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Dedifferentiated Mesonephric-like Adenocarcinoma of the Uterine Corpus

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Abstract. *Background/Aim: We present a case of uterine dedifferentiated mesonephric-like adenocarcinoma (MLA). Case Report: A 54-year-old woman underwent total hysterectomy for a uterine mass under the impression of a uterine sarcoma. Histologically, MLA exhibited various growth patterns including tubular and glandular architecture. Undifferentiated carcinoma (UC) displayed discohesive tumor cells without any obvious architecture. Immunohistochemically, UC was positive for epithelial markers in very few scattered tumor cells. MLA exhibited the wild-type p53 expression pattern, whereas UC showed a uniform and strong p53 immunoreactivity. Targeted sequencing analysis revealed an identical Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation in both components. A pathogenic missense tumor protein 53 (TP53) mutation was detected in UC, but not in MLA. Conclusion: The mutant p53 expression pattern exclusively detected in UC was concordant with the presence of missense TP53 mutation. Our observations suggested that TP53 mutation is associated with the possible transformation from MLA to UC.*

Mesonephric adenocarcinoma (MA) of the uterine cervix is a rare malignant tumor typically associated with mesonephric remnant or hyperplasia (1-6). Histologically, MA is characterized by various growth patterns, including small tubules and glands with intraluminal eosinophilic secretions admixed with papillary, retiform, solid, or spindled architecture (7). MA usually shows lack of estrogen receptor (ER) and progesterone receptor (PR) expression, wild-type p53 expression pattern, and preserved phosphatase and tensin homolog deleted on chromosome 10 (PTEN) immunoreactivity, and it has a unique immunophenotype displaying positive immunoreactivity for GATA-binding protein 3 (GATA3), paired box 2 (PAX2), and CD10 (8-14). Most MAs characteristically harbor somatic mutations of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) (1, 4-6). Mesonephric-like adenocarcinoma (MLA) of the uterine corpus has been newly included in the fifth edition of World Health Organization (WHO) classification of female genital Tumors (15). MLA is characterized by significant histological, immunophenotypical, and molecular similarities to MA; however, it has no association with the mesonephric remnant (16, 17). Previous studies have suggested that uterine MLA displays an aggressive biological behavior (12, 16), but the three-tiered International Federation of Gynecology and Obstetrics (FIGO) grading system, which has been currently used for endometrioid adenocarcinoma, has been shown not to properly reflect the clinical severity of MLA (1, 8). Owing to the rarity of MLA, there is no established histological grading system to predict the biological behavior of MLA.

In the current WHO classification, dedifferentiated carcinoma of the endometrium is defined as co-existence of an undifferentiated carcinoma (UC) and a differentiated component, usually FIGO grade 1 or 2 endometrioid adenocarcinoma. We recently encountered a very rare case of MLA of the uterine corpus co-existing with UC. There were several foci of abrupt transitions from MLA showing well-formed tubules and glands (*i.e.*, the differentiated component) to UC. Hence, our case was considered as dedifferentiated MLA. To the best of our knowledge, there has been no report of UC derived from MLA, and its clinicopathological, immunophenotypical, and genetic features have never been

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Key Words: Uterus, mesonephric-like adenocarcinoma, undifferentiated carcinoma, dedifferentiated carcinoma.

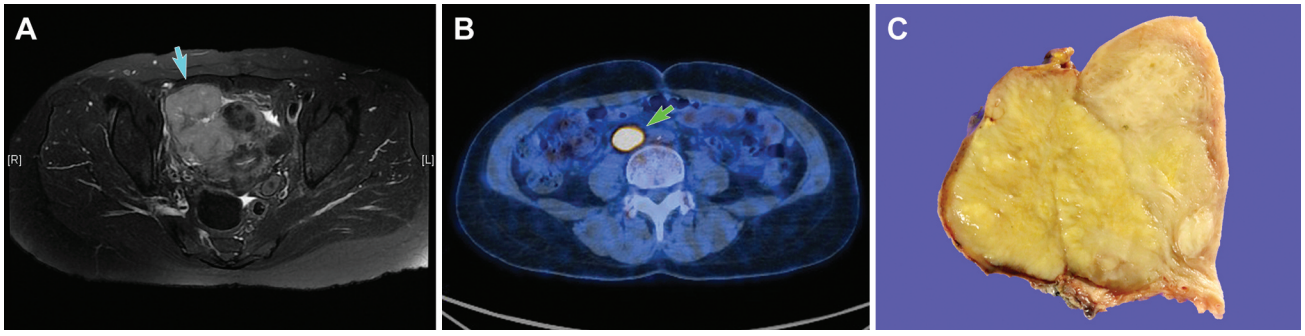

Figure 1. *Imaging and gross findings. (A) Magnetic resonance imaging revealed a 7.1-cm-sized solid uterine mass (blue arrow). (B) Positron emission tomography-computed tomography revealed a hypermetabolic focus in the aortocaval area (green arrow). (C) Grossly, the uterine tumor was lobulated, with yellow-to-white, solid-cut surface, and involved the full-thickness myometrium.*

documented. Herein, we present the first case of a uterine dedifferentiated MLA in a 54-year-old woman with a comprehensive analysis of its clinical, histological, and molecular characteristics.

Case Report

The Institutional Review Board (Samsung Medical Center, Seoul, Republic of Korea) granted permission for this study (2020-10-108) to be published on the condition that no patient-identifiable data are included. A 54-year-old woman who had no previous gynecological history was referred to our institution for examination of a uterine mass, which was found on abdominopelvic magnetic resonance imaging (MRI) for abdominal pain evaluation. MRI revealed a 7.1-cm-sized solid mass growing on the anterior wall of the uterine corpus (Figure 1A) and enlarged pelvic and para-aortic lymph nodes. Positron emission tomography-computed tomography also revealed the presence of hypermetabolic lymph nodes in the right common and bilateral external iliac areas, mesentery, and aortocaval area (Figure 1B), all of which showed findings suggestive of metastatic lymphadenopathy. There was no visible metastatic lesion in the abdominopelvic peritoneum or distant organs. There was no evidence of parametrial or vaginal extension of the lesion. Endometrial or cervical mucosa appeared unremarkable. Because of the clinical impression of a uterine sarcoma, she underwent total hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, and para-aortic lymph node dissection.

Grossly, the anterior uterine wall showed a large, lobulated solid mass with an ill-defined border (Figure 1C). The mass spanned the entire myometrial thickness and appeared to penetrate the uterine serosa. Bladder peritoneum showed several small metastatic nodules. Histologically, the tumor had haphazardly infiltrating borders and destructively invaded the myometrium (Figure 2A). The peritumoral stroma showed scant cellularity and desmoplastic reaction. Extensive lymphovascular invasion and multiple lymph node metastases were identified in the right pelvic and para-aortic lymph nodes. The pelvic peritoneum also showed metastatic carcinoma. The UC cells displayed sheets or nested growth pattern and showed no evidence of glandular differentiation (Figure 2B). Transition from MLA to UC was frequently observed (Figure 2C). Tubular and glandular growth patterns were predominant in the MLA component. The tubules were small, round, and uniform with little intervening stroma, creating a back-to-back or cribriform appearance (Figure 2D). The MLA cells exhibiting glandular patterns were composed of several layers of columnar epithelium containing abundant eosinophilic cytoplasm. Dense or light eosinophilic secretions were readily visible within the glands and tubules (Figure 2E). In some areas, a comedonecrosis-like pattern showing dilated glandular lumina containing necrotic debris was noted (Figure 2F). Tumor cell nuclei of the MLA component were uniform with vesicular chromatin and inconspicuous nucleoli (Figure 2G). In contrast, the UC component consisted of variable-sized discohesive tumor cells without any obvious architecture. The UC cells had vesicular or condensed nuclei with severe nuclear pleomorphism and prominent cherry-red macronucleoli. The cells displayed high-grade nuclear atypia, hyperchromasia, and increased mitotic activity (Figure 2H), as well as large, bizarre nuclei (Figure 2I) and multinucleation (Figure 2J).

Immunostaining was performed for paired box 8 (PAX8), ER, PR, epithelial membrane antigen (EMA), cytokeratin 7 (CK7), CK8/18, vimentin, PAX2, GATA3, mutL homolog 1 (MLH1), human postmeiotic segregation increased 1 homolog 2 (PMS2), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), integrase interactor 1 (INI1), Brahma-related gene 1 (BRG1), and p53, as previously described (17-25). We evaluated the differences in the immunostaining pattern between MLA and UC observed in the areas of transition (Figure 3A). The MLA component displayed

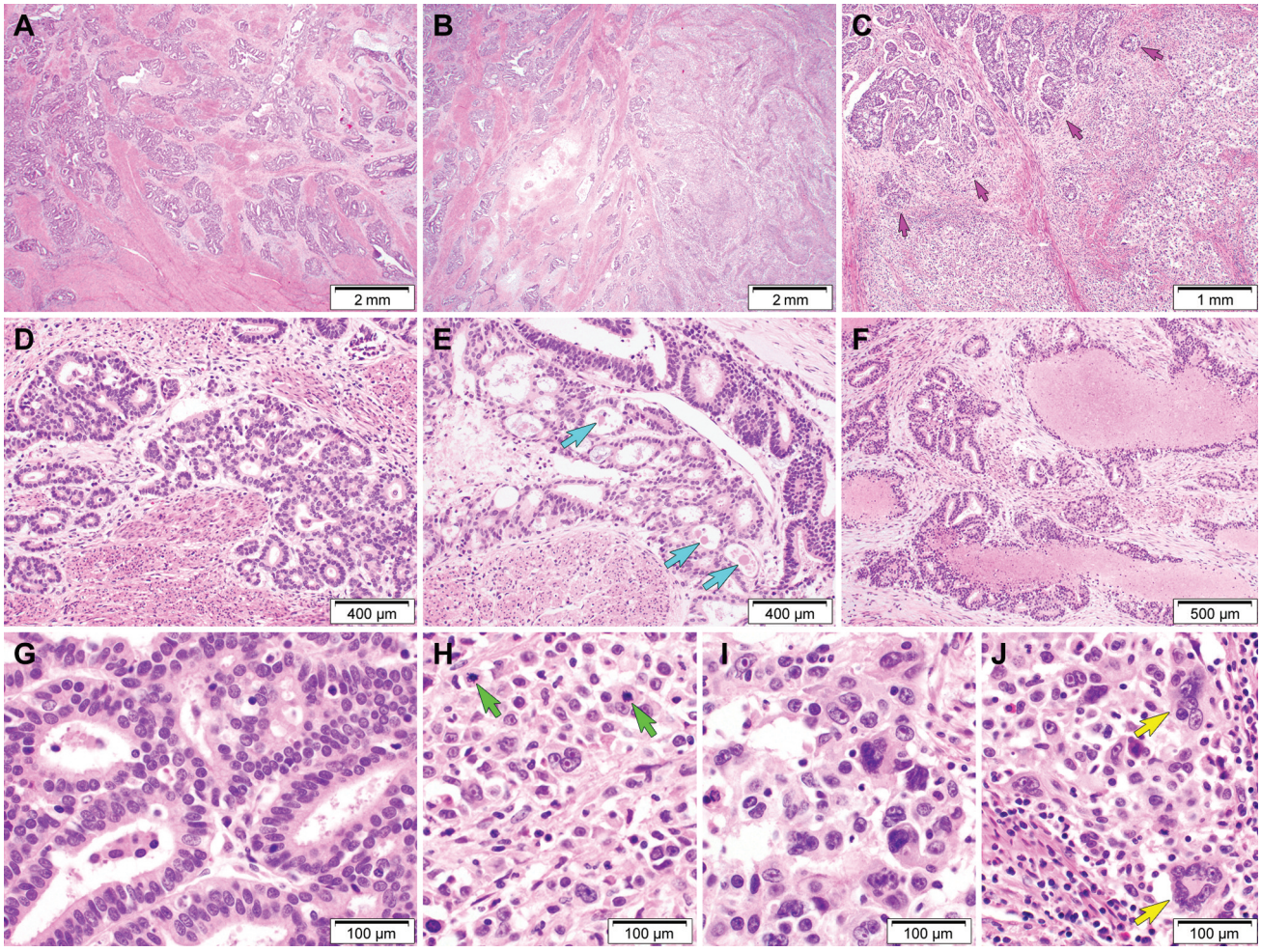

Figure 2. *Histological findings of uterine dedifferentiated MLA. (A) Low-power magnification showed destructive myometrial invasion of MLA. (B) In contrast to MLA (left half), UC (right half) showed no glandular differentiation or organized pattern. (C) The transition (purple arrows) from MLA (left upper corner) to UC was readily identifiable. (D-F) MLA showed predominantly small tubular and glandular growth architecture. The tubules consisted of a single layer of cuboidal cells that were closely packed, with no intervening stroma, forming a back-to-back or cribriform appearance. Intraluminal eosinophilic colloid-like materials (E; blue arrows) were frequently identified. In several foci, comedonecrosis-like pattern (F), showing central necrosis filling the dilated glandular lumina and partially surrounded by tumor glands, was noted. (G) Examination of MLA under high-power magnification demonstrated glandular crowding and focal cribriform architecture. The tumor cell nuclei displayed mild-to-moderate pleomorphism. (H) UC consisted exclusively of sheets of discohesive, variable-sized pleomorphic cells possessing abundant eosinophilic cytoplasm, large vesicular nuclei, and prominent, deeply eosinophilic nucleoli. Mitotic figures (green arrows) were frequently observed. (I-J) In some areas of the UC component, severe nuclear pleomorphism and multinucleated giant cells (J; yellow arrows) were noted. Staining method: A–J, hematoxylin and eosin staining. Original magnification: A–B, 20×; C, 40×; D–E, 100×; F, 80×; G–J, 400×.*

diffuse and strong membranous EMA immunoreactivity (Figure 3B), whereas in the UC, a few scattered tumor cells were weakly to strongly positive for EMA (Figure 3B-C), excluding the possibility of MLA, which showed a solid growth pattern. Similarly, the UC cells were focally and weakly positive for CK8/18 (Figure 3D) and negative for CK7 (Figure 3E) and PAX8. In contrast, the MLA component showed uniform immunoreactivities for CK7 (Figure 3F) and PAX8 with strong intensity. Vimentin expression was absent in both the MLA and UC components, excluding the possibility of a carcinosarcoma. ER (Figure 4A) and PR (Figure 4B) expression was not observed in any area of the tumor. Positive immunoreactivities for PAX2 (Figure 4C) and GATA3 (Figure 4D), which are useful to support the diagnosis of MLA, were observed in both components, even though the staining intensity of PAX2 (Figure 4E) and GATA3 (Figure 4F) was significantly decreased in the UC compared to that in MLA. The MLA component exhibited a

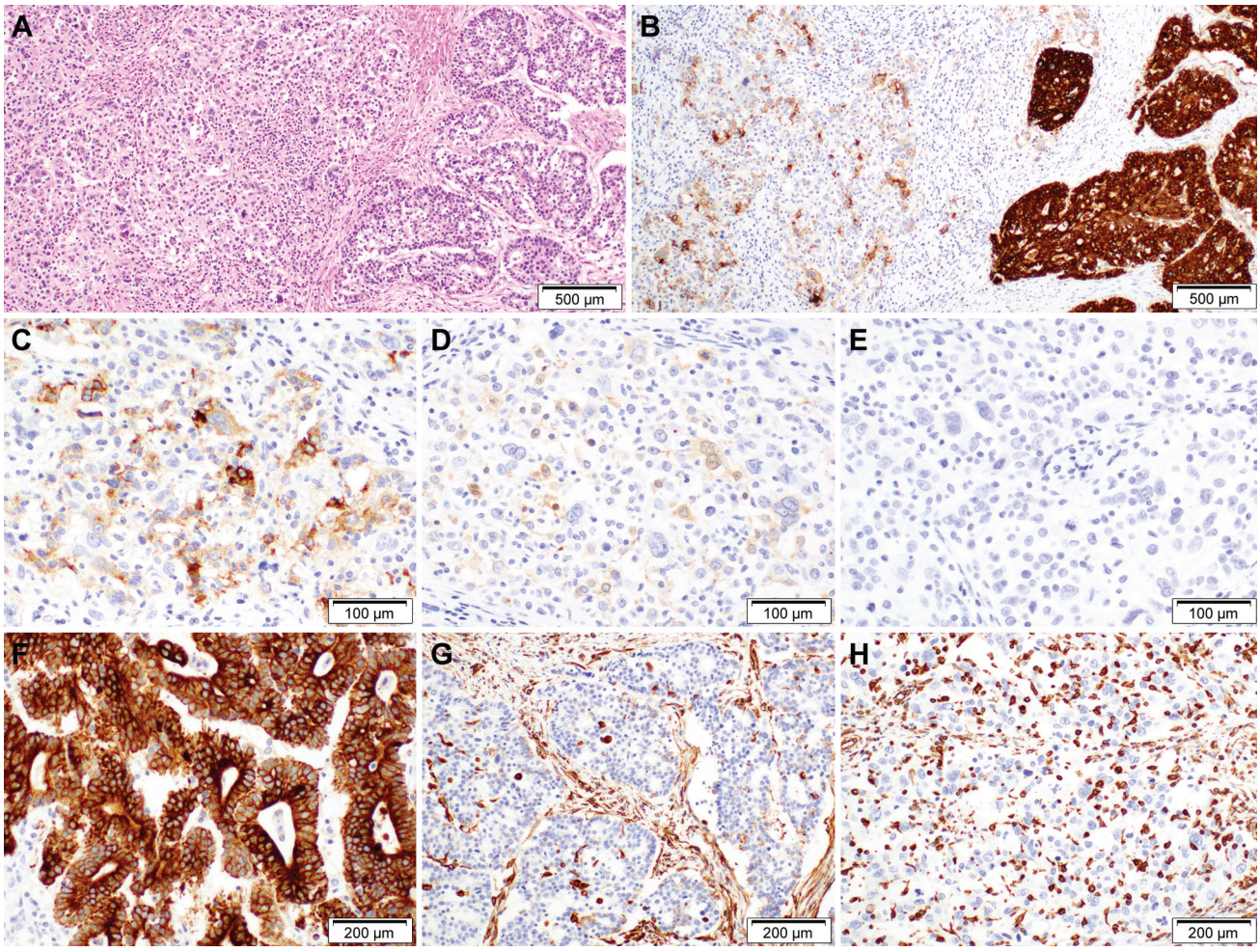

Figure 3. *Immunostaining results in (A) areas of transition between MLA and UC. (B) MLA (right half) displayed diffuse strong positivity for EMA, whereas UC showed focal EMA expression (left half). (C) Even though most of the UC cells that were positive for EMA exhibited weak intensity, a few cells were strongly positive. (D) UC exhibited negativity or faint positivity for CK8/18. (E-F) CK7 expression was absent in (E) UC but diffuse and strong in (F) MLA. (G-H) Vimentin did not react with both (G) MLA and (H) UC. Staining method: A, hematoxylin and eosin staining; B–H, polymer method. Original magnification: A–B, 80×; C–E, 400×; F–H, 200×.*

wild-type p53 immunostaining pattern (Figure 4G-H), in contrast, interestingly, the UC component showed diffuse and strong nuclear p53 expression (Figure 4I-J), indicating missense tumor protein 53 (*TP53*) mutation. There was no loss of expression in mismatch repair proteins (MMRs), INI1, and BRG1 in both MLA and UC components.

Targeted sequencing analysis was performed using Oncomine Comprehensive Assay (Thermo Fisher Scientific, Waltham, MA, USA), as previously described (17, 18, 22). We found that MLA harbored pathogenic *KRAS* mutation. In the UC component, missense *TP53* mutation was detected, in addition to the same mutation in *KRAS* as that found in MLA. In both components, *TP53* mutational status was concordant with the p53 immunostaining pattern.

Discussion

MLA of the uterine corpus is a very uncommon histological subtype of uterine malignancy, accounting for less than 1% of all endometrial carcinomas (3). Although the etiological factor is unclear, MLA shares characteristic morphological, immunohistochemical, and genetic features with MA. In both MA and MLA, diverse architectural patterns are identified, including tubular, glandular, papillary, retiform, sex cord-like, solid, glomeruloid, and spindled (1). The characteristic feature is the presence of intraluminal eosinophilic secretions in small tubules and glands. MLA typically exhibits a wild-type p53 immunostaining pattern and preserved PTEN expression (1). Activating *KRAS* mutations are found in a

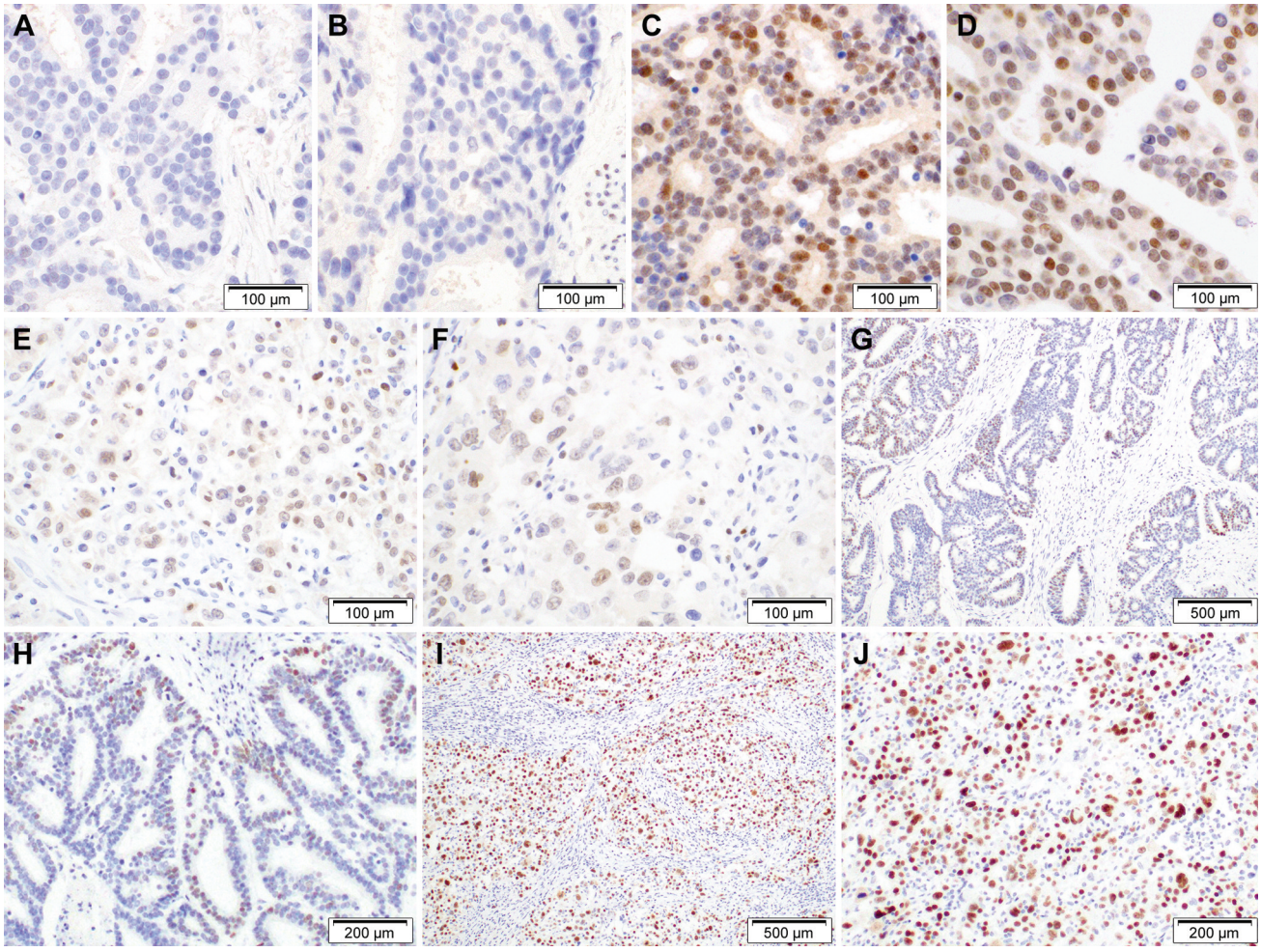

Figure 4. *Expression status of hormone receptor and differences in GATA3, PAX2, and p53 immunoreactivities between MLA and UC. MLA did not react with (A) ER and (B) PR. (C) PAX2 and (D) GATA3 were moderately-to-strongly positive for MLA, whereas UC exhibited focal and weak expression for both (E) PAX2 and (F) GATA3. (G-H) For MLA, p53 staining was patchy positive with variable intensity, representing wild-type p53 expression pattern. (I-J) In contrast, UC exhibited diffuse and strong nuclear immunoreactivity, indicating missense TP53 mutation (mutant p53 expression pattern). Staining method: A–J, polymer method. Original magnification: A–F, 400×; G, 80×; H, 200×; I, 80×; J, 200×.*

high proportion of MLAs, and are thought to be important for the pathogenesis of MA and MLA (1, 5, 6).

High-grade endometrial carcinoma refers to a heterogeneous group of tumors showing clinically aggressive behavior and encompasses FIGO grade 3 endometrioid adenocarcinoma, serous carcinoma, clear cell carcinoma, UC, and carcinosarcoma (26-29). Despite the limited number of MLA cases and the lack of an established histological grading system for them, we consider that MLA can also be designated as a high-grade endometrial carcinoma because it exhibits oncogenic aggressiveness such as deep myometrial invasion, cervical stromal invasion, advanced stage, frequent lymphovascular invasion, and a high rate of recurrence and distant metastasis (1, 16, 30). In a recent study conducted by Euscher *et al*. (16), the median progression-free and overall survival rates for uterine MLA patients were significantly shorter than those for patients with serous carcinoma. In our case, this tumor displayed full-thickness myometrial invasion with serosal penetration, pelvic peritoneal metastasis, and multiple lymph node metastases, as well as frequent lymphovascular invasion and high mitotic activity, reflecting aggressive biological behavior.

Endometrial UC is a rare but distinctive morphological entity characterized by sheets of monotonous, discohesive, and atypical epithelioid cells lacking any differentiating features (31). In dedifferentiated carcinomas, the differentiated component and UC are often sharply delineated. Immunohistochemically, almost all UCs exhibit negative or very focal but intense expression of

EMA, CK8/18, and CK7 (31, 32), whereas these epithelial markers are uniformly and strongly positive for MLAs. UCs are generally negative for PAX8, ER, and PR expression. Uniform and strong p53 immunopositivity is found in approximately one-third of UC cases (33, 34), suggesting that the UC harbors the pathogenic *TP53* mutation. The UC component can be misdiagnosed as other high-grade endometrial carcinomas or carcinosarcoma. Grade 3 endometrioid adenocarcinoma and serous carcinoma showing a solid growth pattern as well as carcinosarcoma are the main features in the differential diagnoses of UC (26). The presence of at least focal epithelial differentiation including glandular or papillary formation and diffuse immunoreactivity for epithelial markers are features suggestive of either endometrioid or serous carcinoma (26). The sarcomatous component of a carcinosarcoma typically shows spindle cell features and is strongly positive for vimentin (15). Although relatively uncommon, a heterologous component showing chondrosarcomatous or osteosarcomatous differentiation supports the diagnosis of carcinosarcoma (15). In our case, the configuration of differentiated (MLA) and undifferentiated (UC) components, which is sharply juxtaposed to each other, suggests the diagnosis of a dedifferentiated carcinoma. Vimentin expression was absent in the undifferentiated area. In addition, UC displayed no evidence of epithelial differentiation and exhibited very focal immunoreactivity for epithelial markers.

In this study, we report the first case of uterine MLA co-existing with UC. Although the association of MLA with a sarcomatous component has been documented in some cases (1), there has been no reported case of concurrent MLA and UC. According to the WHO classification (12), a dedifferentiated endometrial carcinoma is defined as co-existence of UC with a differentiated component, typically of low-grade (FIGO grade 1 or 2) endometrioid adenocarcinoma. However, a case of endometrial UC associated with high-grade endometrial carcinoma has been recently reported in literature (35); furthermore, Busca *et al*. (35) insisted that the definition of dedifferentiated endometrial carcinoma should be expanded to include UC that is derived not only from a low-grade endometrioid adenocarcinoma but also from a high-grade endometrial carcinoma. We considered that the MLA showing definitive histomorphology and immunophenotype as well as the pathogenic *KRAS* mutation is the differentiated component. At the same time, focal immunoreactivities for GATA3 and PAX2 with weak intensity in UC, which showed similarity to MLA, suggested the possible association with MLA. MLAs are usually positive for GATA3 and PAX2, although the intensity and extent of positivity vary among cases (1, 16). Since the expressions for both markers were maintained during dedifferentiation, it is likely that the UC originates from MLA. The frequencies of GATA3 and PAX2 expressions in UC have not yet been reported. Consequently, our case can be identified as a dedifferentiated uterine MLA. Further investigation of the expressions of potential mesonephric markers, GATA3 and PAX2, in more cases of dedifferentiated MLAs is needed to confirm the immunophenotype of the undifferentiated component.

In the dedifferentiated carcinoma, the undifferentiated component harbors additional mutations, in addition to the common mutations shared with the differentiated component. Previous studies have reported that approximately half of UCs arise from endometrioid adenocarcinoma with MMR protein deficiency (36-38) and that inactivation of switch/sucrose non-fermenting-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1 (*SMARCB1*, encoding INI1) or switch/sucrose non-fermenting-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4 (*SMARCA4*; encoding BRG1), which is described as a potential molecular mechanism of histological dedifferentiation, is found in approximately one-third of UCs (33, 39, 40). Kuhn *et al*. (33) suggested that additional mutations of *TP53* contribute to tumor progression from endometrioid adenocarcinoma to UC. Targeted sequencing analysis performed in our case showed that the *KRAS* mutation detected in MLA was also detected in UC. Interestingly, a *TP53* missense mutation was additionally observed in the latter. MMR proteins, INI1, and BRG1 were intact in both components. These findings suggest that the UC is clonally related to the MLA, and *TP53* mutation is a later event during the dedifferentiation process. We demonstrated that the mutant p53 expression pattern in UC was concordant with the missense TP53 mutation detected by targeted sequencing analysis. The identification of additional patients will be needed to clarify the underlying mechanism of the dedifferentiation process in MLA of the uterine corpus.

In summary, we presented the first case of dedifferentiated MLA of the uterine corpus. The differentiated component exhibited typical histological features of MLA including small tubules and glands with intraluminal eosinophilic colloid-like materials and was sharply demarcated from the adjacent UC. The expressions for GATA3 and PAX2, which continued to remain, and the pathogenic *KRAS* mutation in UC suggested the common clonal origin. In addition, UC showed diffuse and strong nuclear p53 immunoreactivity (mutant immunostaining pattern), whereas MLA exhibited a wild-type p53 immunostaining pattern. Consistent with these findings, *TP53* mutation was detected in UC but not in MLA. Molecular characterization with more cases is necessary to elucidate the underlying mechanism of the dedifferentiation process in uterine MLA.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare regarding this study.

Authors' Contributions

All Authors made substantial contributions to the conception and design of the study; the acquisition, analysis, and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; and the final approval of the version to be published.

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