
17 (48)	I	Mut/deficient	Mut/deficient	Mut/deficient
18 (53)	I	Mut/deficient	Mut/deficient	Mut/deficient
20 (50)	III	Mut/deficient	–/–	Mut/deficient

[a]Clinical stages of disease defined by the International Federation of Gynecology and Obstetrics.
Mut, somatic mutations (+); Wt, wild type for exon 9 and 20; –/–, corresponding components were not histologically identified.
The data of this study combined with those obtained from our previous study.[15]

Several recent studies have strongly indicated that loss of ARID1A protein expression and/or its mutations has an important role in the pathogenesis of certain ovarian cancers thought to be derived from endometriosis.[12,13,28] However, in the present study, in 43% (6 of 14) of the cases, loss of ARID1A expression was also associated with another putative ovarian clear-cell carcinogenic pathway, namely, the adenofibroma-associated pathway. These results suggest that regardless of the pathogenic pathway involved (ie, endometriosis-associated *vs* adenofibroma-associated pathways), ARID1A alterations might be commonly associated with the development of ovarian clear-cell carcinoma.

In the present study, excluding the cases of non-atypical endometriosis adjacent to the ARID1A-deficient carcinomas, all lesions analyzed showed diffusely detectable or homogenously undetectable ARID1A immunoreactivity. These findings contrast those of the study by Guan *et al*,[28] in which a fraction of uterine endometrioid carcinomas with *ARID1A* mutations were characterized by a heterogeneous immunostaining pattern for ARID1A. However, this type of heterogeneous loss of ARID1A immunoreactions was only detected in tumors with *ARID1A* mutations and not in those without mutations,[28] suggesting that *ARID1A* mutations occurred in the subclones of cells within these endometrial carcinomas. Wiegand *et al*[32] reported that a loss of ARID1A protein expression was not detected in any of the nine lesions of endometrial complex atypical hyperplasia considered as putative precursors of uterine endometrioid carcinoma. On the basis of the complete data available, it is likely that (1) *ARID1A* mutations occur as very early events in ovarian clear-cell carcinoma development, creating ARID1A-deficient subclones of a neoplastic nature in the endometriosis tissues or facilitating tumor initiation in clear-cell adenofibroma and (2) the biological significance or timing of occurrence of alterations of ARID1A expression might differ between ovarian clear-cell carcinoma and endometrial carcinoma; in the latter, ARID1A alterations may be a late event in tumorigenesis. Moreover, the present analysis showed that, in the three non-atypical endometrioses that showed a pattern of heterogeneous ARID1A immunoreactivity, areas of ARID1A-deficient cells were detected adjacent to those of the ARID1A-intact areas, suggesting that mutations might arise in clones within these lesions.

Another interesting finding of the present study was the frequent coexistence of ARID1A alterations with the *PIK3CA* gene mutations. Guan *et al*[28] showed that the loss of ARID1A immunoreactivity and *ARID1A* somatic mutations were frequently (26 and 40%, respectively) detected in uterine endometrioid carcinoma in comparison with other histological subtypes of uterine carcinomas. Endometrioid carcinoma of the uterus frequently harbors sequence mutations in *PIK3CA* (estimated 24–39% of cases) as well as in the *CCNB1* and *PTEN* genes, and these mutations are rarely found in uterine serous carcinoma.[33–36] Moreover, in a previous comparative study of 44 endometrioid adenocarcinomas and 29 precursor lesions (complex atypical hyperplasias), *PIK3CA* mutations were identified in 39% of the former but only 7% of the latter, suggesting that such mutations represent a late event in endometrial carcinogenesis, which is similar to the data on ARIDA1 alterations in this type of tumor.[32,36] In contrast to endometrial carcinomas, *PIK3CA* mutations can occur as an early event in ovarian clear-cell carcinoma development, usually appearing at the stage of non-atypical endometriosis.[15] Moreover, in the present data combined with our previous study,[15] concurrence of *PIK3CA* mutations and loss of ARID1A immunoreactions occurred at the very early stage of the endometriosis-associated clear-cell carcinoma development (ie, at the non-atypical endometriosis). These findings suggest the possibility of cross-talk between the ARID1A and PI3K signaling pathways. Further investigation of this possible cross-talk and assessment of the contribution of ARID1A inactivation to tumor initiation and progression in these tumors should be conducted. Somatic mutations of tumor suppressor genes such as *ARID1A* could directly lead to epigenetic changes in tumor cells through specific modifications of chromatin proteins. Therefore, by altering the accessibility of transcription factors to chromatin, additional mutations in the PI3 kinase pathway (ie, *PIK3CA* mutation) would promote its oncogenic properties.

In conclusion, loss of ARID1A protein expression (and possible *ARID1A* mutations) appears to be an early molecular event in ovarian clear-cell carcinogenesis, regardless of the carcinogenic pathway involved. Moreover, the coexistence of the loss of ARID1A expression and *PIK3CA* mutations suggested a possible cross-talk between the regulation of ARID1A expression and the PI3K signaling pathway during ovarian clear-cell carcinoma development. An increased understanding of the molecular events involved in the initiation and development of ovarian clear-cell carcinoma will provide a basis for developing novel forms of early diagnosis and therapy.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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LETTER TO THE EDITOR

Second-line chemotherapy with docetaxel and carboplatin in paclitaxel and platinum-pretreated ovarian, fallopian tube, and peritoneal cancer

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Abstract We retrospectively evaluated the efficacy and toxicity of docetaxel and carboplatin in patients with platinum and paclitaxel-pretreated recurrent ovarian, fallopian tube, and peritoneal cancer. Forty-two women (38 with ovarian cancer, 1 with fallopian tube cancer, 3 with peritoneal cancer) whose cancer had progressed within 12 months of their last treatment with both a platinum agent and paclitaxel were treated with docetaxel (70 mg/m^2, day 1) and carboplatin (area under the curve of 4–6, day 1). Thirty-four patients had measurable disease. The objective response rate was 23% within 0–6 months of the progression-free interval, 50% within 6–12 months, and 32% (11 of 34 patients) for both groups. The median time to tumor progression was 28, 49, 34 weeks, and the median overall survival time was 94, 224, 111 weeks, respectively. The most common toxicity was grade 3/4 neutropenia (98% of patients), with 15 episodes (8.4% of courses) of neutropenic fever. The main nonhematologic toxicity was hypersensitivity; 7 patients (17%) required discontinuation of the therapy. The results of our study indicate that the combination of docetaxel and carboplatin is effective against recurrent ovarian, fallopian tube, and peritoneal cancer with progression-free interval of 6–12 months from previous treatment by paclitaxel and platinum. On the other hand, single-agent chemotherapy would be better than this regimen considering its low response rate and severe hematological toxicity for patients with progression-free interval less than 6 months.

Keywords Docetaxel · Carboplatin · Chemotherapy · Early progression · Recurrent ovarian cancer

The standard regimen as second-line chemotherapy in recurrent ovarian cancer has not been established, especially in the patients with a short progression-free interval from the previous treatment. Docetaxel is an active drug as second-line chemotherapy for recurrent ovarian cancer as well as pegylated liposomal doxorubicin, irinotecan, topotecan, gemcitabine, and etoposide [1].

The purpose of this study was to evaluate activity and toxicity of the combination of docetaxel and carboplatin retrospectively in patients with paclitaxel and platinum resistant (progression-free interval less than 6 months) and partially resistant (progression-free interval of 6–12 months) ovarian, fallopian tube, and peritoneal cancers. Forty-two women (38 with ovarian cancer, 1 with fallopian tube cancer, 3 with peritoneal cancer) whose cancer had progressed within 12 months of their last treatment with both a platinum agent and paclitaxel were treated with docetaxel (70 mg/m^2, day 1) and carboplatin (area under the curve of 4–6, day 1). Thirty-four (81%) patients had measurable disease. Twenty-six (62%) patients had experienced progression of disease within less than 6 months of their last treatment, whereas 16 patients (38%) within 6–12 months. The median number of courses of treatment per patient was 4.5 (range: 1–8 courses). The median follow-up period was 107 weeks (range: 9–373 weeks). The objective response rate was 23% within 0–6 months of the progression-free interval, 50% within 6–12 months, and 32% (11 of 34 patients) for both groups. The median time to tumor progression was 28, 49, and 34 weeks, and the median overall survival time was 94, 224, and 111 weeks, respectively. The most common toxicity was grade 3/4 neutropenia (98% of patients), with 15 episodes

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(8.4% of courses) of neutropenic fever. The main nonhematologic toxicity was hypersensitivity; 7 patients (17%) required discontinuation of the therapy. On the other hand, grade 2/3 neuropathy was observed only in two (4.8%) patients.

Several chemotherapeutic agents such as pegylated liposomal doxorubicin, topotecan, irinotecan, gemcitabine, and etoposide have been used in the treatment of platinum-resistant disease with response rates in the range 10–15% [2–5]. The results from our study about overall response rate are in line with other chemotherapeutic agents. Notably, our data about median time to tumor progression and overall survival are longer than the previously reported data of other regimens.

The results of our study indicate that the combination of docetaxel and carboplatin is effective against recurrent ovarian, fallopian tube, and peritoneal cancer with progression-free interval of 6–12 months from previous treatment by paclitaxel and platinum. On the other hand, single-agent chemotherapy would be better than this regimen considering its low response rate and severe hematological toxicity for patients with progression-free interval less than 6 months. However, chemotherapy with docetaxel and carboplatin may improve time to tumor progression and overall survival time in these cases; this regimen can be an alternative in patients whose hematological toxicity is relatively weak at their previous treatment.

Conflict of interest None.

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