Case report

Endometrial cancer arising after complete remission of uterine malignant lymphoma: A case report and mutation analysis

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ABSTRACT

Uterine malignant lymphoma is rare and its association with secondary cancer has not been fully described. Here, we report a rare case of endometrial cancer arising after 1 year of complete remission of uterine diffuse large B-cell lymphoma (DLBCL). An 88-year-old woman was referred to us for abnormal genital bleeding and was diagnosed with uterine DLBCL. She underwent chemotherapy comprising rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone followed by radiation therapy; subsequently, she achieved complete remission. One year later, she noticed genital bleeding recurrence, and endometrial biopsy revealed endometrial adenocarcinoma. Total hysterectomy and bilateral salpingo-oophorectomy were performed. Her pathological diagnosis was endometrial endometrioid carcinoma, grade 1 (pT1aN0). Adenocarcinoma was observed over foamy macrophages aggregates, indicating remission of DLBCL. Targeted sequencing of both DLBCL and endometrial cancer revealed 24 gene mutations including the truncation-type mutations of \textit{ARID1A} and \textit{PTEN} occurring only in endometrial cancer. These multiple somatic gene mutations accumulating within 1 year imply endometrial carcinogenesis induced by DNA damages caused by treatment for DLBCL. Although the epidemiological risk of secondary malignancies after uterine lymphoma remains unclear, the present case serves as a warning for secondary cancer and highlights the importance of early detection and treatment.

1. Introduction

There have been accumulating evidence that survivors of non-Hodgkin lymphoma (NHL) are at increased risk for developing secondary cancers (Baras et al., 2017; Brennan et al., 2005). However, uterine malignant lymphoma is very rare, comprising only 0.18% of all cases of extra-nodal lymphoma, and its association with secondary cancer has not been described (Nasioudis et al., 2017). Furthermore, there have been few reports on gene mutations manifesting as endometrial cancer as a secondary malignancy after NHL treatment.

Here, we report an extremely rare case of endometrial cancer arising 1 year after chemotherapy followed by radiotherapy for uterine malignant lymphoma. Targeted sequencing using a next-generation sequencer revealed somatic mutations in tumor suppressor genes, such as \textit{ARID1A} and \textit{PTEN}, only in the endometrial cancer tissue. These multiple somatic gene mutations accumulating within 1 year imply endometrial carcinogenesis induced by DNA damage caused by chemotherapy and radiotherapy.

2. Case report

An 88-year-old woman, gravida 2, was admitted to our hospital owing to abnormal genital bleeding. Magnetic resonance imaging (MRI) revealed a pelvic mass, measuring 107 × 95 × 67 mm in size, which originated from the uterus. Computed tomography (CT) scan showed enlarged para-aortic and obturator lymph nodes. Fludeoxyglucose-positron emission tomography (FDG-PET) showed an abnormal uptake in the uterine tumor as well as para-aortic and obturator lymph nodes with a maximal standardized uptake value of 30.19 (Fig. 1A). The serum level of soluble interleukin-2 receptor was elevated to 2408 U/mL (normal value: < 496.0 U/mL). The patient underwent endometrial curettage and pathological analysis revealed diffuse large B-cell lymphoma (DLBCL) of germinal center B-cell type (Fig. 1D). The Ann Arbor stage was IIA, and the International prognostic index was 2 (low-intermediate). She underwent six cycles of chemotherapy comprising rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) with a dose reduction of 20%–50% followed by a...
indicated the loss of function of contrast, 24 gene mutations, containing truncating-type mutations that without pathogenic mutation were detected in uterine DLBCL. By containing endometrial cancer (Fig. 2C). A total of 11 gene mutations initial diagnosis of DLBCL (Fig. 1D) and the hysterectomy specimen information. We examined both the endometrial biopsy specimen at targeted genes and the detailed method are provided as supplementary.

2.2. Mutation analysis

Targeted sequencing for 114 cancer-related genes was performed, as reported previously (Nakaoku et al., 2018; Tanabe et al., 2016). All the targeted genes and the detailed method are provided as supplementary information. We examined both the endometrial biopsy specimen at initial diagnosis of DLBCL (Fig. 1D) and the hysterectomy specimen containing endometrial cancer (Fig. 2C). A total of 11 gene mutations without pathogenic mutation were detected in uterine DLBCL. By contrast, 24 gene mutations, containing truncating-type mutations that indicated the loss of function of ARID1A (p.Q633fs*8, p.Y1027delinsX) and PTEN (p.R308fs), were identified in endometrial cancer tissues. Notably, no gene mutation was shared between uterine DLBCL and endometrial cancer (Supplementary Table 2).

3. Discussion

Here, we report a rare case of endometrial cancer arising after complete remission of uterine DLBCL. This is the first report describing somatic gene mutations of endometrial cancer as a secondary cancer after treatment for uterine lymphoma.

The risk of endometrial cancer after uterine malignant lymphoma remains unclear. Although some previous studies indicate that adult lymphoma survivors are at increased risk of developing secondary malignancies, the risks for endometrial cancer appear to be unrelated (Baras et al., 2017; Brennan et al., 2005). However, uterine malignant lymphoma is rare, comprising only 0.18% of all cases of extra-nodal lymphoma (Nasioudis et al., 2017; Vang et al., 2000a). Therefore, only a few similar cases have been reported in the literature. Goker et al. reported a 55-year-old female with endometrial adenocarcinoma arising 14 months after cytotoxic chemotherapy for uterine cervical non-Hodgkin lymphoma (Goker et al., 2005). Vang et al. described a 57-year-old woman with cervical DLBCL who underwent chemotherapy and radiotherapy and presented with endometrial endometrioid adenocarcinoma 5 years later (Vang et al., 2000b). However, that was a cervical NHL case for which gene mutation analysis and immunohistochemical staining were not performed.

Chemotherapy and radiotherapy for malignant lymphoma have been proposed as a cause of the increased risk of secondary malignancies (Mudie et al., 2006). The present case was treated with cyclophosphamide and doxorubicin which caused DNA cross-linking and topoiso merase II inhibition, respectively (Allan and Travis, 2005). Additionally, following chemotherapy, the uterus was subjected to high-dose radiation therapy. Recently, Behjati et al. analyzed the gene mutations of secondary malignancies arising after irradiation, via whole-genome sequencing, and reported a significant increase in small deletions and balanced inversions which resulted in driver mutations (Behjati et al., 2016). Furthermore, combined chemotherapy and radiotherapy reportedly had an additive effect on secondary cancer development (Gilbert et al., 2003). In the present case, mutation analysis revealed the presence of 11 and 24 totally different somatic gene mutations in uterine DLBCL and subsequent endometrial cancer,

total 30 Gy of Involved Site Radiation Treatment. After these treatments, she achieved complete remission confirmed via FDG-PET (Fig. 1B). Endometrial cytology 1 month after treatment showed no evidence of malignancy (Fig. 1E). One year later, she noticed abnormal genital bleeding again. MRI revealed a 33 mm mass in the uterine cavity (Fig. 1C). Endometrial biopsy showed endometrioid carcinoma (Fig. 1F). Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. The patient was discharged without any complication and has recovered without disease recurrence 14 months after the operation.

2.1. Pathological findings

Macroscopically, tan-colored diffuse exophytic tumor was observed in the uterine corpus (Fig. 2A). Microscopically, the tumor consisted of atypical glandular cells forming irregularly branched or fused glands (Fig. 2C). The pathological diagnosis of endometrial endometrioid carcinoma, grade 1, was rendered. The depth of tumor invasion was less than half of the myometrium. There was no cervical stromal invasion, adnexal involvement, or lymph node metastasis (pT1aN0). In the sampled lymph nodes, no residual lymphoma cells were detected. Adenocarcinoma was observed over the aggregates of foamy macrophages which indicated remission of DLBCL (Fig. 2B and D). Residual lymphoma cells were not detected. Immunohistochemically, the loss of ARID1A (Fig. 2E) and PTEN (Fig. 2F) in tumor cells alone was observed.

Fig. 1. Summary of the clinical course. Images and pathological findings of endometrial sampling. A. FDG-PET scan at initial diagnosis of uterine diffuse large B-cell lymphoma (DLBCL). Black arrows indicate abnormal FDG-uptake. B. After performing R-CHOP followed by ISRT, no lesions were observed on FDG-uptake. C. Eighteen months after initial DLBCL diagnosis, MRI scan showed an intrauterine protruded mass (white arrow heads). Representative pathological findings of endometrial sampling (D-F). D. Endometrial biopsy revealed lymphoma cells with diffuse CD20 positivity. E. After chemo-radiotherapy for DLBCL, endometrial cytological specimen shows no malignant findings (Papanicolaou stain). F. Endometrial biopsy obtained at 12 months after DLBCL treatment revealed endometrioid adenocarcinoma (H&E stain). Abbreviations: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone; ISRT, involved site radiation treatment; ATH+BSO, abdominal total hysterectomy and bilateral salpingo-oophorectomy.
respectively. The increased number of different somatic mutations may support endometrial carcinogenesis caused by DNA damages associated with treatment of uterine DLBCL.

Loss of function mutations of ARID1A and PTEN gene were identified only in the endometrial cancer tissue. Furthermore, immunohistochemical staining revealed loss of ARID1A and PTEN protein in the endometrial cancer. ARID1A is a member of the Switch/Sucrose Non-Fermentable family, whose members regulate various gene transcriptions by alternating the chromatin structure; ARID1A is thought to be a tumor suppressor gene (Wilson and Roberts, 2011). PTEN also acts as a tumor suppressor gene, i.e., it constitutes an important pathway regulating the signaling of multiple biological processes such as apoptosis, cell proliferation, and cell growth (Blanco-Aparicio et al., 2007). Furthermore, PTEN reportedly plays an important role in endometrial carcinogenesis (Monte et al., 2010). Mutations in ARID1A and PTEN are frequently observed in 25%–48% and 52%–78% of endometrioid endometrioid carcinoma cases, respectively (Murali et al., 2014). Therefore, the mutated genes of this case are commonly observed in endometrial carcinoma without history of preceding malignant lymphoma.

We should consider the possibility of coexistence of undetectable small endometrial cancer and clinically evident lymphoma at the first diagnosis of DLBCL. In general, low-grade endometrial carcinoma development is believed to be initiated over many years before a clinically evident tumor develops; therefore, the present case showing tumor development within 1 year demonstrates unexpectedly rapid growth. However, 16.8%–32.6% of secondary cancers after NHL treatment were reported to occur in < 1 year; moreover, they occasionally arose outside the irradiation field (Baras et al., 2017; Brennan et al., 2005). This secondary carcinogenesis might be affected by changes of tumor microenvironment rather than DNA damage from irradiation. In the present case, several factors such as aging, lymphoma, and chemo-radiotherapy might induce immunosuppressive and pro-tumorigenic microenvironment for undetectable endometrial cancer cells. However, concurrent clinically detectable endometrial cancer and DLBCL seem to be unlikely for the following reasons: First, no shared somatic gene mutations were detected in the endometrial biopsy specimen before the treatment for lymphoma. Second, after lymphoma treatment, the

Fig. 2. Pathological findings of endometrial cancer (A–F). A. Diffuse exophytic tumor is observed in the uterine corpus. B. At low magnification, the tumor cells spread over the band-like foamy macrophage (inset) aggregates (⁎), suggesting DLBCL remission after treatment. C. Endometrioid adenocarcinoma. The tumor cells form irregularly branched or fused glands. D. Tumor glands show invasion to aggregates of foamy macrophages. E–F. Immunohistochemically, the loss of ARID1A (E) and PTEN (F) expression in tumor glands is observed.
endometrial cytology showed no evidence of malignancy. Finally, endometrial adenocarcinoma was observed over the aggregates of foamy macrophages indicating involution of DLBCL.

Although the patient achieved complete remission of uterine DLBCL, the possibility of DLBCL recurrence should be considered during follow up. The largest study of malignant lymphoma of the female genital tracts, including 98 cases of uterine lymphoma, reported the 5-year overall survival and cancer-specific survival rates as 70.2% and 75.2%, respectively (Nasioudis et al., 2017). The prognosis of DLBCL of female genital tracts after standard therapy reportedly depends on multiple factors including age, stage according to the Ann Arbor system, and histology (Nasioudis et al., 2017). This patient has been carefully followed by both hematologists and gynecologists.

In summary, we firstly reported gene mutations in a rare case of secondary endometrial cancer arising after complete remission of uterine DLBCL. Although the risk of secondary malignancies after uterine lymphoma remains unclear, the present case provides us a valuable lesson for early detection and treatment of a secondary cancer. Further studies are required to elucidate the risk and clinicopathological features of endometrial cancer as secondary malignancy after malignant lymphoma.

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Consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest and source of funding

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