Occult clear cell carcinoma arising from oxidative stress-exposed cystic adenomyosis: A case report

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Abstract. Although adenomyosis is a benign uterine disease, it can turn malignant in rare instances. Cystic adenomyosis is a rare variation of adenomyosis, arising from which 8 cases of clear cell carcinoma have been reported. However, to the best of our knowledge, there have been no previous reports describing the mechanism by which clear cell carcinoma develops from cystic adenomyosis. The present report documents a case of a 73-year-old woman who was referred to Kanazawa University Hospital (Kanazawa, Japan) because of cystic adenomyosis, with a solid part inside the cyst. The patient was diagnosed with cystic adenomyosis at Shonan Obstetrics and Gynecology Hospital (Hakusan, Japan) 17 years prior; however, the size of the cyst increased after menopause. Therefore, malignant transformation was suspected, which warranted simple abdominal hysterectomy and bilateral salpingo-oophorectomy. The final diagnosis of the present case was uterine corpus cancer, clear cell carcinoma, stage IA. Immunohistochemical staining revealed that the normal and transitional atypical epithelial cells lining the cyst wall, in addition to the clear cell carcinoma cells (which were inside mural nodules located on the cyst wall), were positive for 8-hydroxy-20-deoxyguanosine. This observation suggested the presence of chronic oxidative stress around the cystic adenomyosis. Therefore, the present case suggests the possible involvement of chronic oxidative stress in the malignant transformation of cystic adenomyosis to clear cell carcinoma. This mechanism of malignant transformation of cystic adenomyosis appears to be similar to that of the malignant transformation of endometriotic cysts. Therefore, if the size of the cystic adenomyosis increases after menopause or if the solid part appears in the cyst in future cases, then the possibility of malignant transformation should be considered.

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Introduction

Adenomyosis is a benign uterine disease whereby the endometrial glands and stroma are pathologically demonstrated in the uterine myometrium. Before menopause, patients with adenomyosis typically exhibit various symptoms, such as excessive menstruation, dysmenorrhea, pain during sexual intercourse and infertility (1). However, cases of uterine corpus cancer developing from the malignant transformation of adenomyosis have been reported over the past decade (2). In total, 16 cases of uterine corpus cancer arising from cystic adenomyosis, which is a rare variation of adenomyosis, have been reported, of which 8 were clear cell carcinoma. By contrast, the most common histological subtypes of cancer arising from uterine diffuse adenomyosis were endometrioid carcinoma, followed by serous carcinoma and clear cell carcinoma (2). Based on this difference, we hypothesized that different mechanisms are at work when diffuse adenomyosis and cystic adenomyosis become malignant. However, to the best of our knowledge, there have been no reports describing the mechanism of malignant transformation of cystic adenomyosis or why clear cell carcinoma occurs more frequently than diffuse adenomyosis.

In the present report, a case of clear cell carcinoma arising from cystic adenomyosis over a long period of time was documented. Cystic adenomyosis and endometriotic cysts are characterized by the retention of bleeding contents within the cyst for a long period of time. Furthermore, of the 16 cases of malignant cystic adenomyosis that have been reported, 8 cases were clear cell carcinomas, which is consistent with the most common histological type of ovarian cancer derived from endometriotic cysts (3). The present report focused on these similarities and further proposed some of the mechanisms underlying the malignant transformation of cystic adenomyosis in this case.

Case report

A 73-year-old woman, gravida 2, para 2, had been diagnosed with leiomyoma 17 years ago at another hospital. Because she was already menopausal and had no symptoms, she stopped

receiving regular checkups. She was then referred to our hospital, Kanazawa university hospital because of a suspected malignancy on ultrasound and magnetic resonance imaging (MRI) examination. A 5-cm cystic lesion above the uterine cervix was found, with a 1.5-cm solid part inside the cyst on ultrasound. Endometrial cytology was negative. MRI revealed a 5.2-cm cystic mass within the myometrium, where bloody internal fluid was suggested in T2-weighted images, leading to a diagnosis of cystic adenomyosis (Fig. 1A). MRI conducted 17 years ago suggested a 1.5-cm myoma with bleeding between the myometrium and submucosa (Fig. 1B). Positron emission tomography-computed tomography (PET-CT) showed no abnormal accumulation of fluorodeoxyglucose (FDG) in the cyst wall or the solid part (Fig. 1C). Based on the aforementioned findings, a final diagnosis of cystic adenomyosis was made.

Since the size of the cystic adenomyosis increased with the development of a solid part, malignant transformation was suspected. Therefore, simple abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Written consent to participate in the study or to use her tissue and for publication was obtained from the patient according to the principles of the Declaration of Helsinki. Macroscopically, a thick-walled cystic lesion was observed on the posterior myometrial wall of the uterine corpus. The cyst contained brown blood and an organized hematoma, which corresponded to the solid part observed on the preoperative MRI (Fig. 2A). Numerous small, raised lesions were observed in the cyst wall (Fig. 2B). In the uterine cavity, the endometrium was smooth, but tumorous lesions were not observed (Fig. 2C).

On microscopic examination, the cyst wall consisted of smooth muscle cells and hyaline stroma, accompanied by adenomyosis, which was compatible with cystic adenomyosis (Fig. 2D and E). On the surface of the cyst wall, mural nodules of ~3 mm that containing nests of clear cell carcinoma cells were detected (Fig. 2 F and G). In another region of the main cyst wall, a transformation site from columnar epithelium to hobnail-shaped epithelial cells was observed (Fig. 2H and I). In addition, the other intramural small cysts adjacent to the main cystic adenomyosis lesion had hobnail-shaped atypical cells (Fig. 2J and K), suggesting that the atypical transformation from the epithelial cells of cystic adenomyosis had occurred. The depth of tumor invasion from the surface of the cyst wall was within ≤3 mm. Invasion outside the adenomyosis or vascular invasion was not observed. In addition, there were no atypical cells in the endometrium (Fig. 2L).

Subsequently, the degree of oxidative stress in cystic adenomyosis and cancer cell lesions was evaluated by the immunohistochemical staining of 8-hydroxy-20-deoxyguanosine (8-OHdG; a marker of DNA oxidative stress) and 4-hydroxy-2-nonenal (4-HNE; a marker of late-stage of lipid peroxidation). Immunohistochemical staining for 8-OHdG was performed using the standard avidin-biotin complex peroxidase method, as described previously with a minor modification (3). Briefly, endogenous peroxidase blocking with 3% hydrogen peroxide was not performed because the hydroxy radicals generated from hydrogen peroxide can react directly with the normal deoxyguanosine in tissues to produce 8-OHdG. The primary antibody used in the present case was a mouse anti-8-OHdG monoclonal antibody (clone N45.1, catalog#MOG-020P; Japan Institute for the Control of Aging, NIKKEN SEIL Co, Ltd.) at a dilution of 1:200. Immunohistochemical staining for 4-HNE was performed using the same method as 8-OHdG. The primary antibody used in the present case was a mouse anti-4-HNE monoclonal antibody (clone HNEJ2, catalog#MHN-020P; Japan Institute for the Control of Aging, NIKKEN SEIL Co, Ltd.) at a dilution of 1:50. Positive expression of 8-OHdG was observed in the epithelium within cystic adenomyosis (Fig. 3A). At the transition site, both columnar epithelial and hobnail-shaped cells were stained positive for 8-OHdG (Fig. 3B). Almost all of the hobnail-shaped epithelial cells of the cyst wall stained positive for 8-OHdG (Fig. 3C). Inside the cyst wall, 8-OHdG staining was observed throughout the area where hemosiderin was deposited (Fig. 3D). 8-OHdG was also staining strongly positive in the small cysts that were layered with atypical cells. They appeared to be in the early stages of cancerous transformation (Fig. 3E). Although 8-OHdG staining was negative in the majority of the solid cancer nests, clear cell carcinoma cells located on the cyst wall side did stain positive (Fig. 3F). A number of the adenomyotic lesions around cystic adenomyosis also stained positive for 8-OHdG, albeit weakly (Fig. 3G). By contrast, there were no 8-OHdG-positive cells in the normal endometrial epithelium (Fig. 3H). The majority of the clear cell carcinoma cells in the solid cancer nest stained negative for 4-HNE (Fig. 3I). However, 4-HNE staining was positive in areas immediately adjacent to the cancer nest where hemosiderin was deposited (Fig. 3J). The extent of cell proliferation in the cancer cell lesions were next evaluated by the immunohistochemical staining of Ki67. Immunohistochemical staining for Ki67 was performed using the same method as 8-OHdG. The primary antibody used was a rabbit anti-Ki67 monoclonal antibody (clone sp6, catalog#MA5-14520; Thermo Fisher Scientific, Inc.) at a dilution of 1:200. Positive expression of Ki67 was observed in the clear cell carcinoma cells (Fig. 3K), and the atypical cells located on the cyst wall (Fig. 3L).

The final diagnosis was uterine corpus cancer, clear cell carcinoma, pT1aNXM0, stage IA. Since this case was type 2 uterine corpus cancer, which was revealed after total hysterectomy, the necessity of additional retroperitoneal lymph node dissection and adjuvant chemotherapy was considered. However, since there were no tumor lesions in the endometrium, invasion outside the cyst or vascular invasion, the wishes of the patient and her family were considered and no additional treatments were conducted. The patient is currently undergoing out-patient follow-up observation. No recurrence could be observed 6 months after surgery.

Discussion

The diagnostic criteria for the malignant transformation of adenomyosis were first proposed by Sampson (4), before Colman and Rosenthal (5) modified Sampson's criteria. They were as follows: (i) Absence of carcinoma in the endometrium or elsewhere in the pelvis; (ii) demonstration of carcinoma arising from the epithelium of adenomyosis and not invading from other sites; and (iii) presence of endometrial stromal cells surrounding the epithelial glands to support the diagnosis of adenomyosis. The pathological findings of the present case fulfilled (i) and (iii) of the aforementioned criteria. However,

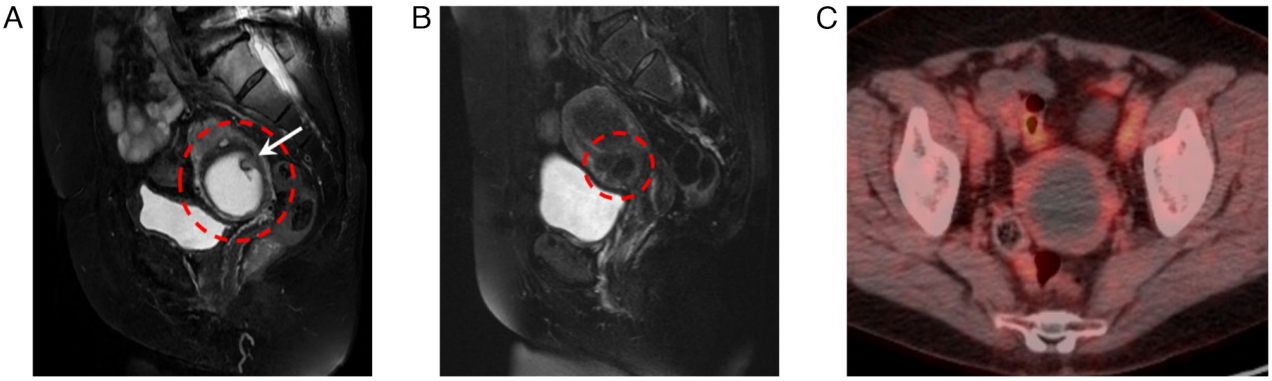

Figure 1. MRI and PET-CT of cystic adenomyosis. (A) T2-weighted MRI of cystic adenomyosis containing the bloody fluid (dotted line). A 5.2-cm cystic mass with a solid part (arrow) was observed within the lower segment of the myometrium. (B) T2-weighted MRI of cystic adenomyosis 17 years ago (dotted line). The presence of a 1.5-cm myoma with bleeding was observed between the myometrium and submucosa. (C) PET-CT image of the cystic adenomyosis. No abnormal accumulation of fluorodeoxyglucose was detected in the cyst wall. PET, positron emission tomography.

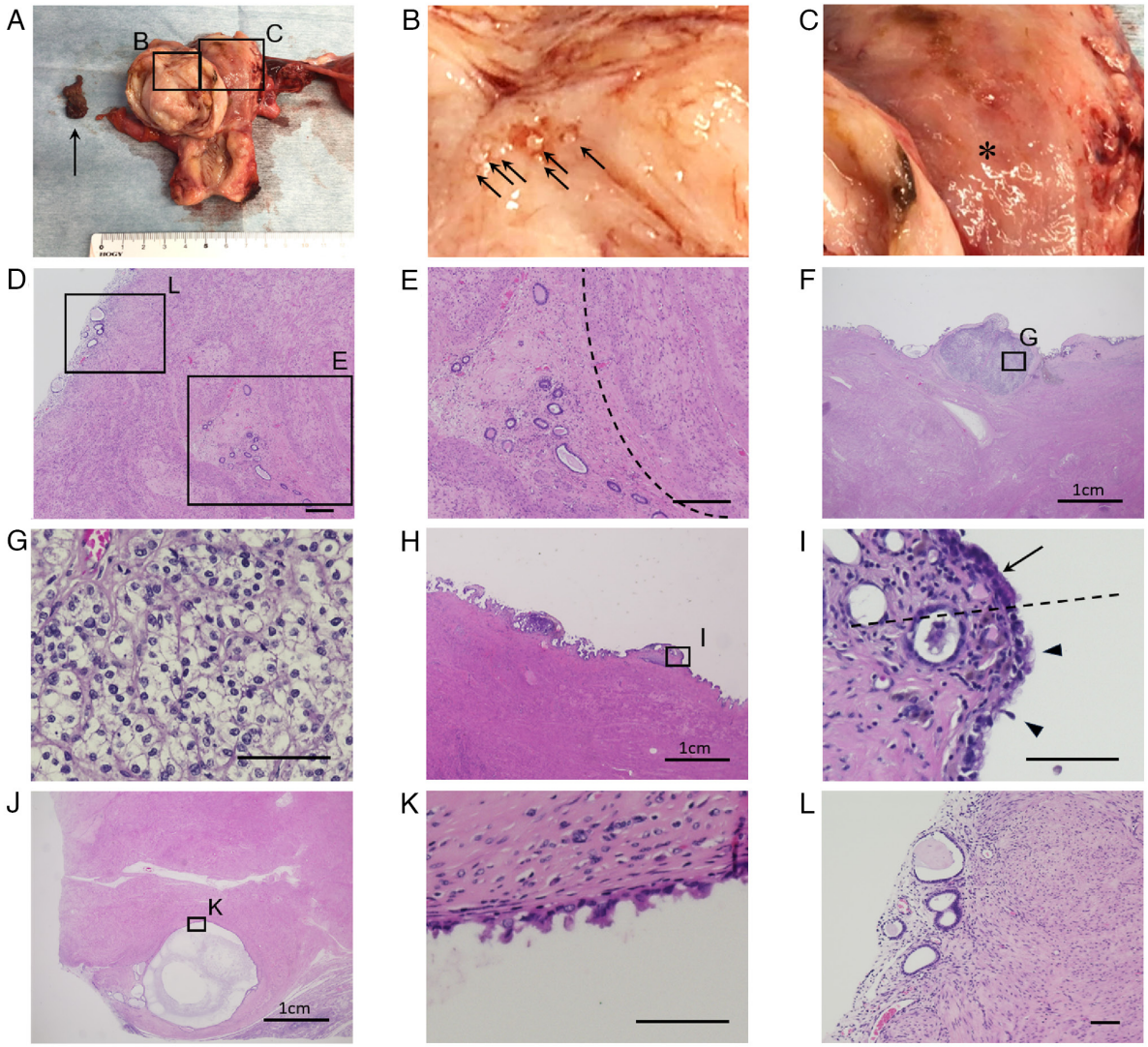

Figure 2. Pathological findings. (A) Macroscopic findings of the uterus. Cystic adenomyosis was located in the lower part of the posterior wall of the uterine corpus. The cyst contained brown blood and an organized hematoma (arrow). (B) A number of small, raised lesions were observed in the cyst wall (arrows). (C) The endometrium was smooth, and pathologically, there were no tumor cells (asterisk). (D) A lower magnification image of (E) and (L) (E) The cyst wall consisted of smooth muscle cells and hyaline stroma, accompanied by adenomyosis. The outer line of the cyst wall is shown as a dotted line. (F) Mural nodules of ~3 mm containing nests of clear cell carcinoma cells were observed on the surface of the cyst wall. (G) A magnified image of the nest region of clear cell carcinoma. (H) The cyst wall of cystic adenomyosis with the transitional zone. (I) A magnified image of (H) The transitional site from columnar (arrows) to hobnail-shaped (arrowheads) epithelial cells is shown (dotted line). (J) Another intramural cyst around the cystic adenomyosis lesion. (K) A magnified image of (J) A lining of hobnail-shaped atypical cells was observed in the intramural cyst. (L) There were no atypical cells in the endometrium. Scale bars, 100 μm or as indicated.

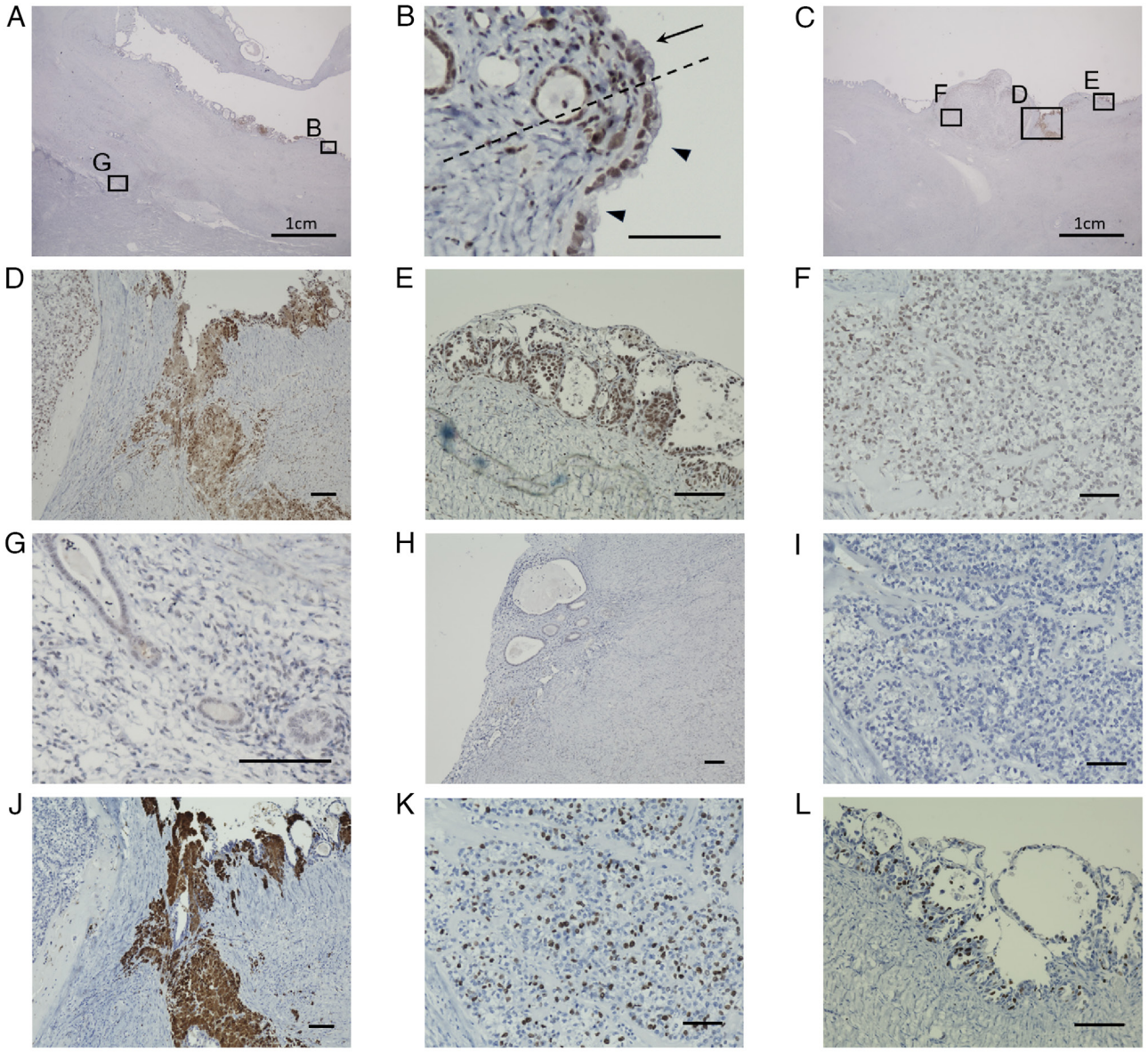

Figure 3. Immunohistochemical staining results. (A) The cyst wall of cystic adenomyosis. Positive staining of 8-OHdG was observed in the epithelium within cystic adenomyosis. (B) In the transition site (dotted line), the nuclear regions of both columnar (arrows) and hobnail-shaped (arrowheads) epithelial cells were stained positive for 8-OHdG. (C) Another region of the cyst wall with solid cancer nests. (D) Inside the cyst wall, 8-OHdG staining was observed throughout the area where hemosiderin was deposited. (E) 8-OHdG staining was strongly positive in the small cysts, which are considered to be in the early stages of cancerous transformation. (F) Clear cell carcinoma cells located on the cyst wall side were stained positive for 8-OHdG. (G) 8-OHdG-negative adenomyotic lesions around the cystic adenomyosis. (H) There were no 8-OHdG-positive cells in the normal endometrial epithelium. (I) There were no 4-HNE-positive cells in the clear cell carcinoma cells in the same field as in (F) (J) 4-HNE staining in the atypical cells of cystic adenomyosis, especially in the area where hemosiderin was deposited. (K) Ki67 was expressed in clear cell carcinoma in the same field as in (F) and (I) (L) Ki67 was expressed in the atypical cells in the same field as in (E) Scale bars, 100 μm or as indicated. 4-HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxy-20-deoxyguanosine.

atypical cells migrated from the normal epithelium of cystic adenomyosis and no invasion of cancer from other sites could be observed. Therefore, the cancer was concluded to be derived from cystic adenomyosis.

Mori *et al* (6) previously described the cystic adenomyosis as a rare variation of adenomyosis, which develops when there is bleeding into the ectopic islands of endometrial glandular tissues surrounded by the myometrium. Repeated hemorrhage during menstruation was proposed to be a cause of extensive cyst formation (6). To the best of our knowledge, no reports demonstrating such a mechanism by which cystic adenomyosis forms exist. However, in the present case, multiple glandular ducts were observed in the area of adenomyosis, where blood accumulated and formed small cysts (Fig. 2J), meaning that there was no contradiction with the findings of Mori *et al* (6). In total, 16 cases of uterine corpus cancer arising from cystic adenomyosis have been previously reported. However, to the best of our knowledge, there have been no reports describing the mechanism by which clear cell carcinoma develops from cystic adenomyosis. Table SI shows the characteristics of the present case and the 16 previous cases where detailed information is available. The long axis of the cysts was 5 cm or more in most cases. Imaging findings showed that many cases had a solid part in the cyst. Epidemiologically, the two main histological

subtypes were clear cell carcinoma (9/17, 52.9%) and endometrioid carcinoma (5/17, 29.4%). Coincidentally, they are also the two main histological subtypes of ovarian cancer derived from the endometriotic cyst, occurring at 69.7% for clear cell carcinoma and 24.2% for endometrioid carcinoma (7). By contrast, the most common histological subtypes of cancer arising from uterine diffuse adenomyosis were endometrioid carcinoma (76.1%), followed by serous carcinoma (15.2%) and clear cell carcinoma (6.5%) (2). Therefore, it was hypothesized that the cystic adenomyosis became malignant through the same mechanism as that of endometriotic cysts. Although endometriosis and adenomyosis are diseases that both originate from the ectopic endometrium, they are reported to utilize different pathways for their formation. According to Sampson (8), retrograde menstruation corresponds to a 'seed' growing in the 'soil' of the peritoneal wall. The cause of endometriosis remains poorly understood. However, the report by Sampson, the presence of immune cells and stem cells in the regurgitated menstrual blood has been found, suggesting that these cells may be a one of the causes of endometriosis. However, how the ectopic endometrium invades the myometrium is important for the formation of adenomyosis. Periodic bleeding from the ectopic endometrium inevitably initiates tissue damage and repair processes, inducing fibrosis. In adenomyosis, high levels of estrogen can stimulate peristalsis of the muscle fibers of the myometrium, causing stress in the endometrial-myometrial junctional zone (9,10). Therefore, it is speculated that the combination of hyperestrogenism and hyperperistalsis causes tissue self-trauma in the endometrial-myometrial junctional zone, favoring the translocation of basal endometrium into the myometrium.

Although there are some differences in the etiology of adenomyosis and endometriosis, they have similarities that they develop from ectopic endometrium, where cysts are formed by the cyclic menstrual blood from ectopic endometrium.

Malignant endometriotic cyst transformation has been reported to be caused by reactive oxygen species accumulation due to oxidative stress as a result of free iron within the hemorrhagic cyst (11,12), which in turn causes genetic mutations (13,14). Oxidative stress is induced by the decomposition products of blood cells, such as iron, heme, and thrombin, which can produce free radicals. Iron is known to generate a hydroxy radicals through the following Fenton reaction: Fe2+ + H_2O_2 → Fe3+ + HO• (hydroxy radical) + OH-.

To validate this oxidative stress hypothesis, immunohistochemistry for 8-OHdG, which is a marker of DNA oxidative stress and 4-HNE, a marker of late-stages of lipid peroxidation, was performed. Both markers are reported to be stain positively in endometriosis-associated ovarian clear cell carcinoma (15,16). Positive staining for 8-OHdG in the atypical cells and in the normal epithelium of cystic adenomyosis was detected. In various adenomyotic lesions around the cystic adenomyosis, the degree of oxidative stress varied depending on the time elapsed since blood had accumulated in the glandular ducts, as some of the ducts were stained weakly for 8-OHdG. 4-HNE positively was also found in the atypical cells of cystic adenomyosis, especially in the area where hemosiderin was deposited. However, 4-HNE stained negative in clear cell carcinoma cells in the cancer nests. Immunohistochemical staining for Ki67 was performed, which found its expression in both atypical cells and clear cell carcinoma cells in the cancer nest. These findings suggest that chronic oxidative stress occurred in the epithelial cells of the cyst wall that were directly exposed to hemorrhage for a long period of time. Marí-Alexandre *et al* (17) previously reported that endometriotic cysts exhibited stronger staining for 8-OHdG compared with adjacent clear cell carcinoma, suggesting that oxidative stress is involved in the process of initiating endometriosis-associated ovarian cancer (17). In the present case, although the majority of the clear cell carcinoma cells within the nodule were negative for 8-OHdG and 4-HNE, the malignant cells located on the cyst wall side were positive for 8-OHdG, supporting the hypothesis that the hemorrhagic contents within the cyst were likely responsible for oxidative stress. Furthermore, Ki67 was found to be expressed in the clear cell carcinoma cells in the cancer nodules and the atypical epithelial cells within the cyst wall. These findings also suggested that after malignant transformation, clear cell carcinoma proliferates regardless of oxidative stress. If we experience a similar case in the future, we would like to confirm the expression of proliferating cell nuclear antigen (PCNA; a marker of cell proliferation). If PCNA is expressed in clear cell carcinoma after malignant transformation, our hypothesis would be further supported.

Oxidative stress has been implicated in the development and progression of cancer through various mechanisms. In endometriosis-associated ovarian cancer, reactive oxygen species can rapidly activate Polo-like kinases (PLK), a mitotic regulator, by regulating DNA replication under stressful conditions, thereby promoting genome stability. PLK phosphorylates early mitotic inhibitor-1 (Emi1) to promotes S-phase and mitosis entry, which suppresses anaphase-promoting complex/cyclosome (APC/C). Overexpression of Emi1 causes mitotic catastrophe and genome instability, which promotes tumorigenesis (18). The Emi1/APC/C pathway has been suggested to be upregulated during occult clear cell carcinoma tumorigenesis during atypical endometriosis (19). These aforementioned previous reports of endometriosis-related ovarian cancer suggest that DNA damage caused by oxidative stress can lead to cell cycle dysregulation and activation of oncogenic signaling pathways (18). Therefore, DNA damage caused by oxidative stress may be a trigger for malignant transformation, and is thought to be an important mechanism in the malignant transformation of cystic adenomyosis. This same mechanism of oxidative stress may also mediate the malignant transformation of endometriotic cysts. Therefore, the use of oral contraceptives, which can prevent the malignant transformation of endometriotic cysts, may also prevent the malignant transformation of cystic adenomyosis (20). Hysterectomy is also recommended if the cystic adenomyosis increase in size after menopause.

One limitation of the present report was the lack of genetic analysis using laser microdissection. Further examination of sequential changes in gene mutations during the transforming process will contribute to clarify the precise roles of oxidative stress in the carcinogenesis of cystic adenomyosis. If we experience a similar case in the future, we would like to perform genetic analysis via laser microdissection.

In conclusion, the present case report proposes the possible involvement of chronic oxidative stress in the malignant

transformation from cystic adenomyosis to clear cell carcinoma. Consistent with the present case, previous reports also demonstrated the late onset of tumor progression and a solid-part appearance after menopause, which suggests the risk of chronic exposure to oxidative stress. If the size of the cystic adenomyosis increases after menopause, the possibility of malignant transformation should be considered in the same manner as ovarian endometriotic cysts.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NH, KK, TI and HF contributed to the study conception and design. NH and KK drafted the first manuscript, and all authors commented on previous versions of the manuscript. SH, SN, KK, MN and TI performed clinical management of the patient. KK conducted immunohistochemistry. NH, KK, TI and HF discussed the results. KK and NH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All study methods were conducted in accordance with the Declaration of Helsinki. Preoperative written informed consent was obtained from the patient prior to the collection of clinical data from their medical record.

Patient consent for publication

Written consent for publication of this case report including all images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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