

Case report

Worsening cytology and lesion enlargement are useful indicators for malignant transformation of lobular endocervical glandular hyperplasia during follow-up: A case report

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1. Introduction

Lobular endocervical glandular hyperplasia (LEGH) is a benign, multi-cystic disorder of the uterine cervix (Nucci et al., 1999; Wilbur et al., 2014). Although difficulties are associated with reaching a pre-operative diagnosis of LEGH, we proposed a diagnostic protocol for LEGH using MRI, cytology, and gastric-type mucin (Takatsu et al., 2011), and verified the usefulness of our protocol in a retrospective follow-up study (Ando et al., 2016). Due to our expanding understanding of LEGH, the number of clinically diagnosed LEGH patients is markedly increasing in Japan. The majority of clinical LEGH patients choose conservative management because of its primarily benign nature. However, previous studies revealed the potential of LEGH as a precursor of minimal deviation adenocarcinoma (MDA) (Takatsu et al., 2013; Mikami et al., 2004). Therefore, it is extremely important to detect the malignant transformation of LEGH at the earliest stage possible during follow-ups. However, useful clinical indicators for this malignant transformation have not yet established. We herein present a case of clinical LEGH that was initially diagnosed by our protocol and transformed into MDA after 5 years of follow-up. This case suggests that worsening endocervical cytology and an increased tumor size are important indicators of the malignant transformation of LEGH.

2. Case report

A 50-year-old woman, gravida 0, visited our hospital for a consultation on a watery discharge and cervical multiple cysts detected at a clinic. Cervical Papanicolaou (PAP) cytology indicated no cellular atypia, but was classified as AGC-NOS (atypical glandular cell-not otherwise specified) because of the presence of 'yellow' or 'orange' mucin, suggesting gastric-type differentiation (Fig. 1A) (Ishii et al., 1999). MRI revealed a normal-sized uterus with clustered small cystic lesions at the inner endocervix surrounded by larger cysts with a clear margin, i.e., "the cosmos pattern" (Fig. 1B and C) (Takatsu et al., 2011; Ando et al., 2016), and the lesion size was 24 × 25 mm. In addition, the HIK1083 latex agglutination assay (Cica HIK gastric mucin®, Kanto Chemical, Tokyo, Japan) revealed the production of gastric-type mucin (Ishii et al., 2001). According to our diagnostic protocol (Takatsu et al., 2011), the initial clinical diagnosis of this patient was LEGH, because we previously indicated that the clinical diagnosis made by our protocol was consistent well with the pathological diagnosis (Ando et al. 2016). In previous report, we explained the possibility of co-existing focal malignant lesions and future malignant changes, and proposed management options, including hysterectomy, cone biopsy, or follow-up. The patient chose follow-up examinations every 3 months.

At the age of 54 years, endocervical cytology worsened to AGC-FN (atypical glandular cell-favor neoplastic) (Fig. 1D). However, cervical

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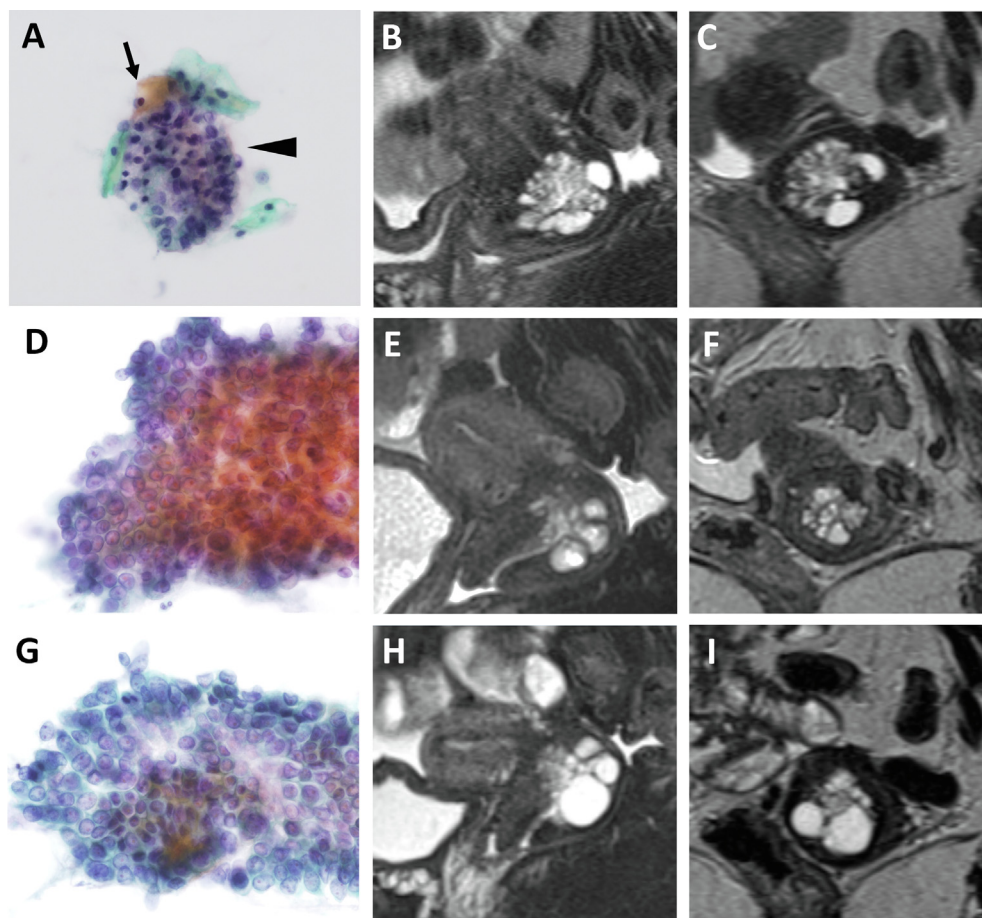


Fig. 1. Endocervical cytology and MRI at the first visit (A–C), at the age of 54 years (D–F), and before cone biopsy (G–I). A, D, and G: Endocervical cytology. Yellow-colored mucus shows gastric-type mucin (arrow) and pinkish mucus is normal endocervical mucin (arrowhead). “A” shows no cellular atypia, but “D” and “G” show mild cellular atypia. B, E, and H: Sagittal sections of a T2-weighted image (WI) with fat saturation (Fat-Sat). C, F, and I: Coronal sections of T2-WI without Fat-Sat. The appearance of a cervical multi-cystic lesion containing a clustered small cystic lesion at the inner layer surrounded by larger cysts at the outer layer with a clear margin as the characteristic findings of LEGH, the so-called “cosmos pattern”. The appearance and size of the multi-cystic lesion in 2nd MRI (E, F) were similar and smaller than those in 1st MRI (B, C). Although the appearance of the multi-cystic lesion was still “the cosmos pattern” in 3rd MRI (H, I), the size of the lesion increased from 2nd MRI (E, F). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

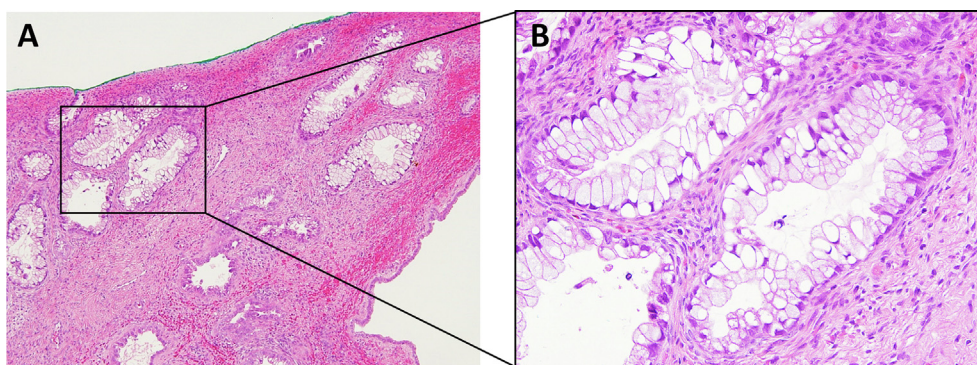


Fig. 2. Microscopic findings of the cervix resected by conization. A: ($\times 100$) Invasive atypical glands with a clear cytoplasm containing abundant mucin were observed at the cervical stroma. The diagnosis was MDA. B: ($\times 200$) Atypical glands at a higher magnification.

punch biopsy and endocervical curettage showed no malignant lesions. Second MRI findings indicated that the size (22×21 mm) and appearance of cervical cysts were similar or smaller than those in 1st MRI (Fig. 1E and F). Although we recommended further examinations, such as conization, the patient continued follow-up examinations because cervical cytology had returned to AGC-NOS in 2nd MRI. Seven months later, cervical cytology again worsened to AGC-FN (Fig. 1G). The pathological diagnosis of cervical biopsy suggested gastric-type adenocarcinoma (GAS). Although 3rd MRI still showed “the cosmos pattern”, lesion size increased to 24×29 mm (Fig. 1H and I). The patient underwent cold-knife conization and the pathological diagnosis was MDA/GAS of the uterine cervix (Fig. 2). Contrast CT revealed no findings suggestive of metastasis to other organs or lymph nodes, and serum tumor markers were not elevated (CA125: 7.1 U/mL, CA19-9:

23.4 U/mL, CEA: 2.5 ng/mL, SCC: 0.9 ng/mL). Accordingly, the final diagnosis was uterine cervical carcinoma, FIGO stage IB1.

After obtaining written informed consent from the patient, abdominal radical hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy were performed. Although no visible peritoneal dissemination was observed, peritoneal washing cytology was positive. The removed uterus microscopically showed LEGH at the endocervical glandular region (Fig. 3A and B) and atypical glandular cells deeply infiltrating the cervical wall without a stromal reaction (Fig. 3A, C–E). The pathological diagnosis was MDA. Histologically, the diameter of the tumor was 30 mm with lymphovascular space and parametrial invasion, but no vaginal invasion, ovarian metastasis, lymph node metastasis, or dissemination to the omentum or peritoneum. The immunohistochemical expression of HIK1083 was positive in MDA and

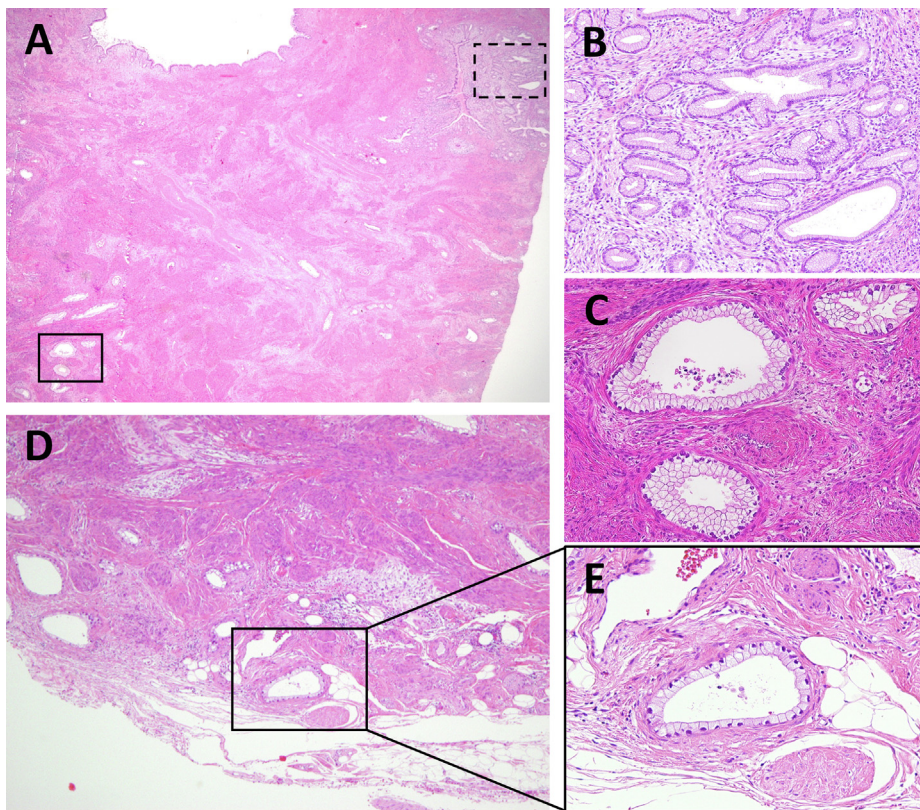


Fig. 3. Microscopic findings of the removed uterus. A: ($\times 20$) The cervical tumor contained LEGH (dashed square) and MDA (solid square). Atypical glands were sporadically located in the cervical stroma. B: ($\times 200$) A high magnification photograph of the dashed-lined square of “A”. LEGH was observed adjacent to endocervical canal. C: ($\times 200$) A high magnification photograph of the solid-lined square of A. MDA with deep stromal invasion was observed without a stromal reaction. D ($\times 40$) and E ($\times 200$): An MDA lesion lacking a stromal reaction was observed at the outer surface of the uterine cervix.

LEGH lesions (Supplementary Fig. 1). The postoperative TMN classification was pT2bN0M0.

Concurrent chemoradiotherapy (CCRT) was performed as an adjuvant treatment. The patient has had no evidence of recurrence for 3.5 years since hysterectomy.

3. Discussion

Although LEGH is a benign proliferative disorder of the uterine cervix, previous studies reported the potential of LEGH as a precursor of MDA (Takatsu et al., 2013; Mikami et al., 2004). Therefore, the precise and early detection of the malignant transformation of LEGH is very important in patients with LEGH who select conservative management. However, useful indicators for the malignant transformation of LEGH have not yet been established. Therefore, the present case provides important information of worsening cytology from AGC-NOS (without cellular atypia but suggesting gastric-type differentiation) to AGC-FN (with mild cellular atypia) as the first indicator of the malignant transformation of LEGH, followed by lesion enlargement.

Limited information is currently available on the follow-up of LEGH and its malignant transformation; there is currently only one case report (Sugihara et al., 2015) and one retrospective study in our hospital (Ando et al., 2016). The clinical course of the reported case (Sugihara et al., 2015) was similar to that of the present case; a 45-year-old patient had multiple cervical cysts with no cytological atypia and with gastric mucin, suggestive of clinical LEGH. This patient developed MDA after 2 years of follow-up, which was associated with worsening cytology (‘no atypia’ to ‘AGC’) and an increased lesion size on MRI (21–31 mm) at the same time. The reported and present cases both indicate the importance of worsening cytology and enlarged lesions for the prediction of malignant changes; however, in this specific case, we observed that worsening cytology precedes lesion size changes. Follow-up data on 42 patients with clinical LEGH in our hospital were described in another study. Three of these patients showed an increased lesion size without cytological changes, with 2 having LEGH with

atypia (55- and 33-year-old patients). This study also suggested the importance of an increased lesion size as a neoplastic change; however, the pathology of the removed uterus was LEGH with atypia. The diagnostic criteria and oncological significance of atypical LEGH currently remain unclear. Accordingly, the present case is the first to show worsening cytology as the first indicator of the malignant transformation of LEGH, followed by an increased lesion size.

The time durations between the initial LEGH diagnosis and change in cytology and/or tumor size in the four reported cases were 3 months (55-year-old patient) (Ando et al., 2016), 2 years (Sugihara et al., 2015), 5 years (present case), and 12 years (33-year-old patient) (Ando et al., 2016). Therefore, although definite recommendations are difficult, a long-term follow-up appears to be necessary, particularly for young patients. The appropriate method of follow-up has also not yet been established. However, we consider that follow-up every six months is preferable, i.e., cytology, gastric-type mucin test and lesion size measurement by transvaginal ultrasonography in every six months, and MRI in every two years.

MRI is regarded as a useful tool in the diagnosis of multi-cystic lesions of the uterine cervix (Takatsu et al., 2011; Ando et al., 2016). An irregular solid component showing high T2-signal intensity with an unclear margin in the stroma is an important indicator of the presence of a malignant lesion (Takatsu et al., 2011). Although this finding was evident in a previous case report (Sugihara et al., 2015), we did not detect it, even in 3rd MRI. The reasons for the lack of stromal invasion on MRI may be explained by the following pathological findings (Fig. 3A, C–E): (1) the ratio of atypical glands and stroma was very low (almost 10% or less) in MDA, particularly in deep stromal invasion sites, and (2) atypical glands located in the deep stroma lacked an apparent stromal desmoplastic reaction, which reportedly affects the T2-weighted signal intensity of MRI (Itoh et al., 2006). Therefore, we need to consider these potential weaknesses of MRI in the detection of fine invasive lesions, particularly when the size of “the cosmos pattern” increases.

Collectively, although we consider that worsening cytology and

lesion enlargement are important signs of malignant transformation, it also should be noted that MRI and cytology may be imperfect to rule out all invasive lesions. Therefore, cone biopsy is an important diagnostic option for women wishing to avoid hysterectomy, while women not pursuing that strategy should be carefully counselled about the risk of delayed detection of malignant lesions. In the present case, the first abnormality detected was worsening cytology from AGC-NOS to AGC-FN. Therefore, we need to be more prudent in management selection. However, our patient did not choose active management, including hysterectomy and cone biopsy, at the first occurrence of AGC-FN cytology because her MRI findings showed no changes. As a result, hysterectomy was delayed by almost one year, which allowed the tumor to progress to pT2b. Therefore, when cellular atypia is detected by PAP cytology, active management needs to be more strongly recommended regardless of MRI findings.

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CRediT authorship contribution statement

Hisanori Kobara: Writing - original draft. **Tsutomu Miyamoto:** Writing - review & editing. **Toshiaki Otsuki:** Data curation, Investigation. **Ayumi Ohya:** Data curation, Investigation. **Tanri Shiozawa:** Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2020.100571>.

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