Biology and management of lobular endocervical glandular hyperplasia

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Abstract
Aim: Lobular endocervical glandular hyperplasia (LEGH) is a multicystic proliferative disorder of the uterine cervix. The aim of this review was to clarify the current understanding of this unique tumor.
Method: This article reviews the chronological progress of research regarding clinico-pathological and genetic aspects of LEGH and related cervical cystic diseases such as Nabothian cyst and adenocarcinoma of gastric type (GAS), using the literature and data from our institute. We also describe clinical management including preoperative diagnosis and adequate surgical/expectant treatment based on the biological features.
Results: Recent studies revealed several unique aspects of LEGH, that is, (i) production of gastric mucin, (ii) symptomatic and histological similarity with minimal deviation adenocarcinoma (MDA), and (iii) frequent association with GAS, including MDA. These findings indicated that LEGH is a gastric metaplasia, as well as pre-cancerous neoplasia. For the preoperative diagnosis of LEGH, the combination of “cosmos” sign on magnetic resonance imaging, detection of gastric mucin, and lack of nuclear atypia on cytology is important. Cone biopsy is effective for pathological diagnosis. Simple hysterectomy is indicated as surgical treatment for LEGH; however, meticulous follow-up is also an option, especially for young patients, because the rate of malignant transformation was reported to be 1%–2%. For LEGH patients who selected follow-up, a worsening cytology and increase in lesion size were important signs of malignant change of LEGH for safe follow-up.
Conclusion: Proper understanding of the characteristics of LEGH is important for adequate management.
Key words: gastric-type mucin, gastric-type mucinous carcinoma, lobular endocervical glandular hyperplasia, magnetic resonance imaging.

Introduction
Due to the prevalence of transvaginal ultrasonography and magnetic resonance imaging (MRI), physicians sometimes encounter patients harboring a cluster of cysts in the uterine cervix. Because diagnostic tissue sampling of entire cystic lesions such as hysterectomy is unrealistic in daily practice, physicians should be aware of the clinico-pathological characteristics of each cystic disease to perform adequate management. Diseases exhibiting such cystic lesions range from benign to malignant disorders. Nabothian cyst (NC) is a representative benign disease, whereas minimal deviation adenocarcinoma (MDA), previously referred to as adenoma malignum, is an important malignant counterpart. In addition, lobular endocervical glandular hyperplasia (LEGH), which was initially reported as a benign disease histologically similar to MDA in 1999, is considered to be a putative precursor of malignancy such as MDA. Therefore,
appropriate understanding of biological and clinicopathological characteristics of these cystic disorders, especially that of LEGH, is important for precise diagnosis and appropriate treatment.

MDA had been considered an “enigmatic” disease up until the 1990s, because preoperative diagnosis of MDA, which is known to show poor prognosis, had been considered nearly impossible due to its paradoxical well-differentiated morphology. In 1996, our research group established a monoclonal antibody termed HIK1083 that recognizes gastric (pyloric) mucin. We reported the expression of gastric mucin in MDA in 1997, and as yellow mucin on Papsmears. We then developed a latex agglutinin kit using HIK1083 antibody that can detect gastric mucin in the cervical mucous in 2001 (Figure S1, Supporting Information). We conducted many hysterectomies of kit-positive patients, however, we encountered many patients who showed good postoperative courses, suggesting the presence of a benign “MDA-like” disease, or a disease such as “adenoma benignum.” Moreover, LEGH was also reported to produce abundant gastric mucin. Accordingly, we considered that a large number of LEGH patients were included in kit-positive patients. This observation prompted us to conduct a multicenter study named “adenoma malignum study” in 2006, and the results were published in 2011. The present review describes the following progress of this area.

In this review article, we first describe histopathological features of LEGH and several related diseases including MDA, mucinous carcinoma of gastric type (GAS), and NC, which require clinical (preoperative) differential diagnosis with LEGH. We then review the immunohistochemical characteristics of LEGH, with reference to morphological and functional aspects of gastric metaplasia. We also mention genetic studies describing the pre-malignant or neoplastic nature of LEGH, including those stating that gastric mucin is a tumor suppressor. We subsequently argue the proper clinical management of LEGH in terms of preoperative diagnosis, and diagnosis-based management and safe follow-up.

Histology

Lobular endocervical glandular hyperplasia

At almost the same time when LEGH was first reported by Nucci, Mikami et al. reported a similar proliferative condition termed “florid endocervical glandular hyperplasia,” which was later confirmed to be identical to LEGH by both reporters. LEGH is a rare disease, with an estimated incidence of 0.7%, and the mean patient age was 48 years. LEGH reportedly occurs in patients with Peutz-Jeghers syndrome with germline STK11 mutation, but high-risk HPV is negative. Histologically, LEGH is characterized by lobular distribution of small glands lined by normal-looking endocervical cells without nuclear atypia, often locating in the upper portion of the endocervical canal (Figure 1a, b). The cytoplasm of LEGH cells is clear and eosinophilic, indicating the secretion of gastric-type mucin. In addition, the apical surface of lining cells is smooth, contrasting with that of normal endocervical glands, which show an apocrine secretion pattern. LEGH glands often extend to the stroma; however, the lesions lack the desmoplastic reaction (pseudo invasion).

LEGH with atypia

Several reports pointed out the presence of LEGH with cytological and architectural atypia without stromal invasion, and it was termed atypical LEGH (Figure 1c). Mikami et al. first proposed this atypical LEGH, which meets several morphological criteria in the lining cells. In this study, nine examples with at least four of these features were identified, six among 20 MDAs, and three in its pure form without associated invasive adenocarcinomas. In these six cases, carcinomatous components were close to or adjacent to foci of LEGH with atypical features. Accordingly, the authors suggest that atypical LEGH is a premalignant form of LEGH.

Although the genetic background of atypical LEGH is not fully understood, Kawachi et al. reported that comparative genomic hybridization revealed chromosomal imbalance (gains of chromosome 3q and loss of 1p), both were found in MDA in 3 LEGH among 14 patients, and these 3 had cytological atypia. These findings support the premalignant nature of atypical LEGH.

Representative cystic diseases similar to LEGH

Nabothian cyst

Cysts are sometimes solitary, but also nested or clustered, around transformation zone of the cervix. NC is lined by a somewhat flattened, single layer of endocervical epithelium (Figure 1d). Functionally, NC is a retention cyst of the cervical glands, and NC does not
produces gastric mucins. NC is a benign condition, and malignant change is very rare.\(^1\)

**Minimal deviation adenocarcinoma**

MDA is an extremely well-differentiated mucinous adenocarcinoma. It is a rare disease, accounting for 1%-2% of adenocarcinomas in the cervix. MDA is also associated with Peutz-Jeghers syndrome.\(^2\) A unique symptom of MDA is a massive watery vaginal discharge with a swollen cervix and multicystic lesions, as seen in LEGH. Furthermore, MDA also produces gastric-type mucin.\(^6,9\) MDA was classified as a highly differentiated type of mucinous carcinoma, gastric type, according to the 2014 World Health Organization (WHO) classification.\(^19\)

Histologically, MDA consists of deceptively normal-looking cervical glands with mild nuclear and apparent structural atypia. Stromal invasion is a diagnostic hallmark of MDA. The cytoplasm is clear, suggesting the presence of gastric-type mucin (Figure 2a, b). Despite the well-differentiated morphology, its associated prognosis is poor with resistance to surgical or medical therapy, and high rates of metastasis have been reported.\(^3,7\) Since cellular atypia of MDA is minimal, the cytology of the cervix is often negative. Difficulties are also associated with obtaining an accurate diagnosis due to limited biopsy samples.\(^7\) Therefore, a preoperative diagnosis of MDA has been considered difficult.

**Mucinous carcinoma, gastric type**

In the WHO 2020 classification, this type of adenocarcinoma was classified as “mucinous carcinoma, HPV-independent gastric type (GAS).”\(^20\) GAS was initially described by Japanese groups.\(^6,21\) Although GAS is considered rare in Western countries, it is common in Japan, accounting for up to 20% to 25% of all endocervical adenocarcinomas.\(^21\) GAS is morphologically characterized by ample and clear cytoplasm, a distinct cell border, and moderate nuclear atypia (Figure 2c).\(^6,21\) GAS was reportedly associated with a poorer prognosis than usual cervical adenocarcinomas due to its resistance to radiation and chemotherapy.\(^22\) There is a report of advanced GAS in a 16-years-old female without a history of sexual intercourse.\(^23\)

**Adenocarcinoma in situ of gastric-type**

Recently, gAIS has drawn attention as another potential precursor of GAS.\(^24\) Currently, however, the evidence supporting the premalignant potential of adenocarcinoma in situ of gastric-type (gAIS) is largely observational, and molecular features remains undetermined. This uncommon form of AIS is HPV-negative, and exhibits a gastric phenotype and shares...
many cytological features of atypical LEGH. Morphologically, gAIS lacks a lobular structure with clusters of small glands surrounding the dilated duct. Tumor cells of gAIS show low-grade nuclear atypia and clear cytoplasm, similar to GAS, but lack stromal invasion (Figure 2d).

Biochemical Characteristics of LEGH

Hormonal aspect of LEGH

Immunohistochemical expression of estrogen receptor (ER) was positive in both epithelial cells and stroma of normal endocervical glands. In LEGH, the expression of ER was negative in the epithelium of LEGH, but in the stroma was positive (Figure S2a, b). In MDA, the expression of ER was negative both in the epithelia and stroma (Figure S2c, d). Mikami et al. reported that the expression of ER became negative in stroma invaded by MDA, because normal stroma was replaced by ER-negative tumor stroma, showing a contrast to that of LEGH. This may aid differential diagnosis between MDA and LEGH. Although the hormone-dependency of the growth of LEGH lesions is unclear, we found several LEGH cases whose size reduced after menopause.

Histochemical characteristics

Gastric mucin

Biochemically, gastric-type mucin is neutral mucin, showing a contrast to acid mucin produced by normal endocervical glands. Gastric mucin is detected by Alcian Blue-Periodic Acid Schiff (AB-PAS) staining, that is, gastric mucin is stained red in LEGH and MDA (Figure 3a, b, d, e). Gastric mucin can also be detected by a monoclonal antibody (HIK1083) that specifically recognizes the gastric (pyloric) mucin structure (N-acetylglucosamine α1 → 4galactose → R (αGlcNAc-R)) and detects the immunohistochemical expression of gastric mucin in MDA and LEGH cases, indicating that it may be a useful tool to detect LEGH/MDA (Figures 3c, f and S3).

Structure and function of gastric mucin

Structurally, gastric mucin is a glycoprotein. Gastric gland mucin contains O-linked oligosaccharides (O-glycans) with terminal α1,4-linked N-acetylgalactosamine (αGlcNAc) residues attached largely to an MUC6 scaffold (Figure S3). Muc6 is a core structure protein of gastric-type mucin. HIK1083 antibody recognizes the terminal sugar chains consisting of αGlcNAc. The MUC6 core protein, to which αGlcNAc is connected, is positive in both normal endocervical glands and
gastric mucin in LEGH/MDA. Therefore, HIK1083 antibody is highly specific for gastric mucin and a useful tool to detect gastric mucin production.

Regarding the function of gastric mucin, our colleagues reported that gastric mucin strongly suppressed the growth and migration of *Helicobacter pylori*, suggesting an anti-oncogenic function of gastric mucin. In addition, our colleagues isolated cDNA encoding α1,4-N-acetylglucosaminyltransferase (α4GnT), the enzyme catalyzing αGlcNAc biosynthesis (Figure S3), and then generated A4gnt-deficient mice. These mutant mice showed αGlcNAc loss in gastric gland mucin and naturally developed gastric adenocarcinoma, indicating that gastric mucin is a tumor suppressor. We report decreased expression of gastric mucin in MDA/GAS compared with LEGH, also suggesting a tumor suppressor function of gastric mucin in the LEGH-MDA/GAS sequence. Interestingly, also, decreased expression of gastric mucin was associated with shorter survival of GAS patients.

**Other antigens**

More recently, a study reported that the expression pattern of trefoil factor family 2 protein (TFF2), which is secreted in the stomach, was very similar to that of antigens recognized by HIK1083 antibody, also suggesting an additional approach to detect gastric mucin. LEGH was shown to express CK7+/20, indicating a Mullerian origin, and chromogranin-positive endocrine cells. Chromogranin A was positive in about 50% of LEGH. The expression of claudin 18, a linker protein of the gastric mucosa, was positive for LEGH. The expression of carbonic anhydrase type IX (CA-IX), which is reportedly involved in gastric carcinogenesis, is positive. The expressions of P53 and CEA are largely negative. Collectively, the expressions of digestive tract markers are often positive, but HPV markers are negative.

**LEGH as pyloric metaplasia**

Recent pathological and immunohistochemical studies indicated that pyloric metaplasia is causative of LEGH. Moreover, an entire LEGH lesion morphologically and functionally exhibited similarity to pyloric mucosa, that is, cluster of small glands, as well as accompanying irregular-shaped elongated glands in LEGH corresponding to acinar glands and

![Figure 3 LEGH (a, b, c) and MDA (d, e, f) by Alcian-blue PAS (AB-PAS) staining (b, e) and HIK1083 immunostaining (c, f). Epithelial cells of both LEGH and MDA predominantly produce neutral mucin (red) and HIK1083-positive gastric mucin.](image-url)
connecting ducts in pyloric mucosa, respectively. In addition, LEGH epithelial cells produce abundant pyloric mucin. This morphological metaplasia in association with functional change observed in the entire LEGH area to the pyloric mucosa was termed “organoid differentiation” (Figure 4).12

LEGH as a precursor of MDA

Histopathological observation of LEGH led to the proposal that LEGH may be a precursor of MDA or adenocarcinoma. Other studies reported that LEGH has been identified adjacent to up to 50% of MDAs and 20% of gastric-type adenocarcinomas.6,34 A study reported a transition from LEGH to adenocarcinoma in the epithelium of a LEGH gland.35 As mentioned previously in this text, common immunohistochemical expression of gastric markers in LEGH and MDA also supported the possibility of LEGH as a precursor of mucinous adenocarcinoma. Nara et al. reported that the common expression of HIK1083-positive gastric mucin was present in both LEGH and adenocarcinoma areas of five cases of LEGH associated with mucinous adenocarcinoma.34

In addition, several genetic studies also demonstrated this possibility. Comparative genomic hybridization revealed recurrent chromosomal imbalances, that is, gains of chromosome 3q and a loss of 1p, which were common to MDA and LEGH, in 3 of 14 LEGHs analyzed (21%). Dual-color fluorescence in situ hybridization confirmed the gain of a chromosome 3 fragment in these cervical glandular lesions.17

Genetic characteristics of LEGH

As discussed in the previous part, the question of whether LEGH is a metaplasia (non-neoplasm) or neoplasm has been considered. In addition, it remains unclear whether LEGH is a precursor of MDA/GAS, because frequent association of LEGH with MDA has been reported. To address this, we performed clonality analysis using the FUMARA method.5 The results indicated that approximately half of LEGH cases were polyclonal, that is, non-neoplastic (metaplastic), and half were monoclonal (neoplastic). We performed whole-exome sequencing of three nonatypical LEGH, and interestingly we found no pathogenic mutation.36 The presence of polyclonal LEGH and result of a mutational study supported the metaplastic nature of LEGH. We also examined the clonal status in cases which have both LEGH and MDA parts. The results indicated that in most of the cases examined, both LEGH cells and MDA cells were monoclonal, and the X-chromosome inactivation patterns of both LEGH and MDA sites were identical. In addition, STK 11 mutation, which was originally discovered as a causative gene alteration of Peutz-Jegars syndrome,7 and has already been reported in MDA,37 was observed only in the MDA part in one case with both MDA and LEGH lesions. These data showed that a part of LEGH is a precursor of MDA, and that STK11 abnormality is
involved in the progress of the disease from LEGH to MDA.5

Oncogenic mutations in the GNAS gene were recently identified as a cause of mucin-producing neoplasms in the pancreas and gastrointestinal tract.38 The GNAS gene encodes the alpha-subunit of the stimulatory guanine nucleotide-binding protein (Gsa), which transduces signals from a G-protein-coupled receptor. GNAS has been shown to elevate intracellular cAMP levels by stimulating adenyl cyclase, which provokes cellular proliferation through the Protein kinase A-ERK signal pathway.39 Previous studies detected these mutations in glandular neoplasms in the pancreas, colon, etc.38,40 Matsubara et al. also identified GNAS gene mutations in 42% of LEGH.41 However, the relationship between GNAS mutations and the clinical courses and histological types of LEGH remains unclear. To address this issue, we analyzed GNAS mutations in 17 patients whose clinical course data were available and evaluated the implications of these mutations in the management of LEGH. Accordingly, we found no GNAS mutations in usual (nonatypical) LEGH, but found the mutation in glands of atypical LEGH.42 Although the reason of the discrepancy in LEGH cases between the previous study and ours has not been elucidated, the GNAS mutation may be in part involved in the pathogenesis.

Recently, results of targeted sequencing of 68 GAS cases have been reported.43 They reported the frequent mutation of TP53 (41%), CDKN2A (18%), KRAS (18%), and STK11 (10%), and suggested the involvement of p53 signaling, PIK3/AKT/mTOR, and Notch pathways. However, the genetic link between GAS and LEGH has not been elucidated. The possible pathogenetic processes of these diseases are summarized in Figure 5.

**Clinical Management**

**Preoperative diagnosis**

**Cervical cytology**

Cervical cytology (Papanicolaou stain) is also an important approach to obtain a correct diagnosis. For this purpose, endocervical cytology is more preferable. A cytological diagnosis was made according to the Bethesda system. NC cases generally show NILM, whereas most MDA/GAS shows AGC-FN, AIS, or adenocarcinoma. Especially, AGC-NOS suggested benign (nonatypical) LEGH, whereas AGC-FN suggested atypical LEGH or MDA/GAS.44,45 Collectively, cervical cytology is useful to distinguish benign LEGH and MDA/GAS/atypical LEGH.14,26,42 (Figure 6a, b).

**Magnetic resonance imaging**

MRI is an important diagnostic tool for the cystic disorders of the cervix.14,26,42,46,47 We classified T2-weighted MRI findings of the abovementioned cervical disorders often presenting with multicystic lesions as follows: (i) solid pattern (a solid component was noted), suggesting malignancy such as MDA/GAS; (ii) invasion pattern (diffuse and solid high T2-weighted signal with an unclear margin in

Figure 5 Suggested pathogenetic process of LEGH and MDA/GAS
the cervical stroma), also suggesting malignancy; (iii) cosmos pattern (diffuse or microcystic parts surrounded by medium to large cysts), suggesting LEGH; (iv) microcystic pattern (aggregation of small cysts without peripheral large cysts), suggesting LEGH or malignancy; (v) coarse cystic pattern (irregular aggregation of medium to large cysts without a solid or microcystic component), suggesting a NC (Figure 6c, d, e). The correct rate of the MRI classification for diagnosing LEGH and MDA/GAS was 85% ~ 90% and 67% ~ 70%, respectively.\textsuperscript{27,43} However, MRI diagnosis alone makes it difficult to detect focal malignancy in patients with LEGH, which make up several percent of all LEGH patients, being the most important weakness of MRI. Ohya et al. also reported the difficulty of diagnosing focal MDA in LEGH by MRI.\textsuperscript{46}

Recently, Omori et al. reported additional MRI finding of LEGH, termed the raspberry pattern, that is, close aggregation of small cysts, lacking surrounding outer larger cysts (Figure 6f). They reported that surgically confirmed LEGH exhibited a raspberry pattern on MRI and was often postmenopausal and associated with AIS.\textsuperscript{47}

\textbf{Gastric mucin}

Gastric-type mucin in the cervical mucus was examined using a latex agglutination assay (Cica-HIK gastric mucin, Kanto Kagaku, Tokyo, Japan)\textsuperscript{11} (Figure S1) or by the detection of “yellow” or “orange” mucin in the cervical Pap smear\textsuperscript{16} (Figure 6a, b). NC is negative for gastric mucin. LEGH strongly expresses and secretes gastric mucin. In MDA and GAS, the expression of gastric mucin is positive; however, the positive rate and amount of mucin secretion are lower than in LEGH.\textsuperscript{28} Collectively, gastric mucin is useful to distinguish NC and LEGH.

\begin{figure}
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\caption{Representative findings of cervical PAP smear (a and b) and MRI (c-f). (a) AGC-NOS, with yellow gastric mucin (arrowhead) and pinkish normal endocervical mucin (arrows) indicating a “two-color pattern,”\textsuperscript{10} but without nuclear atypia (dotted square and inset), suggesting LEGH. (b) AGC-FN, with the “two color pattern” and nuclear atypia (dotted square and inset), suggesting MDA/GAS. (c) Coarse cystic pattern, suggesting Nabothian cyst (NC). (d) Small cysts and solid parts are surrounded by larger cysts (cosmos pattern), suggesting LEGH. (e) Solid and part with an unclear margin to the stroma, suggesting malignancy. (f) Microcystic pattern without outer larger cysts (raspberry pattern), suggesting LEGH.}
\end{figure}
Preoperative diagnosis according to the combination of MRI, cervical cytology, and gastric mucin

Based on the abovementioned features of three parameters, we proposed a diagnostic flowchart for these disorders\(^{14,26,42}\) (Figure 7). The patient was clinically diagnosed with suspected MDA or adenocarcinoma (sMDA-Ca) when pelvic MRI revealed a predominant solid component or invasive lesion and/or atypical glandular cells-favor neoplastic (AGC-FN) in the Pap cytology. A patient was clinically diagnosed with suspected LEGH (sLEGH) when the cosmos pattern on MRI, normal, or atypical glandular cells-not otherwise specified (AGC-NOS) cytology, and gastric mucin were noted. A patient was clinically diagnosed with suspected NC (sNC) when MRI showed coarse, multiple cysts with a clear margin, with negative cytology, and gastric-type mucin. This diagnostic protocol is useful, because the rate using this classification to correctly diagnose LEGH and MDA/GAS was approximately 80% and 70%, respectively.

Treatment

Surgery

According to the management flowchart, patients with sMDA-Ca are recommended to undergo immediate biopsy and curative hysterectomy.\(^{14,26,42}\) Patients with sLEGH are recommended to undergo surgery (conization or hysterectomy) or follow-up every 3–6 months (Figure 7). In clinical LEGH cases when the diagnosis is unclear, we recommend conization. Of note, the conization cannot resect the entire lesion, and making the final diagnosis by analyzing the resected tissue is theoretically impossible. However, the concordant rate of pathological diagnoses between conization-resected tissues and retained cervical tissues after hysterectomy was unexpectedly high (12/13, 92%) in our previous study.\(^{14}\) Therefore, we consider conization to be an important diagnostic approach. Whereas in cases with LEGH, conization is sometimes technically difficult because the LEGH lesion often anatomically arises at a higher site (uterine site) of the cervical canal, which makes the surgical approach difficult. Recently, several surgical devices have been applied. We used the trans-cervical resectoscope in cases with LEGH, located in a higher part of the endocervical canal. The patient with sNC was recommended to undergo follow-up every 6–12 months.

Expectant management (follow-up of LEGH)

When a clinical LEGH diagnosis is made, most patients select expectant management (follow-up).

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**Figure 7** Management flowchart for cervical multicystic diseases. This is a modified version of Figure 1 in our previous report.\(^{42}\) AGC, atypical glandular cells; AGC*, cells producing gastric mucin without cellular atypia; AGC-FN, atypical glandular cells-favor neoplastic; AIS, adenocarcinoma in situ; MRI, magnetic resonance imaging; NILM, negative for intraepithelial lesion or malignancy; sLEGH, suspected lobular endocervical glandular hyperplasia; sMDA-Ca, suspected minimal deviation adenocarcinoma or carcinoma; sNC, suspected Nabothian cyst; SH, simple hysterectomy; RH, radical hysterectomy

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However, there are no reliable markers to detect the early stage of malignant transformation. In this regard, an informative report\textsuperscript{45} and our report\textsuperscript{44} suggested that an increase in lesion size and worsening cytology were important markers to detect malignant change of LEGH. In reference with these reports, we also carefully followed up 69 cases of clinical LEGH, we found one MDA patient. These results indicate that the rate of malignant transformation of LEGH was limited (1.4\%, 1/69), and these two parameters were effective for the early detection of malignancy.\textsuperscript{26} These results also showed that the expectant management of LEGH patients is a safe option, especially for those in young, child-bearing generations.

**Future Subjects**

We suggest that consideration of the following points is necessary to further understand and manage the disorders.

**Elucidation of natural history**

The natural history of LEGH is not fully understood. When we started the collaborative study in 2006, the collected patients were mostly 45 to 55 years old. However, recently, we sometimes see patients in their 30s. Despite being in such a young generation, patients sometimes have a large LEGH lesion, that occupies most of the cervical canal. It is unknown when such a large lesion was formed. Also, we encounter patients whose lesions tend to reduce after menopause. This phenomenon suggests the potential hormone dependency of LEGH, such as leiomyoma. Collectively, it is very important to further understand the natural history of LEGH throughout the patient’s lifetime for appropriate management.

**Genetic background of two clonality types**

Clonal analysis using the FUMARA method demonstrated that nonatypical LEGH had two subtypes, monoclonal and polyclonal. Polyclonal cases suggest a metaplastic origin, whereas monoclonal cases may suggest a neoplastic nature, and this is supported by the fact that the atypical part in monoclonal LEGH showed the same inactivation pattern. However, the genetic background of these subtypes is unknown. Does a polyclonal case change to a monoclonal one? If so, what is the genetic change? Therefore, the molecular pathway from normal endocervical epithelium, nonatypical LEGH, atypical LEGH, and MDA/GAS should be more clearly elucidated.

**Effective method to detect malignancy**

To detect the malignant change of LEGH except for lesion enlargement and worsening cytology, for example, the effectiveness of simple molecular markers such as GNAS mutation should be explored. A more effective histological examination method for LEGH except for conization, for example, the use of an endocervical resectoscope or a simple trachelectomy, should be applied. The development of effective treatments for GAS, including novel molecular targeted drugs, is awaited.

**Conclusion**

A large amount of information as to LEGH has been recently accumulated. This review summarized reports of the disease mechanism, diagnosis, and management of LEGH and related cystic disorders obtained from the literature and data from our institute. Especially, knowledge of metaplastic and precancerous natures of LEGH, and biological characteristics-based management are of importance to detect malignancy, as well as to avoid unnecessary hysterectomy. Further understanding of this disease is expected.

**Author contributions**

All three authors directly contributed to the conception of the work, making figures, drafting this manuscript, and revising it critically for important intellectual content.

**Conflict of interest**

The authors declare no competing interests.

**Data Availability Statement**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.
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