Histological appearance and immunohistochemistry of DNA mismatch repair protein and p53 in endometrial carcinosarcoma: Impact on prognosis and insights into tumorigenesis

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ABSTRACT

Endometrial carcinosarcoma (ECS) is a rare and aggressive mixed-type epithelial and mesenchymal tumor. This study focused on the histological appearance, loss of DNA mismatch repair (MMR) protein expression, and aberrant p53 expression in the epithelial component, and overall prognosis of 57 cases with ECS. Histologically, 21 and 36 cases exhibited low-grade (endometrioid grade 1 and grade 2) and high-grade (others) epithelial components, respectively. In a Kaplan–Meier analysis, patients with a high-grade epithelial component exhibited worse progression free survival (PFS), compared to those with a low-grade component. Although the former group also exhibited worse overall survival, the difference was not significant. Thirty-six cases exhibited aberrant p53 expression. Of these, 5 cases exhibited focally aberrant p53 expression in carcinomatous components with diffuse aberrant p53 expression in mesenchymal components. Aberrant expression of p53 did not show significant association with prognosis. Six patients with MMR-deficiency exhibited relatively better PFS. In conclusion, a low-grade epithelial component is a superior predictors of the PFS of ECS, compared to MMR protein and p53 expression status. In some cases of

ECS, *TP53* mutation may be a late event associated with histogenesis of the sarcomatous component.

KEYWORDS

endometrial carcinosarcoma, p53, MMR deficiency, prognosis, tumorigenesis

INTRODUCTION

Endometrial carcinosarcoma (ECS) is a rare and aggressive solid malignancy comprising epithelial and mesenchymal components. This tumor type accounts for approximately 5% of all endometrial malignancies, (1) (2) and a multi-institutional study of Japanese patients with ECS reported 5-year disease free and overall survival OS) rates of 40.4% and 53.6% respectively. (3) In most cases, the epithelial and mesenchymal components of ECS share identical molecular abnormalities and are derived from a single clone. (4)

The carcinomatous component can be of various histological types, including low-grade endometrioid, high-grade endometrioid, serous, or clear cell carcinomas. Previous clinicopathological studies that aimed to clarify the prognostic factors of ECS have yielded inconsistent results. Accordingly, some authors have proposed that the characteristics of the epithelial component determines the biological behavior of ECS. (5-7)

Recent comprehensive molecular studies of endometrial cancer revealed that classification can be conducted according to molecular abnormalities; ultramutated

(*POLE* -mutated), hypermutated (DNA mismatch repair deficiency [MMR-D]), copy number-low, and copy number-high (p53 abnormal). (8)

In this study, we investigated the relationships of the morphology, MMR-D, and p53 immunohistochemical status of the carcinomatous component with the survival prognosis of patients with ECS.

MATERIALS AND METHODS

Patients

In this retrospective study, we reviewed the medical records of 57 patients with UCS who were treated at the Department of Obstetrics and Gynecology of Okayama University Hospital, Hiroshima City Hiroshima Citizens Hospital, and the National Hospital Organization Fukuyama Medical Center between January 2007 and August 2017. Clinical data were extracted from medical charts. Patients who received neoadjuvant chemotherapy and/or underwent noncurative resection were excluded from this study.

All patients were treated according to the Japan Society of Gynecologic Oncology clinical guidelines. Adjuvant chemotherapy was administered depending on risk factors (FIGO stage and histology), patient's preference, and physician's discretion. Chemotherapy comprised 3-6 cycles of paclitaxel (infusion of 175 mg/m^2 over 3 hours) and carboplatin (dose to achieve an area under the concentration-time curve of 5).

All patients underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy with or without pelvic and/or

para-aortic lymphadenectomy. Pelvic lymph node dissection included the right and left common iliac nodes, external and internal iliac nodes, and the supra-inguinal, obturator, sacral and parametrial nodal chains. Para-aortic lymph node dissection included nodes located from the aortic bifurcation to the renal vein level. In 17 patients, the lymph node status was assessed using computed tomography (CT) with or without positron emission tomography (PET). Lymph nodes with short-axis lengths >10.0 mm on PET-CT or CT were defined as metastatic.

Histopathological review

Histological slides from all cases were reviewed by the authors (MS, NI and HY), who were blind to the clinical course and p53 expression status data. The epithelial component was classified according to the World Health Origanization (WHO) classification of endometrial carcinoma.(9) Tumors in which the carcinomatous component exclusively comprised endometrioid carcinoma grade 1 (G1) or grade 2 (G2) were classified as low-grade; all others were classified as high-grade. The mesenchymal component was classified as homologous or heterologous.

Immunohistochemistry

Slides from representative formalin-fixed paraffin-embedded blocks were stained with primary antibodies to p53 (mouse, monoclonal, DO-7, 1:50; Agilent, Santa Clara, CA, USA), MLH1 (mouse, monoclonal, ES05, prediluted; Agilent), MSH2 (G219-1129, prediluted; Ventana Medical Systems, Tucson, AZ, USA), MSH6 (rabbit, monoclonal, SP93, prediluted; Ventana), and PMS2 (mouse, monoclonal, A16-4, prediluted; Ventana). Immunostaining was performed using an automated staining device (Benchmark Ultra; Ventana) and ultraView staining kit (Ventana) for p53 and MSH6 or OptiView staining kit (Ventana) for MLH1, MSH2, and PMS2.

Aberrant expression reflective of *TP53* mutation was defined as strongly positive nuclear staining in >80% of tumor cells or completely negative staining (i.e., "null" pattern). Cases exhibiting focally aberrant expression were also included among the aberrant expression cases. The tumors with diffuse negative nuclear stain of at least one MMR protein (MLH1, MSH2, MSH6, and PMS2) were regarded as MMR-D. Focal loss of these proteins was defined as negative staining in less than 10% of tumor cells

and noted but not regarded as indicative of MMR-D. Non-neoplastic cells such as lymphocytes adjacent to tumor cells were used as an internal control.

Statistical analysis

Differences between groups were analyzed using Student's *t*-test for continuous variables or the Mann–Whitney U test when a normal distribution was not assumed (i.e., nonparametric test). Categorical variables were compared using contingency tables. Pearson's χ^2 test was used to evaluate the significance of comparisons. Survival was analyzed using the Kaplan–Meier method. Recurrence curves were compared using the log-rank test. Cox proportional hazards model was used to conduct analyses of potential predictors of progression-free survival (PFS) after adjusting for the effects of known prognostic factors. All analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

RESULTS

The clinicopathological characteristics of ECS patients are summarized in Table 1. All patients were Japanese. The ages at diagnosis ranged from 25 to 87 years (median, 64 years), and 66.6% of patients were diagnosed with early-stage disease (FIGO stage I/ II). The epithelial components were low-grade and high-grade in 21 (36.8%) and 36 cases (63.2%), respectively. Only one patient had a history of prior radiation therapy for uterine cervical cancer and none had received tamoxifen therapy. Patients were followed for 1–112 months, and the median PFS of the whole cohort was 25.2 months.

Representative histological images of ECS are shown in Figure 1. The most common histologic subtype was endometrioid carcinoma G1 (28.1%), and the non-endometrioid carcinoma cases included serous (22.8%), small cell (1.8%), mixed (12.3%), and undifferentiated carcinomas (1.8%). Furthermore, 25 (43.9%), and 32 (56.1%) of tumors contained homologous and heterologous mesenchymal components, respectively. The most frequent heterologous sarcomatous component was rhabdomyosarcoma (14 of 32).

Figures 2 and 3 depicts representative images of p53 immunohistochemistry. Regarding the epithelial component, aberrant p53 expression was observed in 42.9% of low-grade (9 of 21), and in 75.0% of high-grade cases (27 of 36). Regarding the mesenchymal component, aberrant p53 expression was observed in 72% of homologous (18 of 25), and in 71.9% of heterologous cases (23 of 32). In 91.2% of cases, the epithelial and mesenchymal components had identical p53 expression status. In 5 tumors, focal aberrant p53 expression was observed in the epithelial components (Figure 4); of these, the mesenchymal components exhibited diffuse or focal aberrant expression in 3 and 2 cases, respectively.

MMR-D was identified in 6 cases (10.5%). A representative result of loss of MMR protein is presented in Figure 5. All MMR-D tumors were low-grade, except for one tumor with mixed G1 and G3 endometrioid carcinoma. Patterns of staining were as follows; loss of MLH1 and PMS2 in 1 case, isolated loss of PMS2 in 3 cases, loss of PMS2 and focal loss of MSH6 in 1 case, and isolated loss of MSH6 in 1 case. Focal and isolated loss of PMS2 in epithelial components was found in 3 additional cases; sarcomatous components of these cases demonstrated retained expression of PMS2.

We also investigated the relationship between epithelial type and clinicopathological characteristics and found that patients whose tumors contained a high-grade epithelial component were significantly older (p = 0.002) (Table 2). A high-grade classification was also significantly associated with aberrant p53 expression in the carcinomatous and sarcomatous components (p = 0.023 and 0.007, respectively). In contrast, MMR-D was associated with low-grade epithelial components (p = 0.022). Although low-grade cases tended to exhibit positive peritoneal cytology, the difference between low-grade and high-grade was not statistically significant (p =0.158).

Table 3 summarizes an analysis of the correlations of aberrant p53 expression with clinicopathological characters. Although aberrant p53 expression tended to be associated with an older age, this difference was statistically insignificant (p = 0.079). Aberrant p53 expression was associated significantly with the high-grade epithelial component (p = 0.023), but not with the mesenchymal type. Two low-grade cases showed both aberrant p53 expression and MMR-D. The association between MMR-D and aberrant p53 expression was not statistically significant (p = 0.179).

MMR-D was associated with low-grade epithelial components (p=0.022). (Table 4) The association between MMR-D and p53 aberrant expression was marginally significant (p=0.058). Other clinicopathological characters did not demonstrate any relationship with MMR-D.

A Kaplan–Meier survival analysis revealed that the patients with a high-grade epithelial component had a worse PFS, compared to patients with a low-grade component (p = 0.020) (Figure 6a). By contrast, although patients with a high-grade component had a slightly worse OS, the difference was not significant (p = 0.210). Aberrant p53 expression did not exhibit significant associations with PFS and OS (p = 0.970 and 0.050, respectively, data not shown). Although MMR-D phenotype was associated with better PFS, the difference was statistically insignificant. Among MMR intact cases, PFS was almost identical between p53-wild and p53-aberrant cases (Figure 6b).

Cox univariate analysis (Table 5) was used to assess the correlations between clinicopathological factors and PFS, and a significant association between a high-grade

epithelial component and a worse PFS (p = 0.030) was identified. Other factors did not show significant association with PFS.

DISCUSSION

ECS is characterized by extremely aggressive behavior and, consequently, a poor prognosis. Although ECS comprises both epithelial and mesenchymal components, the myoinvasive and metastatic lesion is often reported as an epithelial tumor. Furthermore, some authors suggest that ECS should be classified as carcinoma, as its biological behavior appears to be dictated by the carcinomatous component. (7) In this study, we focused on the associations of the histological type and immunohistochemistry (IHC) of the MMR protein and p53 in the carcinomatous component with the prognosis of ECS. To the best of our knowledge, this was the first study to compare the prognostic impacts of the carcinomatous component morphology and MMR protein and p53 IHC in the same series of ECS cases.

Previous studies of ECS have reported different distributions of the histological type of the carcinomatous component. For example, Ferguson reported that 26% of ECS cases contained endometrioid carcinoma, (10) whereas other studies reported that more than 70% of cases harbored this histological type. (11)(12) In our study, a pure endometrioid carcinoma component was detected in 63% of ECS cases.

Furthermore, we observed a prevalence of low-grade endometrioid carcinoma in ECS of 37% in our case series of Japanese women. Interestingly, a previous large-scale study of ECS reported that Asian women had a low-grade endometrioid carcinoma (G1 and G2) frequency of 42%, consistent with our study, whereas non-Asian women had a corresponding frequency of 13%.(13) In addition to these findings**,** the existing literature suggests a difference in the biology of ECS between Asian and non-Asian women. In another Japanese study, 88% of ECS tumors contained an endometrioid carcinoma component, and most cases were classified as grade 1 or 2. (12) By contrast, some studies of the frequency of low-grade endometrioid carcinoma in ECS among non-Asian populations reported relatively lower values. For example, Chen reported that only 19% of a cohort of at Columbia University harbored low-grade endometrioid carcinoma. (14)

Previous studies investigated the association between the histological appearance of the carcinomatous component of ECS and prognosis. Silverberg et al. reported that among clinical stage I and II ECSs, the serous and clear cell types were more frequently metastatic, compared to the endometrioid type. (5) Furthermore,

Matsuo et al. demonstrated that a low-grade carcinomatous component correlated with a better OS and PFS, compared to a high-grade component. (13) In this study, we observed that high-grade cases had a significantly worse PFS, compared to low-grade cases; although high-grade cases also had a poorer OS, this difference was not statistically significant. We note that some other studies failed to show an association between the histological type of the carcinomatous component and prognosis. (15) (16) This discrepancy might be attributable to the use of different system to classify the carcinomatous component, which may have affected the prognostic analyses.

Overexpression of p53 was associated with a worse prognosis among patients with morphologically ambiguous endometrial cancer(17) and with a worse clinical outcome than normal p53 expression among patients with grade 3 endometrioid carcinoma.(18) These observations suggest that the p53 immunohistochemistry status may be useful as an adjunctive predictive marker in some subsets of endometrial carcinoma. Previous studies of p53 expression in ECS have reported a wide range of overexpression frequencies from 12% to 100%. (19) This may attributable to

differences in the cut-off values used to define abnormality, immunohistochemical antibodies, and staining methods.

Previous studies of p53 expression in ECS considered only overexpression to be abnormal. However, some types of mutation in *TP53,* the gene encoding p53, result in a loss of antigenicity, which yields a completely negative immunohistochemical result (i.e., "null" pattern). This pattern has been observed in endometrial serous carcinoma as the results of an insertion in *TP53*.(20) Therefore, we included the null pattern as an abnormal p53 expression pattern suggestive of *TP53* mutation in our study. Accordingly, 36 cases (63%) of ECS in our study exhibited aberrant p53 expression, including 3 with the null pattern. In these latter tumors, both the carcinomatous and sarcomatous components were p53 null, suggesting a shared origin from a single clone.

In most previous studies of ECS, p53 overexpression was not associated with survival prognosis.(19) In fact, only 1 study reported that ECS with p53 overexpression was associated with a shorter survival duration.(21) Therefore, our finding that the p53 expression status did not correlate with either PFS or OS in our cohort is consistent with the existing body of evidence, despite the use of different criteria. We suggest that p53

abnormalities are not associated significantly with biological behavior in ECS. However, we found that aberrant p53 expression was associated with an ECS high-grade histology and low frequency of MMR-D. Patients whose tumors exhibited aberrant p53 expression tumor tended to be older and to have more advanced (Stage III or IV) tumors, compared to those with a wild-type p53 expression pattern.

Our immunohistochemical analysis identified aberrant p53 expression in 43% of cases of ECS with a low-grade carcinoma component. This frequency was higher than expected, given that previous studies detected *TP53* mutations in less than 10% of cases of G1 and G2 endometrioid carcinoma.(8)(22) Additionally, Taylor reported that 58% of ECS showed p53 overexpression and found no relationship between *TP53* mutation and the histological type of carcinomatous component of ECS. (23)

Moreover, in our study, 5 cases exhibited regional aberrant expression of p53 in low-grade endometrioid carcinomatous component (Figure 4). The sarcomatous component of these cases showed aberrant p53 expression also. These findings suggest that occurrence of a *TP53* mutated clone in a *TP53*-wild low-grade endometrioid carcinoma may promote its sarcomatous transformation (Figure 7). Although Taylor

proposed that *TP53* mutation is an early event in the tumorigenesis of ECS, (23) our observations suggest that this event occurs rather late in the established low-grade endometrial carcinoma and the sarcomatous component of ECS may arise from a mutated clone in some cases.

The results of previous immunohistochemical studies of MMR-D in ECS was inconsistent. De Jong et al. reported that 41% of ECS showed loss of MMR protein (MLH1, MSH2, and MSH6). (24) In contrast, Hoang et al. showed that only 6% of ECS demonstrated an MMR-D phenotype. (25) Our result was similar to that of the latter study. As stated by Hoang, criteria of MMR-D evaluation or staining method may cause these differences. In our series, MMR-D was observed in both the epithelial and mesenchymal components and focal loss of MMR proteins was seen in only the epithelial component. These observations suggest that MMR-D is an early event of tumorigenesis in a minority of ECS cases and not involved in sarcomatous transformation in these cases. This speculation is consistent with that by Taylor. (23) Some reports showed better prognosis of high- grade endometrial carcinoma with MMR-D. (26)(27) In our series, although prognosis of ECS with MMR-D tented to be

better than cases without MMR-D, we failed to showed statistical significance, most likely because of the small scale of our study.

In conclusion, we found that in ECS, a low-grade histological appearance of the carcinomatous component correlated more strongly with PFS than did MMR-D and aberrant p53 expression. We have demonstrated that in some cases of ECS, p53 mutation is a late event that may induce sarcomatous transformation. Our findings suggest that aberrant p53 expression may correlate with the histogenesis of the sarcomatous component of ECS but not with the aggressive tumor behavior. MMR-D is a minor abnormality in ECS and associated with low-grade morphology of the carcinomatous component and a relatively better PFS.

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FIGURE LEGENDS

Figure 1. Histological spectrum of the epithelial component of endometrial carcinosarcoma. (a) Appearance of low-grade endometrioid carcinoma in low-grade cases. Undifferentiated sarcomatous component was seen (upper right). (b) Appearance of serous carcinoma in high-grade cases.

Figure 2. Representative p53 immunohistochemical staining pattern in endometrial carcinosarcoma. Diffusely strong positivity (a) and completely negative staining (b) were considered as aberrant expression. Scattered positive cell patterns represent wild type (c).

Figure 3. Low-grade carcinoma with aberrant p53 expression: (a) tubular proliferation of columnar cells represents endometrioid carcinoma, grade 1 (lower left) with sarcomatous component (upper right), (b) overexpression of p53 was seen in both carcinomatous and sarcomatous components.

Figure 4. (a) Focal aberrant p53 expression in the carcinomatous component of endometrial carcinosarcoma (right). (b) In this case, the sarcomatous component exhibited diffuse, strongly positive p53 staining.

Figure 5. Loss of DNA mismatch repair protein. Both carcinomatous and sarcomatous components lack PMS2 expression instead of positive staining of lymphocytes.

Figure 6. Kaplan–Meier analysis of progression-free survival (PFS), stratified by histological type (a) or MMR and p53 status (b).

Figure 7. Conceptual schematic of the transformation from a low-grade endometrioid carcinoma component to a sarcomatous component via p53 mutation.